QATAR UNIVERSITY

COLLEGE OF PHARMACY

COST-EFFECTIVENESS ANALYSIS OF SEDATIVES IN THE MANAGEMENT OF NEONATES UNDERGOING MECHANICAL VENTILATION IN THE INTENSIVE CARE SETTING IN QATAR

BY

DINA HAMDI ABUSHANAB

A Thesis Submitted to the

Faculty of the College of Pharmacy

in Partial Fulfillment of the Requirements for the Degree of

Masters of Science

in Pharmacy

June 2017

COMMITTEE PAGE

The members of the committee approve the thesis of Dina Hamdi Abushanab defended on 01/06/2017.

_____

Associate Professor Daoud Al-Badriyeh, PhD

Thesis Supervisor

_____

Assistant Professor Esther Chan, PhD

External Committee Member

_____

Professor Ibrahim Al-abbadi, PhD

Committee Member

_____

Assistant Professor Hazem Elewa, PhD

Committee Member

_____

Professor Mohamed Izham Mohamed Ibrahim, PhD

Committee Member

_____

Professor Feras Qasem Alali, PhD

Committee Member

Approved:

_____

Mohammad Diab, Dean, College of Pharmacy

ABSTRACT

Abushanab Dina H, Masters:

June: 2017, Pharmacy

Title: Cost-Effectiveness Analysis of Sedatives in the Management of Neonates Undergoing Mechanical Ventilation in the Intensive Care Setting in Qatar

Supervisor of Thesis: Dr. Daoud Al-Badriyeh, PhD

Background. Neonates with respiratory distress syndrome (RDS), admitted to the neonatal intensive care unit (NICU) at the Women's Hospital (WH) in Qatar, often require mechanical ventilation (MV) to maintain ventilator synchrony. No economic evaluations of morphine or fentanyl as stands alone or in combination with midazolam for sedation in NICU exist in the literature. The objective of this study was to evaluate the clinical and economic impact of sedatives in mechanically ventilated neonates with RDS in the Qatari NICU.

Methods. A comparative retrospective cost-effectiveness study sought to evaluate 126 critically ill neonates receiving morphine versus fentanyl, 64 patients receiving morphine monotherapy versus morphine plus midazolam, and 268 patients receiving fentanyl monotherapy versus fentanyl plus midazolam at WH in Hamad Medical Corporation (HMC), Qatar. Available medical records in the duration from October 2014 to January 2016 were utilized. Decision analytic models from the hospital perspective were designed to measure all the possible consequences of all comparisons. The primary

endpoints were the successful drug sedation rate, based on the Premature Infant Pain Profile (PIPP) scoring scale, and the overall direct medical cost of therapy. Sample size calculations were to achieve results with 80% power and a significance level of 0.05. Sensitivity analyses were conducted to enhance the robustness and generalizability of the results.

Results. Morphine monotherapy achieved sedation success in 68% of patients with an incremental cost-effectiveness ratio (ICER) of QAR 490.36 per additional sedation success compared to 43% with fentanyl. Morphine also produced better sedation in neonates with an ICER of QAR 21, 206.85 compared to its combination with midazolam (66% versus 34%). The fentanyl monotherapy dominated the combination of fentanyl and midazolam, with a net cost saving of QAR 43,811.83 per patient and a 51% successful sedation rate, compared to 33%. Here, the study group of fentanyl plus midazolam combination did not achieve the calculated sample size and, hence, the evaluation of this group is piloting in nature. Sensitivity analyses demonstrated robustness of all study conclusions.

Conclusion. The current study is the first clinical and economic analysis of morphine, fentanyl, and midazolam in the NICU in literature, including in Qatar. Morphine monotherapy produced higher sedation levels over fentanyl monotherapy and the morphine plus midazolam combination but with higher costs. Fentanyl monotherapy had cost savings over its combination with midazolam, while its reported higher clinical effectiveness over the combination cannot be interpreted due to the limited sample size.

ACKNOWLEDGMENTS

It was two years full of challenges, troubles and triumphs. MSc has been a life changing experience for me and would not have been possible without the support of many people in my life. I believe few words of acknowledgment in this thesis would not be enough to truly extend my appreciation and gratitude to everyone who helped me scientifically, emotionally, and financially.

First and foremost, I thank Allah Almighty for giving me the guidance, patience and strength to conduct this work, persevere and finish it successfully after all the challenges.

I would like also to thank and appreciate the many people who have supported me towards achieving this degree.

First, I would like to express my deepest gratitude and appreciation to my supervisor, Dr. Daoud Al-Badriyeh, who accepted me as his MSc student and believed in me in following my dreams and taking my own path. You have provided me with strength, excellent guidance, tremendous support, patience, constructive criticism, and insisted that I do and give the best of myself. Thank you for helping me overcome the heavy stress, obstacles, and toughest moments I faced in my work. Thank you very much also for helping me improve my writing skills, you always make my writing better. I am grateful for all the efforts and the time you spent reviewing my papers, and I truly appreciate all your assistance in getting my research ready to present. Thank you for being a role model, an inspiration to me at all times and for transforming your passion in pharmacoeconomics and outcomes research to me and I hope to influence others in my

life as you have done for me. I hope to continue working with you and be my supervisor or collaborator in my future PhD research.

I would like also to express my heartfelt gratefulness to Prof. Feras Alali, for not only being a committee member of my research, but also for being a “truly human”. Thank you for all the support, strength, confidence I learned from you throughout the two years. I believe you are the backbone to me and to all students in the college. I am also grateful to Prof. Mohamed Izham, Dr. Hazem Elewa and Dr. Ahmed Awaisu for all their advices about my research.

I seriously appreciate all the support I received through the collaborative work with Dr. Omar Alsoukhni, Clinical Pharmacy Specialist and Dr. Fouad Abounahia, Consultant-Neonatologist from the Neonatal Intensive Care Unit (NICU) at Hamad Medical Corporation (HMC). You were always supportive, available, providing me with assistance, feedback, and invaluable advice about my research.

Special thanks and appreciations go out to the NICU team at the Women’s Hospital for providing me with local statistical data from Vermont Oxford database to support my thesis and overall research. My thanks also go to the finance department at HMC for providing me with cost data that helped me to conduct and complete this research.

I would like to give special thanks to the Office of Academic Research for the research grant I received to complete this research.

The travel fund committee at the college of pharmacy deserves also special thanks for all the financial support that l received to present my research in the International

Society for Pharmacoeconomics and Outcomes Research Conference in Boston, USA in May 2017.

I would like also to take this opportunity to thank the Dean Dr. Mohammad Diab, faculty, and administrators at the college of pharmacy for all the support I received over the past six years, including my undergraduate studies.

To all my friends and colleagues, thank you for all the support, encouragement, advice, the great times we shared together. Special thanks to my friend and sister “Myriam Jam”, you were always around whenever I needed a friend. We shared together everything in the college over the past six years; good and bad days, memories, struggles, fun, and laughs. We graduated together from the BSc two years ago, and now we are graduating again together with an MSc, Insha’Allah.

I must express my warmest gratitude to the Pharmacy Postgraduate Society, especially Prof. Feras Alali and Dr. Alla El-Awaisi for placing their trust and confidence in me to assume the position of the president of the society. I am also thankful to all the executive members of the society; Alya Babiker, Myriam Jaam, and Dana Elkhalifa for all the efforts they put in for making the society a success.

Above all, my wholehearted thanks go to my family. I am tremendously indebted to my parents, brothers, and extended family for their love, support, warmth, and always being there for me throughout the research process. Thank you for your patience and understanding my disappearance during the months that I was focusing on the research. Mom and dad, I cannot thank you enough for believing in me, supporting me emotionally and financially, giving me the opportunity to chase my dreams, and be where I am today.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ARF	Acute Respiratory Failure
ACV	Assist-Control Ventilation
ADRs	Adverse Drug Reactions
ACER	Average Cost-Effectiveness Ratio
BDP	Bronchopulmonary Dysplasia
CMV	Continuous Mandatory Ventilation
CEA	Cost-Effectiveness Analysis
CMA	Cost-Minimization Analysis
CBA	Cost-Benefit Analysis
CUA	Cost-Utility Analysis
CPAP	Continuous Positive Airway Pressure
CNS	Central Nervous System
COI	Cost of Illness
CCA	Cost-Consequence Analysis
CPI	Consumer Price Index
CONSORT	Consolidated Standards of Reporting Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CA	Cost Analysis
EI	Endotracheal Intubation
EPAP	Expiratory Positive Airway Pressure

GDP	Gross Domestic Product
HMC	Hamad Medical Corporation
HR	Heart Rate
HIE	Hypoxic Ischemic Encephalopathy
Hr	Hour
IPAP	Inspiratory Positive Airway Pressure
IMV	Intermittent Mandatory Ventilation
IM	Intramuscular
ICU	Intensive Care Unit
ICER	Incremental Cost-Effectiveness Ratio
IVH	Intraventricular Hemorrhage
IRB	Institutional Review Board
IV	Intravenous
mmHg	Millimeter of Mercury
MV	Mechanical Ventilation
mg	Milligram
Mcg	Microgram
MRC	Medical Research Center
MAP	Mean Blood Pressure
mL/kg	Milliliter/kilograms
MDI	Mental Development Index

NIV	Noninvasive Ventilation
NIPSV	Noninvasive Pressure Support Ventilation
NICU	Neonatal Intensive Care Unit
NHS	National Health Services
NEC	Necrotizing Enterocolitis
NIPS	Neonatal Infant Pain Scale
NFCS	Neonatal Facial Coding System
N-PASS	Neonatal Pain, Agitation, Sedation
PDA	Patent Ductus Arteriosus
PEEP	Positive End-Expiratory Pressure
PIP	Peak Inspiratory Pressure
PSV	Pressure Support Ventilation
PIPP	Premature Infant Pain Profile
PCS	Postoperative Comfort Score
PICU	Pediatric Intensive Care Unit
PDI	Psychomotor Development Index
QAR	Qatari Riyal
QOL	Quality of Life
QALY	Quality-Adjusted Life Year
RDS	Respiratory Distress Syndrome
RCTs	Randomized Controlled Trials

RSS	Ramsey Sedation Scale
RR	Respiratory Rate
RASS	Richmond Agitation and Sedation Scale
SIMV	Synchronous Intermittent Mandatory Ventilation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SAS	Sedation-Agitation Scale
US	United States
WH	Women's Hospital
VAS	Visual Analogue Scale

Chapter 1: Introduction

1.1 Respiratory distress syndrome (RDS)

The standard definition of RDS was originally described by Bernard et al in the American/European Consensus Conference in 1994 as patients who have bilateral pulmonary infiltrates along with arterial hypoxemia. To make a diagnosis of RDS, the ratio of a patient's concentration of arterial oxygen in the blood over the inspired fraction of oxygen (PaO_2/FiO_2) should be less than 200 millimeter of mercury (mmHg), and the incidence of left atrial hypertension should be excluded (1, 2). Later in 2012, Ranieri et al updated the definition of RDS and classified it into three categories based on the range of hypoxemia: mild ($200< PaO_2/FiO_2 \leq 300$ mmHg), moderate ($100< PaO_2/FiO_2 \leq 200$ mmHg), and severe ($PaO_2/FIO_2 \leq 100$ mmHg) (3). As a result, the arterial hypoxemia occurs due to the accumulation of edema fluid in the distal air spaces of the lung, disturbing the blood gas exchange. The excretion of the carbon dioxide is also affected, which leads to increasing the respiratory rate and the effort of inhalation (4-6). Several clinical disorders have been associated with the RDS development, including in patients with established respiratory or non-respiratory infections. Here, pneumonia, whether bacterial, viral, or fungal, has been found to be the main cause of RDS development. This is followed by severe sepsis, which is often associated with the pneumonia or other extra-respiratory source of infection, such as peritonitis (7-9). Aspiration of gastric contents, hemorrhage, shock after major trauma, severe acute pancreatitis, pulmonary injury associated with transfusion, and drug reactions are other common causes of RDS (9).

Notably, many patients who are diagnosed with acute respiratory failure (ARF) following RDS can also develop non-respiratory organ failure, such as hematologic anomalies, including anemia and thrombocytopenia (10), cardiac failure that needs vasopressor support, and renal failure that needs dialysis. In the majority of cases, the non-respiratory organ failures are due to severe sepsis, and in other cases they may be related to shock (11).

1.2 Pathology of RDS

In 1977, Bachofen et al and colleagues first described the pathological characteristics of the lung in patients with RDS. They identified several ultrastructural details that were observed during different phases of the disease, with these being the acute, subacute, and chronic phases (8), (**Figure 1.1**):

a. During the acute phase, defined as the first six days, the interstitial and alveolar edema with accumulation of neutrophils, macrophages, and red blood cells in the alveoli is found (**Figures 1.1.a and 1.1.b**). This is added to injury in the endothelium and epithelium (**Figure 1.1.c**) and the hyaline membranes in the alveoli (**Figure 1.1.b**).
b. During the subacute phase, defined as the next 7–14 days, reabsorption happens in an effort to repair the edema, and alveolar epithelial type II cells proliferation results. Further, fibroblasts are infiltrated and deposition of collagen is noticed.
c. During the last phase, i.e. chronic phase, that happens after 14 days, the infiltration of the acute neutrophilic is resolved except in cases of superimposed

nosocomial pneumonia. More mononuclear cells and alveolar macrophages, and more fibrosis and alveolar epithelial repair are also seen.

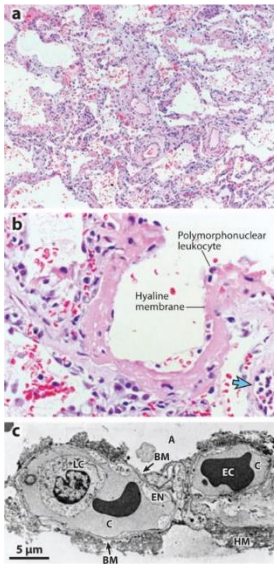


Figure 1.1 Phases of the lung during RDS (8)

Abbreviations in section c: A: alveolar space; BM: exposed basement membrane; C: capillary; EC: erythrocyte; EN: endothelium; LC: leukocyte

1.3 RDS in newborn

RDS has multiple synonyms in neonates including:

- Hyaline membrane disease
- Neonatal respiratory distress syndrome
- Infant respiratory distress syndrome
- Surfactant deficiency

Some premature infants born before 28 weeks of gestation in the first 24 hours (hrs) after birth develop RDS due to deficiency in surfactants, resulting in low lungs

compliance, alveolar surface tension, declined gas exchange and the need for high ventilatory pressures. RDS rarely happens in full term neonates and sometimes proceeds to bronchopulmonary dysplasia (BPD) which is a chronic lung disorder that occurs due to prolong use of mechanical ventilation (MV). Risk factors of RDS include prematurity, stress during delivery, especially in case of blood deficiency, infection, gestational diabetes, and when an emergency cesarean delivery is required (12). RDS in newborn is diagnosed through the clinical signs and symptoms of the infants along with the chest radiograph features that include, low lung volume and ground glass appearance called reticulogranular with air bronchograms (**Figure 1.2**). In order to discuss the pathophysiological features of neonate's RDS, understanding the development of normal fetal alveolar is essential. The fetal alveolar development undergoes four stages (13):

- Embryonic stage: The first appearance of the fetal lung as foregut protrusion starts during this phase at around 26 days gestation. Then the lung begins to extend forming the main bronchi at around 33 days gestation, which later extends to developing mesenchyme and segmental bronchi.
- Pseudoglandular stage: During this phase, which occurs at 16^{th} to 25^{th} weeks of gestation, approximately 15 to 20 airway branches are developed from the segmental bronchi forming the terminal bronchioles. Then the blood vessels and epithelial cells develop.
- Canalicular stage: This stage occurs at 16^{th} to 25^{th} weeks of gestation, where the bronchioles and alveolar ducts of the gas exchange area are created and the

mesenchyme cells are more vascular. Later, the differentiation of cuboidal epithelial cells into type II of alveolar cells as well as the cytoplasmic lamellar body formation occurs, which indicate the presence of surfactant.

- Saccular stage: This phase happens at around 24 weeks of gestation where the formation of alveoli (responsible for air exchange) occurs.

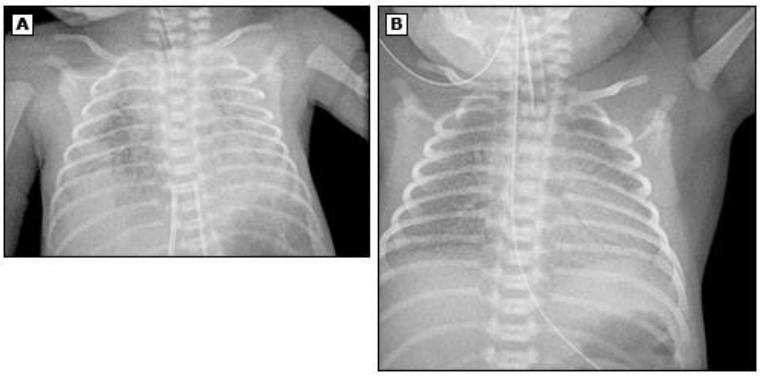


Figure 1.2 Chest radiograph of neonatal RDS. (A) shows the severe RDS which indicates the low lung volume compare to (B), moderate RDS which indicates high lung volume (14)

1.3.1 Pathophysiology of RDS in neonates

- **Surfactant deficiency**

Deficiency of surfactant, which is a complex of 90% lipids and 10% protein (13, 15) is the main cause of RDS that has effect on reducing the alveolar surface tension and collapse atelectasis, increasing the lung volume, enhancing the alveolar expansion and lung compliance, and maintaining the blood oxygenation. The production of surfactant is developmentally regulated, therefore the deficiency of surfactant is most commonly seen among preterm infants (16).

In addition to the deficiency, inactivation of surfactant may play a role in respiratory distress development due to different factors such as aspiration of meconium and blood in the alveoli, proteinaceous edema and inflammatory cells in addition to congenital pneumonia (17, 18).

- **Inflammation and lung injury**

Animal experiments suggested that surfactant deficiency is associated with accumulation of neutrophils in the lung that leads to increasing the permeability of protein, pulmonary edema, and drainage of liquid and protein. The study was done in ten preterm lambs with gestation age of 127 ± 1 days undergoing MV for eight hrs (19). Pulmonary edema occurs due to the deficiency in the fluid pulmonary absorption in the fetus lung which is mediated by the sodium channels found on epithelial cells (ENaC). The expression of these channels increases with the gestational age and, thus, the preterm babies born with insufficient numbers of ENaC, leading to the development of fluid retention. Another study was conducted in human preterm showed that decreased polymorphonuclear leukocytes (PMNs) and platelets, and increased release of elastase and thromboxane release, were associated with RDS (20)

1.4 Epidemiology of RDS in neonates

Internationally, the mortality in the infant population due to RDS has obviously declined in the United States (US), for example, from 268 deaths per 100,000 live births in 1971 to 15 per 100,000 live births in 2008 (21)**.** Around 30% to 40% of neonates admitted to hospital due to RDS and about 7% to 50% of neonates are diagnosed with

RDS (22). Approximately 92% of premature infants born at 24 to 25 weeks of gestation are diagnosed with RDS, 88% in 26 to 27 weeks, 76% in 28 to 29 weeks, and 57% at 30 to 31 weeks. Prematurity has been shown to be a serious and wide problem that results in neonatal mortality, with many of the mortality and morbidity cases attributed to RDS. Globally, around fifteen million babies are born preterm annually and the complications of preterm birth are the primary cause of mortality among pediatrics under five years of age with an estimation of one million deaths in 2013. Among 184 countries, the rate of preterm birth of babies born ranges between 5% and 18%. There are variations in the countries in relation to the survival rates. In low-income countries for example, half of the neonates born at or below 32 weeks and die because of the dearth in the cost-effective care, including warmth, breastfeeding provision, and essential infections care. However, the majority of the babies survive in high-income settings (23).

On the other hand, in the adult population around 200,000 were annually diagnosed with RDS in the US, for example, where 40% died due to the same reason. The African American and Hispanic patients have also a greater incidence of mortality due to RDS compared with Caucasian patients. RDS has been shown to be an essential cause for ARF in pediatric patients as well (24).

The signs and symptoms of RDS arise either at birth or afterwards and they include:

- Respiratory signs and symptoms: tachypnea, grunting sounds, apnea, cyanosis, inspiratory stridor.
- Retractions in the intercostals, subcostal, or suprasternal spaces.
- Poor feeding.

- Sharp pulling in of the chest below and between the ribs with each breath.
- Flaring of the nostrils.

Complications of RDS include (12):

- Pulmonary complications include:
  - Atelectasis.
  - Pneumothorax.
  - Hemorrhage.
- Blood and blood vessel complications include:
  - Sepsis.
  - Patent ductus arteriosus (PDA).

The management of RDS includes (12):

- Surfactant replacement therapy.
- Oxygen therapy.
- Invasive or non-invasive MV.

Oxygen therapy was the only strategy of management of neonates with RDS before 1960. Later in 1970s, continuous positive airway pressure therapy (CPAP) and antenatal corticosteroids were proposed. After that in 1990, surfactant replacement therapy was introduced. Although no complications of surfactant administration were reported, infants treated with an early surfactant therapy tended to have a higher prevalence of

PDA. After that, ventilators were introduced to greatly enhance the outcomes of patients with RDS (22).

1.5 Noninvasive ventilation (NIV)

The NIV is the ventilatory support or positive pressure into the lungs through a mask without any use of invasive endotracheal airway (25, 26). It is used to prevent the problems associated with endotracheal intubation (EI) and conventional MV, mainly the ventilator-associated pneumonia (27, 28). Noninvasive pressure support ventilation (NIPSV) is the main modality of the NIV. CPAP has also been used in many cases of ARF (29, 30).

Modes of NIV:

- CPAP: this mode is a substitute for invasive ventilation that does not need an endotracheal tube (ETT) and allows spontaneous breathing during continuous pressure that is applied in the patient's nares. It enhances the gas exchange and surfactant production, improves the chest wall stabilization, and reduces the breathing effort, intubation and surfactants (31).
- NIPSV: This type involves a ventilator with two levels of pressure; expiratory pressure [expiratory positive airway pressure (EPAP) or Positive end-expiratory pressure (PEEP), like CPAP and inspiratory positive airway pressure (IPAP)]. Once the patient begins the inspiration, the ventilator delivers the inspiratory and pressure support via a decelerated flow, resulting in constant IPAP. After finishing

the inspiratory process, the pressure support is stopped and the pressure decreased to the preset EPAP (31).

1.6 Invasive MV

Noninvasive MV does not always deliver effective oxygenation and stable pulmonary procedure. Therefore, invasive MV is an important and life-saving method to save patients, including the preterm neonates, with RDS in particular, when the non-invasive technique fails. Invasive MV has been shown to prevent lung damage development and BPD, and reduce the mortality rate in preterm newborns. MV is based on volume-cycled and pressure-cycled ventilations and are supplied at various rates, volumes, and pressures (21).

Modes of MV:

- Volume-cycled mode: A constant inspiratory flow is used to deliver the gas leading to peak pressure applied to the airways that is greater than that needed for lung distension (plateau pressure). The applied airway pressures vary according to changes in the pulmonary compliance (plateau pressure) and airway resistance (peak pressure) (21). This mode of ventilation is widely used as a first choice in the emergency department (ED). However, the main drawback of this mode is that high airway pressures may need to be applied, which cause barotrauma. Hence, close monitoring of patient's lung status is required to avoid cases such as RDS deterioration, pneumothorax, chest-wall rigidity, increased intra-abdominal pressure and psychomotor agitation and, thus, increased peak pressure.

- Pressure-cycled mode: The delivery of volume depends on the compliance of patient's pulmonary status. Peak inspiratory pressure (PIP) is used and the difference in the pressure between the MV and the lungs increases until the peak pressure is achieved. As the lung inflates, the inspiratory flow decreases, resulting in an equal distribution of gas all over the lungs. Close monitoring is very important to avoid changing in the tidal volumes (21).
- High-frequency oscillatory support: Ultra-high respiratory rates (180-900 breaths per minute), low tidal volumes (1-4 milliliter/kilograms (mL/kg)), and high airway pressures (25-30 mmH_2O) are used in this mode. The mode is used in intensive care units (ICUs) especially for preterm neonates with RDS to improve oxygenation and restore lung functions (21).

Examples of modes of ventilatory support (32):

- Continuous Mandatory Ventilation (CMV): Regardless of the patient's pulmonary effort, the delivery of breath is supplied at preset periods. It is commonly used in paralyzed patient.
- Assist-Control Ventilation (ACV): The ventilator supplies the breaths in synchronization with the patient's respiratory drive, and with each inspiratory effort, a complete tidal volume is delivered by the ventilator. This mode allows spontaneous breathing between ventilator and the breaths, and it is the mode of choice for patients with intact respiratory effort.

- Intermittent Mandatory Ventilation (IMV): In this mode, preset breaths are delivered and unlike ACV, spontaneous breathing is not accepted.
- Synchronous Intermittent Mandatory Ventilation (SIMV): The ventilator supplies the breaths in synchronization with the patient's respiratory effort, which limits the barotrauma that may happen with IMV in patients who are forcefully exhaling. It also allows the spontaneous breathing. A major disadvantage of this ventilator is that the breathing efforts of the patients are increased.
- Pressure Support Ventilation (PSV): This ventilator is used for spontaneously breathing patients to reduce the incidence of barotrauma and breathing effort. In this type of ventilation, a support pressure is set to help each spontaneous breath. It is used in patients with mild to moderate respiratory failure and patients with sufficient respiratory effort.

1.7 Neonatal Intensive Care Unit (NICU)

NICU is a specialist hospital ward that provides intensive care treatment and monitoring for critically ill neonates, such as preterm neonates with low birth weight babies [less than 2494.756 grams (g)], or with medical conditions that need special care (33).

Factors that increase the risk of babies to be admitted to the NICU (33):

- Maternal factors:
  - Age younger than 16 or older than 40 years.
  - Drug or alcohol exposure.

- Diabetes and hypertension.
- Bleeding.
- Sexually transmitted diseases (STD).
- Multiple pregnancy.
- Too little or too much amniotic fluid.
- Premature rupture of membranes.

- Delivery factors:
  - Fetal distress/birth asphyxia.
  - Breech delivery presentation.
  - Meconium.
  - Nuchal cord.
  - Forceps or cesarean delivery.

- Baby factors:
  - Birth at gestational age less than 37 weeks or more than 42 weeks.
  - Birth weight less than 2,500 g or more than 4,000 g.
  - Resuscitation in the delivery room.
  - Birth defects.
  - Respiratory distress including rapid breathing, grunting, or apnea.
  - Infections, seizures, hypoglycemia.

- Need for extra oxygen, special treatment or procedures such as a blood transfusion.

1.8 Opioids

Opioids are considered the most effective and best choice of drugs for fighting moderate to severe pain. Examples of opioids are: morphine, fentanyl, codeine, hydrocodone, methadone, oxycodone, hydromorphone, and meperidine. Opioid receptors are generally presented in the central nervous system (CNS) but are also found in the peripheral tissues. The stimulation of these receptors is produced by the endogenous peptides (34). Opioids are classified into four groups (34):

- Opioids that are produced by the human body, known as endogenous opioid peptides, such as enkephalins and endorphins.
- Opioids that are generated from the nature, which are called alkaloids like morphine and codeine.
- Semisynthetic opioids made by synthesis from a natural substance, with hydrocodone and oxycodone as examples.
- Synthetic opioids made by chemical synthesis, including methadone and fentanyl.

The main types of opioid receptors (34) are:

- Mu receptors. These are mostly located in the brainstem to produce different types of effects such as supraspinal analgesia, respiratory depression, urinary retention, sedation, euphoria, constipation, and physical dependence.

Enkephalins, morphine, fentanyl and codeine are known as weak agonists of Mu receptors, and others like naloxone and naltrexone are antagonists of these receptors.

- Kappa receptors. These are found in the spinal cord in addition to the brainstem and they are responsible for the effects of spinal analgesia, dysphoria, sedation, and respiratory depression. Dynorphin is an agonist, whereas naloxone and naltrexone are antagonists of kappa receptors.

- Delta receptors. The brain is the only location of these receptors, which are in charge for supraspinal and spinal analgesia, respiratory depression, urinary retention, and physical dependence. Examples of agonists of these receptors are enkephalins and meperidine.

The use of opioids as sedatives is necessary for patients undergoing MV with RDS to facilitate the stressful procedure of MV, enhance the ventilator-patient synchrony, eliminate pain, and maintain the neuro-endocrine system, pain, and biomedical and physiologic responses (35). Sedative medications are used extensively for pain relief in critically ill neonates and have been shown to improve the ventilator synchrony and pulmonary function and reduce the neuro-endocrine responses (36). Here, morphine, fentanyl, and midazolam are the main sedation of focus of research in the current thesis. These as well as other sedatives that are used commonly in the NICU settings are discussed below:

1.8.1 Morphine

Morphine, a phenanthrene derivative is the main alkaloid of opium. It is the prototype opiate analgesic and narcotic, and acts mainly in the CNS and the smooth muscle through the opioid Mu receptor. It is used for the relief of moderate to severe pain in addition to its sedative effect. Morphine sulfate injection is a sterile, non-pyrogenic isobaric solution free of antioxidants, preservatives or added neurotoxic substances administered as intravenous (IV), epidural or intrathecal (37). According to the formulary of Hamad Medical Corporation (HMC, the main health care provider in Qatar, comprising eight major hospitals), each mL injection contains 15 milligram (mg) of morphine sulfate which allows for single use only. It has been reported that, in 2013, 523,000 Kg of morphine were produced, 45,000 kg was utilized for pain relief in the developed countries, and around 70% of morphine was used to produce other opioids such as hydromorphone, oxycodone and heroin (34).

1.8.2 Fentanyl

Similar to morphine, fentanyl is a Mu opioid agonist used to relieve moderate to severe pain in addition to its sedative effect, and is about 80 times more potent narcotic analgesic compared to morphine. It is a sterile, non-pyrogenic, preservative free aqueous solution for IV or intramuscular (IM) injection. After that, many analogues of fentanyl were developed, including:

1. Alfentanil (Alfenta®), an ultra-short [5-10 minutes (min)] acting analgesic.

2. Sufentanil (Sufenta®), an exceptionally potent analgesic (5 to 10 times more potent than fentanyl) for use in cardiac surgery (41).

In 2012, fentanyl was the most commonly utilized synthetic opioid in clinical practice. In 2013, 1700 kg were used worldwide (42).

Each mL of solution contains fentanyl citrate equivalent to 50 microgram (mcg) of fentanyl base, adjusted to pH 4.0 to 7.5 with sodium hydroxide according to HMC formulary.

1.8.3 Diamorphine

Diamorphine hydrochloride is a prodrug, derivative of morphine, acts on the Mu opioid receptor, and is more potent compared with morphine. It is recommended to relieve severe pain, particularly in terminally ill patients who need palliative care. Diamorphine is metabolized into morphine through acetylation once it reaches the brain by injection. But, if taken orally, it is metabolized into morphine before passing the blood brain barrier. The main excretion occurs through the kidney as glucuronides mostly, in addition to as morphine as well. Approximately, 7 to 10% of the drug is eliminated into the feces by the biliary system (43).

1.8.4 Midazolam

Midazolam hydrochloride is available as a sterile, pyrogenic-free and intended for the IV or IM injection dosage form (44). Midazolam is a hypnotic-sedative with anxiolytic and amnestic properties. Each mL is comprised of midazolam hydrochloride that is equivalent to five mg of midazolam compounded with 0.8% sodium chloride and

0.01% disodium edetate, and 1% preservative of benzyl alcohol, based on HMC formulary. In 1970s until 1990s, the anticonvulsant characteristics of midazolam were studied and, in 2010, midazolam was considered the most widely used benzodiazepine as an anesthetic (39).

1.8.5 Pancuronium

Pancuronium is a synthetic, long-acting steroid neuromuscular blocking drug, and it competitively binds to the nicotinic receptor at the neuromuscular junction, inhibiting the binding of acetylcholine and leading to skeletal muscle relaxation and paralysis effects. As a neuromuscular inhibiting medication, it can seriously affect the respiratory function resulting in respiratory paralysis, thereby it should be given to patients who are maintaining an adequate airway and respiratory support (45). At HMC, each mL contains two mg of pancuronium.

1.9 Pharmacoeconomics

1.9.1 What is pharmacoeconomics?

Pharmacoeconomics is the field of study that evaluates the costs and consequences of pharmaceutical products and services. Pharmacoeconomics has been defined as “the description and analysis of the costs of drug therapy to the health care system and society”. It combines the descriptive and analytic methods to evaluate the pharmaceutical interventions and deal with three types of outcomes: economic, clinical and humanistic, referred to as ECHO model, to prevent, treat, diagnose, or manage diseases (**Figure 1.3**) (44).

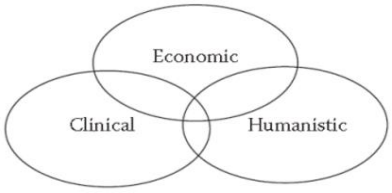


Figure 1.3. ECHO model (49)

What are the features that characterize the economic evaluations? (49)

- Pharmacoeconomics deals with both the costs and outcomes, better guiding the decision making to take the best decision.
- The pharmacoeconomics analysis deals with choices. Because of resource scarcity and the inability of humans to produce all the required consequences, it is necessary that choices must be taken considering all areas of human activity.

The above two features of pharmacoeconomics analysis led the scientists to describe the pharmacoeconomics evaluation as the comparative analysis of alternative actions in relation to their costs and outcomes. As a result, the pharmacoeconomics evaluation is used to identify, measure, value, and compare the costs and outcomes of different pharmaceutical alternatives (**Figure 1.4**). It helps clinical decision makers to prioritize different and competing health care services in relation to the use of interventions, drug formularies and achieving the efficient utilization of resources (49).

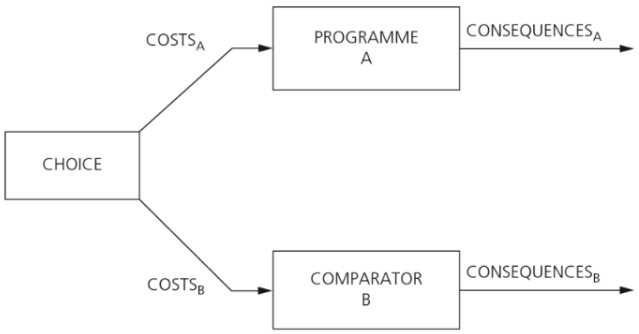


Figure 1.4 Economic evaluation as the comparative analysis of alternatives (49)

1.9.2 Classification of cost (48)

- Direct cost. It is the exchange of money for the consumption of the resources, which can be further classified into:
  - Direct medical cost, which involves costs of medical services such as clinical services, diagnostic and laboratory tests, hospitalizations, interventions, intervention's monitoring, home medical services, and nursing services.
  - Direct nonmedical cost, which involves costs that are not associated with medical services such as travel cost to receive health care, hotel stays, and children care.
- Indirect or productivity cost. It is the unpaid resource commitment such as lost patient's time or productivity from work due to the illness.

Costs can be also classified into (48):

- Fixed cost. It is the cost that does not vary when the output is increased or decreased, such as building cost and employee salary.

- Variable cost. This is the cost that does change with an increase or decrease in the output, such as choosing between different medication products for the same indication.
- Average cost. This is the resources consumed per unit of output.
- Marginal cost. It is the change in the total cost of generating one more or one less unit of output.
- Opportunity cost. It is the amount that a resource could earn in its greatest value of the alternative use.
- Intangible cost. This is the unphysical cost, such as cost used to treat pain or fatigue.

1.9.3 Four types of pharmacoeconomics evaluations to assess the costs and consequences of different alternative therapies (44, 48, 50)

- **Cost-Effectiveness Analysis (CEA)**

CEA is a technique designed to compare programs or interventions with different levels of efficacy or safety outcomes. Costs are measured in monetary unit whereas outcomes are measured and expressed in natural units depending on a specific therapeutic outcome. Examples of natural units are: lives saved, cases succeed, life expectancy, or drop in blood glucose.

Costs and effects of interventions can be combined into an average cost-effectiveness ratio (ACER/CER) or an incremental cost-effectiveness ratio (ICER):

- An ACER is the total cost of a program or intervention divided by its therapeutic outcome. While ACER can help clinical decision makers recognize cheaper alternatives, ACER does not enable calculating the additional cost associated with an intervention as compared to a cheaper one. ACER can be described as follows:

$$\text{ACER} = \frac{\text{health care costs}}{\text{clinical outcome}}$$

Figure 1.5 ACER equation (44)

- ICER is the ratio of the difference in the costs divided by the difference in the effectiveness which represents the incremental cost associated with one intervention over another. The ICER can be summarized as follows:

$$\text{ICER} = \frac{\text{cost}_A - \text{cost}_B}{\text{effect}_A - \text{effect}_B}$$

Figure 1.6 ICER equation (44)

There are three advantages of CEA:

- It is easy to perform as the practitioners are generally very familiar with the national unit as a measure of effect.
- Unlike cost-benefit analysis, the clinical outcomes are not expressed in the difficult-to-measure monetary unit.
- Unlike cost minimization analysis, different treatment options with different levels of an outcome can be compared.

Disadvantages of CEA are:

- Different treatment options can only be compared at a time against the same type of outcome.
- Multiple CEAs in a single comparison may be needed, to compare alternatives against multiple types of outcomes.
- It cannot combine the humanistic type of outcome with the natural unit outcome into a single unit of measurement. It does not consider the multi-dimensional nature of outcomes.

- **Cost-Minimization Analysis (CMA)**

This type of analysis is used when two or more interventions are evaluated and compared in which the outcome is therapeutically equivalent, but with the costs, including the acquisition, preparation and administration costs, being considerably different. An example of this is comparing two generics for the same consequence. The disadvantage of CMA is that it assumes both treatment options have the same effectiveness and, thus, its application to interventions is limited.

- **Cost-Benefit Analysis (CBA)**

CBA is a tool that allows the clinical decision makers to identify, measure, and compare the benefits accrued from a program or intervention with the costs of providing it. The program or the treatment should measure and convert the costs and the benefits of the program or intervention into equivalent monetary units. The decision makers express the costs and benefits as benefit to cost ratio (B:C) or a net benefit, to then favor the

intervention that has the highest net benefit or B:C ratio, or the lower net cost or C:B ratio (44).

The advantage of CBA is that it can be used to compare interventions with different outcome measures, because all types of outcomes are unified by being valued in monetary units. A disadvantage however is that no universal agreement on using one standard method for evaluating the monetary values of outcomes exist.

- **Cost-Utility Analysis (CUA)**

CUA is a tool used for comparing treatment options when taking in consideration the quality of life (QOL) of patients. CUA considers the cost, and the quality and quantity of patient-years. Cost is expressed in monetary units, and the outcome is measured in the quality-adjusted life year (QALY), which is based on patient-weighted life utility. Utility is a scale measure of patient satisfaction in health, with '0' represents death, a utility score of '1' represents full health, and the scores between > 0 to <1 representing morbidity. The incremental cost-utility ratio (ICUR) is used to express the incremental cost to the additional QALY gained by the patient. QALY indicates the number of life years throughout which adjustment (enhancement) in QoL takes place out of the total numbers of life years.

Advantages of CUA include:

- Alternatives that have different type of outcomes can still be compared.
- Integrates mortality and morbidity into a single common unit.

- Utility adjustment over the years can be conducted to consider the long term varying status of disease morbidity.

Disadvantages of CUA include:

Lack of consensus on the best methods for measuring accurate utilities. There are three methods to measure the utilities: rating scale, standard gamble, and time tradeoff. There is no consensus to use a standard method due to subjectivity in measuring patient preference. Summary of the four studies is shown in **Table 1.1.**

Table 1.1. Summary of the four different pharmacoeconomics methodologies (48)

Method	Cost	Outcome	Goal
CMA	Monetary value	Assumed equal	To determine the lowest cost of treatment
CBA	Monetary value	Monetary value	To yield the greatest net benefit or B:C ratio
CEA	Monetary value	Natural unit	To determine the additional cost per a unit of effectiveness gained when one treatment option is compared to another
CUA	Monetary value	QALY	To determine the additional cost per a unit of quality gained when one treatment option is compared to another

Other types of economics evaluations (48):

- **Cost of Illness (COI)**

This type of economic evaluation is often referred to as burden of illness, which is to measure the direct and indirect costs associated with a particular illness. This method is

not used to compare between treatment options but to give an estimation of the financial burden of an illness.

- **Cost-Consequence Analysis (CCA)**

CCA is a technique in which the clinical outcomes and costs of programs or interventions are calculated and reported separately in studies.

1.9.4 Decision Analysis

Decision analysis is a systematic quantitative tool for evaluating and comparing the relative value of different decision options. It was developed as an approach to assist the health care providers in making decisions in relation to managing patient's diseases by providing data about which program or intervention has the greatest value or outcome. This model is usually used for CEA and CUA, especially when the clinical decision is complex, with uncertainty in outcomes generated (51).

Steps for conducting the decision analysis (44, 50):

- Identifying and framing the research question:

The researcher should clearly describe the problem or the research question in an appropriate level of detail. This includes the determining of the perspective, objective, and duration of follow up of the analysis.

- Specifying the treatment alternatives:

The researcher ideally studies the alternative under assessment against the best of standard treatments. Where appropriate, a treatment alternative or drug therapy is also compared to no therapy (placebo).

- Constructing the decision tree:

Lines are drawn to link the branching points that are called “nodes”. Nodes are places where different patient management pathways generate.

The decision tree consists of nodes, branches, and outcomes.

- Nodes can be decision or chance nodes:
  - (i) Decision nodes indicate points where different management pathways generate based on a decision, and these are represented by square boxes.
  - (ii) Chance nodes indicate points where different consequence pathways generate by chance, and these are represented by circles.
- Lines are drawn out of the nodes, and they connect between the different nodes from right to left, to form branches. Branches are made of consequent outcomes of interest to be followed up until final outcomes. Outcomes can be, for example, death, disability or health, with the end of follow up in a branch represented by triangles in the tree.

- Estimating the probabilities:

Different sources of data can be used to find and estimate the unbiased probabilities for the different outcomes in a tree. For example, parameters in relation to the effectiveness of an intervention can best be retrieved from randomized controlled trials

(RCTs), meta-analysis (MA) studies, or observational studies. Due to the different levels of evidence provided by different sources of data, sensitivity analysis is used to enhance confidence.

- Analyzing the decision tree:

After estimating the probabilities and outcomes, the researcher needs to analyze the data by a process called “folding back and averaging out”, where the researcher has to calculate the overall probability of a whole pathway by multiplying all the probabilities of different outcomes considered in this pathway.

If the cost of the intervention is of interest, the calculated probability of the whole pathway is then multiplied of the overall cost of the pathway to generate the proportional cost of the pathway. Then, the sum of the proportional costs of all pathways is the total cost of the intervention, which as an example can be utilized into a cost-effectiveness equation.

- Conducting a sensitivity analysis to test the uncertainty:

Once the modeler has finished the baseline analysis, sensitivity analysis, known as “uncertainty analysis” should be carried out to enhance the robustness and increase the generalizability of the results. Sensitivity tests, which can be deterministic or probabilistic depending on the type of variable, are produced by modifications to the base case values of several key variables, such as costs and probabilities, to evaluate the robustness of the study economic outcome. Base case values are substituted by the highest and lowest values within a reasonable uncertainty range of the baseline values.

Where a substitution changes the study economic conclusion, more values within the range replace the base case value. This is repeated until the exact variable value, at which the study outcome changes, is identified. Reporting this as part of the study results does not only better indicate the robustness of results, but also boosts the generalizability of them when being interpreted by decision makers in other settings, with different model inputs, e.g. different drug prices.

Main different types of sensitivity analysis (50, 51) are:

- One-way sensitivity analysis is the simplest type of sensitivity analyses, used when the changes in the outcomes are assessed against adjustments in one variable at a time, while the values of all other inputs are remaining constant at baseline. Adjusting one variable at a time can be also via what is called 'scenario sensitivity analysis', where a whole methodological scenario of interest is introduced into the baseline model for assessing the influence on the outcomes.
- Multivariate sensitivity analysis: when the changes in the outcomes are evaluated as the value of two or more variables are changed, while the values of all other inputs are remaining constant at baseline.
- Threshold analysis or break-even point. This is an extension of a sensitivity analysis in which the baseline input value is changed to the exact point where the study's conclusion changes.

There are important issues for consideration in the conduction of decision tree (44, 50)**:**

- Perspective:

The perspective, which is whose point of view the clinical or policy decision is being made from, is important in the pharmacoeconomics analysis as it determines the type of cost and outcome to include in an analysis. There are three main types of perspectives:

  - Payer perspective. The cost of obtaining a service is included in the analysis. Examples of this perspective include insurance companies, Medicare, and Health Maintenance Organization (HMOs).
  - Provider perspective. The cost of providing a specific service is included in the analysis, such as hospitals, health system, and provider group.
  - Society perspective. The broadest and most comprehensive type of perspectives, which includes all costs and effects regardless of who bears them.

- Setting:

The population of the study must be clearly defined by stating the inclusion and exclusion criteria to which the results will apply.

- Granularity:

The researcher must determine the best amount of detail to include in the decision analysis of a particular clinical decision and its outcomes. It is the one of the most

difficult decisions the researcher might face. For example, a researcher decides to look at the adverse reactions of a medicine, the researcher can engage and collaborate with experts or clinicians to help him obtain the sufficient level of detail to present the problem.

- Time horizon:

It indicates the time period of interest, during which the relative outcomes will occur and decision options, including costs and effects, are considered.

1.9.5 Time adjustment for costs (48, 50):

Same monetary units from different time points have different values for them, hence for the purpose of calculation, these need to be adjusted.

Transformation accounts for:

- Inflation. Accounts for changes in purchasing power of monetary value over time in the past. Common measures of inflation include:
  - Consumer price index (CPI). It measures the variation in the price level based on a stable market basket of services or goods.
  - Gross domestic product price index. This is the total monetary value of goods and services generated in a country in a certain time period. Unlike CPI, it is not based on a stable market basket of services or goods.
  - Personal consumption expenditures (PCE) Index. It involves the actual and imputed expenditures of households.

- Time preference (social discount factor). Future costs and outcomes are adjusted to their current values through the discounting, whereby these are valued differently depending on how far in the future they occur.

1.10 Opioids and cost

The worldwide market of opioids was estimated to be more than US$50 billion in 2009. There has been a 10-fold rise in the use of opioid medications since the 1990s, which has attributed to a critical economic burden on the health care system. Florence et al and colleagues found that the health care accounts for approximately one third of costs attributable to the prevalence of opioids' prescriptions, which indicates a huge economic burden on the health care system. Globally, between 2004 and 2008, out of all opioids, the consumption of morphine and fentanyl were increased by 19.8% and 31.1%, respectively. In 2008, the consumption of morphine was 54.6% in US, 26.4% in Europe, 6.4% in Canada, 3.3% in Australia and New Zealand, 0.9% in Japan, and 8% in other regions, whereas, the fentanyl consumption was 48.1%, 40.8%, 3.2%, 1.2%, 1.3%, and 5.4%, respectively, in the same countries. In relation to the Middle East region within the period 2004-2008, the growth in the morphine consumption was moderate as observed in Israel, Jordan, Saudi Arabia, and Egypt, while a higher rate of increase in the consumption was reported for fentanyl in Israel, Cyprus, Turkey, Egypt, and Jordan, during the same period (52).

1.11 Qatar country profile

Qatar is independent state located in the Middle East, Asia with an area of 11,586 square kilometers. In 2016, the population reached 2,258,283 living in Qatar. The population growth rate was 2.64% in 2016 and ranked 16 compared to the world. Arabic is the official language, whereas English is considered the second language of the country. Also, Qatari Riyal (QAR) is the main currency used in the country (53, 54). The total public health expenditure on health was 1.875% of gross domestic product (GDP) per capita in 2014 (55). As long as the investment continues to increase with increasing demand for excellent health care providers, the growth of the population will continue in the years ahead. The national growth in the health care and hospital activity provision and the demand for professionals in Qatar can be illustrated in **Figure 1.7** (56).
Under the umbrella of the Ministry of Health in Qatar, the services of health are provided via (i) the primary health care centers, constituting the basic care provided at 21 medical centers, (ii) specialized clinics, and (iii) hospitals, and (iv) the private sector that plays an adjunct role in providing health services, mostly via 3 general hospitals, 131 dental clinics, and 128 clinics for medical services. In the past, Qatar provided free health care services to all people until 1999, when Qatar faced an increased pressure on budgets. This forced the country to shift toward health insurance (57).

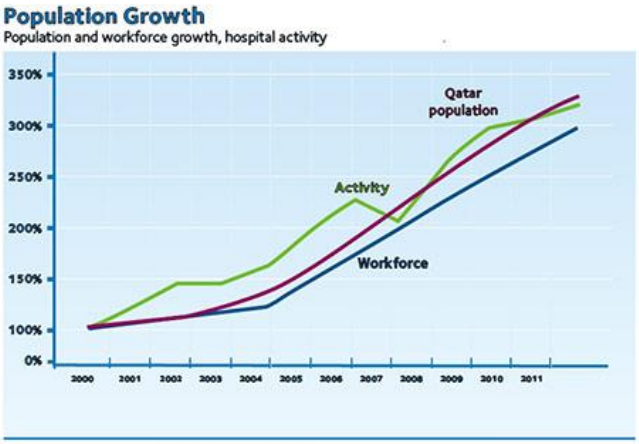


Figure 1.7. The Nation's growth in Qatar (56)

1.11.1 Statistics from Qatari NICU setting

With regards to the local Qatari setting, the total number of admissions in 2015 to the NICU at Women's Hospital (WH) in HMC, a tertiary referral unit and the major and busiest NICU in Qatar, was 2,094 cases. Twenty-one neonates were admitted with gestational age of less than 24 weeks, 77 with gestational age of 24-26, 121 with gestational age of 27-29 weeks, 268 with gestational age of 30-32 weeks, 620 with gestational age of 33-36 weeks, 988 with gestational age of 37-41 weeks, and 8 with gestational age greater than 41 weeks. Of admissions, 101 patients (4.8%) died because of a variety of reasons. (Unpublished data, extracted from the local statistical Vermont Oxford database, NICU, WH at HMC).

Similar to the international data, prematurity was the major reason for the NICU admission in Qatar (n= 1101, 53%), followed by RDS (n= 629, 30%), and major congenital anomalies (n= 174, 8.3%). Up to 183 patients (8.7%) were admitted due to other

reasons. 1,204 (57.5%) were admitted after cesarean delivery, while 890 (42.5%) were normally delivered. Around 1297 (62%) of admitted neonates received oxygen therapy. Noninvasive nasal CPAP ventilation was used among the admitted neonates (n= 877, 41.9%), and 137, (6.5 %) used other types. For those who received MV, 375 (17.9%) underwent the conventional type of ventilation, 108 (5.2%) received high frequency ventilation, and 378 (18.1%) received any other ventilations. Out of the total number of admissions, 1940 patients (92.6%) have been successfully discharged to home from the NICU, whereas 54 (2.6%) neonates were transferred to other hospitals. (Unpublished data, extracted from the local statistical Vermont Oxford Database, NICU, WH at HMC).

1.11.2 Status of sedation use in the Qatari setting

The current drug sedation use in the NICU of HMC is not based on a local comparative evidence. There is no universal protocol for the use of sedatives in the NICU settings of HMC. In relation to the NICU population of HMC, different hospitals in within the corporation use morphine and fentanyl as sedatives for the pain associated with MV to different levels, including the extent to which the economic outcomes are considered. Al-Wakra Hospital of HMC, for example, is using fentanyl as a first-line of therapy to manage the neonates pain with MV, and it has been doing so for years. This is when, for more than a year now, since 2015, the WH of HMC, who used to also rely on fentanyl, changed practices to use morphine for the same population. Different NICU settings, therefore, are using different treatment strategies in within HMC. There is even no agreement on the strategy of using a medication as a first line. While some clinicians use morphine as monotherapy, a combination of morphine with midazolam is

commonly used by others in the same population. A similar adjunct therapy also exists when fentanyl is used. All this is associated with confusion by decision makers throughout HMC in relation to what constitutes the best approach to management in the NICU populations.

Chapter 2: Review of literature

Sedative medications are commonly used to relieve the pain associated with the invasive MV among critically ill patients in general. In the neonatal population, the comparative evaluations of morphine and fentanyl, whether as head-to-head or against other sedatives, are relatively very limited in the literature. Only eight studies have been conducted in this population, which focus on the efficacy and safety type of outcomes in which the economic evaluations were not considered.

- Direct comparison between morphine and fentanyl

The only study that directly compared between fentanyl and morphine in neonates undergoing MV was conducted by Saarenmaa et al, in Finland in 1998. A total of 163 infants with gestational age of 24 weeks or more and with different underlying diseases, including RDS, were randomized to receive a continues infusion of either fentanyl (10.50 mcg/kg/hr, followed by 1.50 mg/kg/hr) or morphine (140 mcg/kg/hr followed by 20 mg/kg/hr) for at least one day. Saarenmaa et al assessed the severity of pain by measuring physiological parameters, hormonal response, and behavioral pain scale. The study illustrated that a statistically significant difference in relation to b-Endorphin in favor of fentanyl. During the opioid infusion, the mean arterial blood pressure constantly persisted in both therapy groups without any difference in the need for vasoactive agents. After two hrs of infusion, there was no statistical difference in the heart rate (HR). After 24 hrs however, the HR decreased by –8 and –3 beats/min (bpm) in the fentanyl and morphine groups, respectively. Noradrenaline and adrenaline

plasma concentration reductions were similar in all patients. With respect to the safety parameters, neonates receiving morphine developed significantly lower gastrointestinal motility (47%), as compared with the fentanyl group (23%) (P< 0.01). Necrotizing enterocolitis (NEC) and urinary retention were more frequently associated with patients sedated by fentanyl (12% and 56%), respectively compared with morphine (10% and 55%) (58).

- Direct comparison between morphine and midazolam

Anand et al conducted, in 1999, a pilot RCT in nine centers of 67 mechanically ventilated preterm neonates, with gestational age of 24 and 32 weeks, who received loading and maintenance doses of morphine, midazolam, or placebo for 14 days. This study was to investigate the incidence of poor neurologic outcomes in patients, at 0 to 28 days of age, receiving either morphine or midazolam, compared to placebo. The severity of illness was measured via the Clinical Risk Index, the level of sedation by the COMFORT score, and the level of pain by the Premature Infant Pain Profile (PIPP) scale. The findings of this trial demonstrated poor neurological outcomes in 32%, 24%, and 4% in neonates given midazolam, placebo, and morphine, respectively (P= 0.03). There was no statistically significant difference in the severity of illness during birth among all patients. At the time of hospital discharge, the Neonatal Medical Index Risk was significantly different among the three groups (P= 0.01) in which Grades I, II, and IV were higher in the midazolam group, Grade III was higher in the morphine group, and Grade V was higher in the placebo group. With respect to the level of sedation, at 12 hrs after finishing the therapy infusion, this decreased as COMFORT scores were

significantly increased in neonates given morphine (P= 0.005). Other groups did not show any difference after the treatment. The pain level was significantly reduced in morphine (P< 0.001) and midazolam groups (P= 0.002) but not in patients receiving placebo. In relation to the secondary outcomes, the duration of MV, NICU stay, hospital stay, and oral enteral feeding did not significantly change among sedation groups. Two cases of mortality occurred in the placebo group, one case in the midazolam group, and none in patients given morphine (59).

- Comparison between two different durations of morphine

While the neurodevelopment outcomes were evaluated in the short term follow up by Anand et al, Grunau et al (2009) assessed the neurological outcomes in the longer term, at 8 and 18 months, by using the Bayley Mental Development Index (MDI) and Bayley Psychomotor Development Index (PDI) questionnaire. Here, morphine was administered to 137 preterm (≤ 32 weeks) and 74 full-term mechanically ventilated babies. High administration of morphine was significantly correlated with low PDI at 8 months (r= -0.43) only. Spending more days on MV and the lower gestational age however, were significantly associated with low MDI and PDI at 8 months (r= −.33; r= −.43) and (r= .21; r= .26), respectively (60).

- Direct comparison between morphine and diamorphine

In another study conducted in the United Kingdom, in 1998, by Wood et al, 88 mechanically ventilated preterm neonates of less than 35 gestational age, greater than two hrs but less than 48 hrs old, who needed intermittent positive pressure ventilation

(IPPV) and had respiratory diseases, were randomized to receive either morphine (bolus dose: 200 mcg/kg over two hrs, followed by continuous infusion of 25 mcg/kg/hr) or diamorphine (bolus dose: 120 mcg/kg over two hrs, followed by continuous infusion of 15 mcg/kg/hr). Three different steps were performed to assess the level of sedation. Initially, the authors assessed the beat to beat variability of the arterial blood pressure (ABP), then the nurses completed a sedation score for the neonates, and finally plasma concentrations of adrenaline and noradrenaline were measured. Both groups did not show a statistically significant increase in the mean ABP after 24 hrs of continuous infusion. The sedation score was also similar between the two groups after 24 hrs of sedation. While the adrenaline level decreased significantly in neonates treated with both medications after 24 hrs of infusion, the noradrenaline concentration was reduced statistically significantly in the neonates given morphine only (61).

- Direct comparison among morphine, pancuronium and morphine plus pancuronium combination

Another RCT evaluating the use of morphine, but against pancuronium and the morphine plus pancuronium combination, in 95 preterm infants (≤ 34 weeks) with RDS that underwent MV, was conducted by Quinn et al in Ireland in 1992. Neonates who received morphine were started on a dose of 50 mcg/kg/hr and then increased to 100 mcg/kg/hr if the neonate was still anxious after two hrs of the previous dose. Neonates on pancuronium received doses of 100 mg/kg/hr, and those on combination therapy received 50 mcg /kg/hr of morphine and 100 mcg/kg/hr of pancuronium. The authors assessed the blood pressure, HR, peak inspiratory pressure, oxygen concentration,

adrenaline and noradrenaline levels, Intraventricular hemorrhage (IVH), pneumothorax, pulmonary interstitial emphysema, PDA, duration of MV, and mortality. The blood pressure increased significantly in the combination group, the three groups showed significant changes in the peak inspiratory pressure and none demonstrated significant change in the HR and oxygen concentration. The level of adrenaline did not change significantly in any of the groups, however, the noradrenaline level decreased significantly in the morphine group only ($P< 0.02$). There was no significant difference among all groups in relation to the clinical outcomes (62).

- Direct comparison between morphine and placebo

In a 2003 study, by Simons et al in Netherlands, the routine use of morphine infusion was reported in 150 newborns (younger than 3 days after delivery) with different medical disorders, including RDS undergoing MV, who included neonates with postnatal age younger than three days and required MV for less than eight hrs. Neonates were randomized to receive either morphine with a loading dose of 100 mcg/kg, followed by continuous infusion of 10 mcg/kg/hr or placebo for less than seven days. The clinical outcome was based on the analgesic and the sedation effect using three scales: PIPP, Neonatal Infant Pain Scale (NIPS), and Visual Analogue Scale (VAS). Simons and colleagues reported that there was no statistically significant difference in any of these scales between the two study groups. This is added to that the stay at the NICU was similar in both groups. Morphine however, significantly reduced the incidence of IVH as compared to the placebo ($P= 0.04$).

- Direct comparisons between fentanyl and placebo

Orsini et al evaluated the use of fentanyl in twenty premature infants received MV due to RDS in the USA in 1995. The patients were randomized to receive either fentanyl (5 mcg/kg bolus over 20 mins followed by maintenance dose of 2 mcg/kg/hr for 72 hrs, which was then reduced to 1 mcg/kg/hr for the following 24 hrs and 0.50 mcg/kg/hr for the last 24 hrs, after which, the infusion was discontinued) or placebo. Orsini et al utilized a behavioral state score to assess the behaviors of the neonates through measuring the incidence of IVH, PDA, BPD, sepsis, NICU stay, and the duration of MV. The study showed that fentanyl decreased the behavioral states statistically significantly as compared to the placebo at 16 hrs, 24 hrs and 48 hrs, ($P= 0.04$, $P= 0.01$, and $P< 0.001$, respectively). Fentanyl did not have a statistically significant effect on the duration of NICU stay (63).

Guinsburg et al also compared between fentanyl and placebo in Brazil in 1998, in which the premature infants who underwent MV were randomized to receive either fentanyl (3 mcg/kg) or placebo (0.20 ml of normal saline). Similar to Orsini et al, Guinsburg et al assessed the behavioral outcome of patients but using different criteria; Neonatal Facial Coding System (NFCS) and postoperative comfort score (PCS). The study reported that fentanyl significantly increased the level of PCS score ($P< 0.00001$). Also reported, is a significant reduction in the HR as compared to placebo ($P= 0.003$), ($P= 0.011$), respectively (64).

The eight different studies utilized different primary endpoints to assess the sedation status of the neonates. The sedatives also performed differently using these different outcome measures, and performed differently in studies in different settings, providing a very limited aggregate evidence to guide decision makers in other settings in relation to which sedative is better over the other.

2.1 Study rationale

Based on the literature review conducted (above), particularly in relation to the Qatari status as discussed in the introduction of the thesis, under section "1.11.2", there are no pharmacoeconomics studies in literature, including in Qatar, that have evaluated the economics of fentanyl and morphine in neonate population whether as a standalone or relative to others, as a monotherapy or in combination with midazolam, and for whatever underlying medical condition. Also, a systematic review is needed to answer questions in relation to characteristics and quality of research, including the strength and limitation of methodological aspects used, of fentanyl and morphine in patients with respiratory disorders in the ICU. With the lack of research method standardization and a typical lack of compliance with established standards, answers to the study questions in relation to literature characteristics and trends will be of practical value as recommendations for consideration by researchers, in settings like the Qatari ICU, in planning and organizing their research, especially in relation to the important pharmacoeconomics research as approximately 20% of the total hospitals budgets go to ICU expenses (65). This is added to enabling a better understanding of the quality of

evidence by decision makers as they contrast this against current strengths and weaknesses of methods in literature.

2.2 Significance of the research

The findings from the proposed study will be of immediate and major significance to the management of neonate agitation in the ICU setting, internationally, regionally, as well as at the Qatari level.

At the international level, the fact that the current investigation focuses 'in particular' on evaluating fentanyl versus morphine is of at most significance. While fentanyl and morphine are the most widely used opiates in the NICU, to the best of our knowledge, there is only one literature study that compared directly between fentanyl and morphine in neonates. The significance of the study also extends to the incorporation of an evaluation of the monotherapy versus combination sedation of neonates. The study evaluates fentanyl versus its use with adjunct midazolam, and also morphine versus its use with adjunct midazolam. To date, there are no any reports in literature that have explored the benefit of sedative combinations in the neonatal ICU settings. Also, the economic analysis component in this study is of a unique significance. To our knowledge, there are no pharmacoeconomics evaluations that have assessed the economics of fentanyl and morphine in neonates alone or in comparison in literature. The economic analysis is essential as in settings where resources are scarce and/or ICUs are busy, such as in the NICUs at the HMC, the longer is a duration of action for a sedative, the fewer occasions for doctors to be called in, which results in a reduced need

for additional drugs over hours. Within this context, the performance of the different sedatives in practice and, hence, their economic impact should be evaluated.

At the regional level, the project's aims are also novel, and at all levels of the ICU population. While the morphine and fentanyl were internationally evaluated in adult populations of the ICU for different underlying conditions, no research project has been undertaken with the same aims in the region, whether in neonates, pediatrics or adults. Furthermore, no other academic unit or health institution in Qatar (or the region) has attempted to evaluate the sedation management of acute agitation in the ICU through a comparative evaluation that is based on economic modeling.

2.3 Objectives

The overall goal of this research is to generate information to facilitate the delivery of safe, efficacious and cost-effective management of morphine, fentanyl and midazolam in patients undergoing MV due to RDS in the local Qatari NICU and global settings as well. To achieve this, the research needed to go through two phases:

Phase 1:

A comprehensive systematic review was conducted to summarize the quality of the methodological aspects, including strength and weaknesses, of the comparative evaluations, especially the economic evaluations, on the use of fentanyl, morphine, and midazolam in neonates with respiratory disorders undergoing MV in the ICU. This is not to review the evidence and the use of sedatives, but to guide future research in relation to the evaluation of the study sedatives.

Phase 2:

To comparatively evaluate the use of the sedative agents in the management of acute agitation in the mechanically ventilated patients in the Qatari NICU, three objectives were developed;

1. Perform a clinical and economic analysis of morphine monotherapy versus fentanyl monotherapy.
2. Perform a clinical and economic analysis of morphine monotherapy versus morphine and midazolam combination.
3. Perform a clinical and economic analysis of fentanyl monotherapy versus fentanyl and midazolam combination.

Chapter 3: Materials and Methods

3.1 Phase 1: ***Systematic review of literature methods***

3.1.1 Literature review

The electronic databases MEDLINE, EMBASE, OVID, Science Direct, Springer Link, and EconLit were utilized to identify studies. The following keywords were used to capture a broad sample of studies: “morphine”, “fentanyl”, “hypnotics”, “sedatives”, “sedation”, “respiration”, “respiratory”, “artificial, respiration”, “mechanical ventilator”, “mechanical ventilation”. The search strategy in **Appendix 1** was used for PubMed, including operators and MeSH, and this was adapted for other databases. The search included gray literature, such as books, dissertations, conferences, working papers, government publications, and was supplemented with a general internet search using Google and Google Scholar, where free text searching used the same search terms as in the main search. Manual screening of reference lists in found articles was also carried out.

3.1.2 Inclusion and exclusion criteria

Inclusion criteria:

- Literature publications were included until December 2016. No considerations were made of whether articles are freely available.
- Therapy based comparative study. No considerations were made of whether studies are retrospective or prospective.

- Study of either fentanyl or morphine, or both.
- Mechanically ventilated subjects with respiratory disorders in the ICU.

Exclusion criteria:

- Non-English language.
- Non-human studies.
- Non-comparative research, e.g. letters, general reviews, editorials.
- Non-respiratory underlying indications.

3.1.3 Data collection and handling

Articles identified as eligible for inclusion were categorized based on whether a study is of a clinical or an economic evaluation. Eligible articles were reviewed independently by two investigators, where key information was extracted. These included author, year of paper, country, ICU setting, interventions, comparators, medical conditions of the subjects, inclusion and exclusion criteria, sample size, study design, stratification, primary and secondary outcome measures, type of pharmacoeconomics evaluation, modelling, perspective, types of cost, time adjustment, sensitivity analyses, and sources of data. All investigators have training in pharmacoeconomics research. For validation purposes, the third investigator reviewed the extraction (and database population) of the relevant data from each included article. Disagreements, including in relation to miscoding, were further discussed until agreement is achieved.

Numerical and percentage measures were used to describe the distribution of variables, and cross tabulation was used to provide information about comparison of frequency data. The PRISMA checklist has been followed in completing the systematic review, as shown in **Appendix 2**.

3.1.4 Quality assessment

A quality assessment was independently conducted by investigators, as already discussed above. The Consolidated Standards of Reporting Trials (CONSORT) (66) was used to assess the quality of RCTs, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (67) was used for cohort studies, and the pharmacoeconomics studies were assessed via the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (68).

3.2 Phase 2

Corresponding to the study objectives, methods of the study relate to three different evaluations:

- *Evaluation 1: morphine monotherapy versus fentanyl monotherapy*
- *Evaluation 2: morphine monotherapy versus morphine plus midazolam combination*
- *Evaluation 3: fentanyl monotherapy versus fentanyl plus midazolam combination*

In overall, the research is of comparative retrospective observational cohort studies. In cohort studies, a free-outcome population that is under exposures of interest is

followed up retrospectively or prospectively throughout time to examine the development of specific outcome measures of interest. In this study, morphine and fentanyl were retrospectively evaluated due to that (as discussed above, under sedation in Qatari setting) fentanyl is not a currently available option for sedation in the NICU of WH in HMC, which is the setting of the current study. Here, the medical records of the neonates in the WH of HMC were utilized. In all evaluations, study groups were comparatively examined via CEAs.

3.2.1 Ethics approval

The observational research received the required ethics approval from the ethics committee of the Medical Research Center (MRC) at HMC on March 13th, 2016. (See **Appendix 3**).

No informed consent was required as the study was a retrospective cohort study.

3.2.2 Setting

HMC is the main non-profit public health care provider in Qatar, with 23,500 staff and 2100 beds in 2015. It is the only public institution in Qatar to provide a wide range of the safest and most effective health care services, covering the needs of about 90% of the population in Qatar. HMC leads multiple health areas, for example diabetes, cancer, women's health, pediatrics' health, organ transplantation, dialysis, and mental health. The eight hospitals that HMC comprises are classified into three categories: tertiary hospitals, continuing care and general hospitals. WH is a tertiary hospital and the largest delivering center with 300 beds, providing different services, such as

women's care, obstetrics, high risk births, gynecological, and neonatal care services. HMC has the Joint Commission International accreditation, USA, and was the first health care organization in the region that receives the Institutional Accreditation Council for Graduate Medical Education (56).

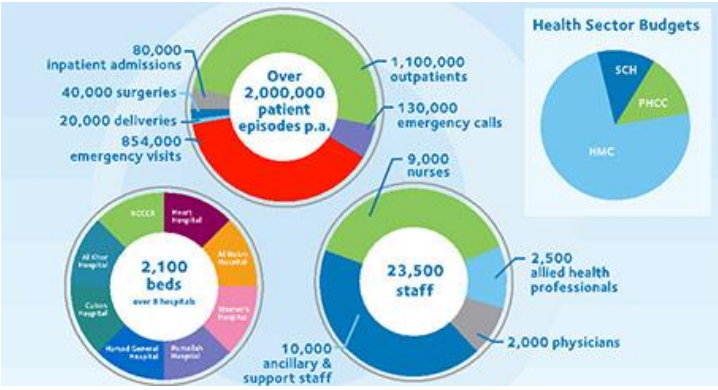


Figure 3.1. Sheer scale of HMC services, including as compared to Supreme Council of Health and Primary Health Care Corporation (56)

The NICU in WH is a specialized, advanced tertiary ward, and the largest NICU in the region that offers the greatest kind of care for newborns who are critically ill, including premature babies, babies with RDS, cardiac disorders, congenital anomalies, multiple organ failure, and many other medical conditions. The unit has recently been extended to deliver a total of 107 beds in both the intensive and intermediate care units. The WH's NICU provides rooms for breastfeeding, and counselling (69).

3.2.3 Population

All agitated neonate patients, including preterm and full term, who underwent MV in NICU due to RDS were eligible for inclusion. Included neonates in addition, received initial therapy of any of the study therapy groups.

The study groups, including medications and standard doses, were:

Evaluation 1: morphine monotherapy versus fentanyl monotherapy

- Fentanyl monotherapy
  - (0.5-3 mcg/kg loading dose, followed by 1-5 mcg/kg/hr continuous infusion).
- Morphine monotherapy
  - (100-200 mcg/kg loading dose, followed by 15-30 mcg/kg/hr continuous infusion).

Evaluation 2: morphine monotherapy versus morphine plus midazolam combination

- Morphine monotherapy
  - (100-200 mcg/kg loading dose, followed by 15-30 mcg/kg/hr continuous infusion).
- Morphine + midazolam combination
  - Morphine (100-200 mcg/kg loading dose, followed by 15-30 mcg/kg/hr continuous infusion).
  - Midazolam (0.1-0.2 mg/kg, followed by 0.01-0.06 mg/kg/hr continuous infusion).

Evaluation 3: fentanyl monotherapy versus fentanyl plus midazolam combination

- Fentanyl monotherapy:
  - (0.5-3 mcg/kg loading dose, followed by 1-5 mcg/kg/hr continuous infusion).
- Fentanyl + midazolam combination:
  - Fentanyl (0.5-3 mcg/kg loading dose, followed by 1-5 mcg/kg/hr continuous infusion).
  - Midazolam (0.1-0.2 mg/kg loading dose, followed by 0.01-0.06 mg/kg/hr continuous infusion).

Exclusion criteria:

- Neonates who received surgeries, major procedures (such as intercostal drains, chest-drain removal, intubation), and retinal examinations for retinopathy of prematurity.
- Neonates with congenital anomalies, birth defects, and hypoxic ischemic encephalopathy (HIE).
- Not ventilated or not sedated neonates.
- Neonates with pulmonary hypertension or pulmonary hemorrhage.
- Neonates received sedation for other indications, such as neonate with burn or cardiac problems.

3.2.4 Outcome measures

- Primary measures:
  - The groups were compared according to the rate of successful sedation, based on a PIPP scale as documented by the nurses in Cerner. PIPP scale is one of the most valid and reliable measures used in literature to reflect the clinical and agitation status of the patient and neonate's need of sedation (70). The agitation is measured by the nurses at the NICU to monitor on drug sedation. The PIPP scale consists of questions regarding seven criteria, each question has score range from 0-3 to give a total score range of 0-21 (**Table 3.1**).
  - Resource utilization, including an estimation of the overall direct medical costs of managing acute agitation in the neonate study population.
- Secondary measures:
  - Need for alternate sedation with initial sedation failure.
  - Adverse drug reactions (ADRs).
  - Need for increased medication doses.
  - Length of NICU stay.
  - Duration of MV in the NICU.
  - Duration of sedation in the NICU.
  - Withdrawal symptoms.
  - Mortality.
  - Persistent agitation.

PIPP procedure

- A PIPP total score range between 0 and 6 indicates no or mild pain, thus no action is required.
- A PIPP total score range from 7-12 reflects a moderate pain and, therefore, the clinicians start implementing non-pharmacological measures, such as heat or cold therapy, sucrose solution, blanket application, pacifier, swaddling, nesting, breast feed, quite environment (reducing light, noise and activity around the neonate), and soothing voice.
- A PIPP total score greater than 12 indicates that the baby is feeling severe pain, hence pharmacological intervention is initiated.

Table 3.1. PIPP assessment tool for neonates

Indicators	**0**	**1**	**2**	**3**	**Score**
Gestational age	≥ 36 weeks	32- 35 weeks	28-31 weeks	< 28 weeks	#
Behavioral state	Active, awake, eyes open, facial movements	Quiet, awake, eyes open, no facial movements	Active, awake, eyes closed, facial movements	Quiet, asleep, eyes closed, no facial movements	#
HR maximum (bpm)	0-4/min increase	5-14/min increase	15-24/min increase	≥25/min increase	#
Oxygen saturation	92-100%	89-91%	85-88%	84% or less	#
Brow bulge	None	Minimum	Moderate	Maximum	#
Eye squeeze	None	Minimum	Moderate	Maximum	#
Nasolabial furrow	None	Minimum	Moderate	Maximum	#

#: total score

Definition of the outcome measures:

- Successful sedation

Successful sedation was defined as an agitated neonate's final PIPP score that is reduced to less than seven or maintained less than seven following receiving any of the initial study sedation when the initial PIPP score was greater than seven.

- Sedation failure

This is defined as the agitated neonate's final PIPP score remaining above seven following receiving any of the initial study sedation when the initial PIPP score was greater than seven. Here, the consequences were:

- Receiving increased dose.
- Switching to an alternative.
- Developing withdrawal symptoms: including known related symptoms; seizure, agitation, irritability, and tachycardia that appeared after the fifth days of receiving sedation (71), and the final PIPP score of the baby increasing to more than seven after the initial score was below seven following initiating sedation.
- Death: defined as any death case that arose during receiving sedation during the first 28 days of life defined by World Health Organization (WHO) (72) and the United Nations Children's Fund (73).
- Developing persistent agitation: when the patient did not respond to the any of the clinician's decisions, which was reflected on the neonate's high final PIPP score.

3.2.5 Sample size

Sample size was calculated for each study evaluation of phase 2 by utilizing ClinCalc.com, which is a tool used for evidence-based clinical decision support (50).

- **Evaluation of morphine monotherapy versus fentanyl monotherapy**

There is only one study that compared between morphine and fentanyl in a head to head comparison by Saarenmaa et al (58), that showed that the level of pain using b-Endorphin was significantly reduced in favor of fentanyl. Based on this result and the estimation from specialists at the Qatari NICU of 70% success rate with morphine, a sample size to measure an anticipated sedation rate increase of at least 30% (i.e. an anticipated over 90% success rate with fentanyl), with alpha= 0.05 and power= 80%, 62 needed to be included in the morphine monotherapy and 62 in the fentanyl monotherapy group (total= 124).

- **Evaluation of morphine monotherapy versus morphine plus midazolam combination**

There are no studies in literature that evaluated morphine monotherapy versus morphine and midazolam combination. Midazolam was studied as a sole therapy in a study by Anand et al, where it demonstrated to significantly reduce the PIPP scores (59). Based on this and the measured outcome of morphine (68% success rate, *vide infra*) in our evaluation of morphine monotherapy versus fentanyl monotherapy, a sample size to measure an anticipated sedation increase by at least 40% (i.e. an anticipated 95% success rate with the midazolam combination), at alpha= 0.05, power= 80%, 31 needed

to be enrolled in morphine monotherapy and 31 in morphine plus midazolam (total= 64).

- **Evaluation of fentanyl monotherapy versus fentanyl plus midazolam combination**

As with the morphine versus combination evaluation, based on the performance of fentanyl monotherapy (43% success rate, *vide infra*) in our evaluation of it against morphine monotherapy, and the performance of midazolam in literature, as discussed above (59), a sample size to measure an anticipated sedation increase by at least 40% (i.e. an anticipated 60% success rate with the midazolam combination), at alpha= 0.05, power= 80%, 134 needed to be included in fentanyl monotherapy and 134 in fentanyl plus midazolam (total= 268).

3.2.6 Data collection

Study neonates were identified through the Cerner electronic medical records database at the NICU in WH in HMC between October 2014 and January 2016. The Cerner database was not available before then, where the data extraction from the physical older medical records was not feasible due to availability and time challenges. Data were collected from October 2014 till January 2016. The collection was stopped in January 2016 due to the HMC ethics restriction which prevents collecting data after the date of getting the approval. Data related to study medications were recorded as de-identified data. Medical records were ordered based on their Health Care (HC) numbers. Each HC number received a unique and random code. Lists of patients in each study

group were selected and sent separately by the HMC collaborator based on their HC numerical order. For example, the patient lists for the first study included 63 patients in each group before the final selection of patients based on the inclusion and exclusion criteria. The excluded patients were replaced by additional patients sent by the HMC collaborator until sample size was achieved. Then the selection of patients for analysis was based on the shortest duration of sedation or NICU stay. With a similar trend, the patients were separately selected for the second and third evaluations. No single patient was included in more than one study group in the evaluation. The subject identifier and its corresponding code were kept in a separate document. The codes were used in the data collection sheet by the student research in the current thesis, while the HC numbers were kept with HMC collaborators. Access to patient data was performed through access provided by the HMC collaboration. Patients' identification information was maintained in a data collection sheet, stored and secured on HMC collaborators' computers. No identifiers were included in the data analysis. The data collection form can be seen in **Appendix 4**.

3.2.7 Statistical analysis

Patient baseline demographics were analyzed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Based on input of practitioner authors in this research, the only demographic characteristics of interest in relation to being similar between study groups are (i) full-term versus pre-term status of neonates and (ii) extent of vecuronium use. Nevertheless, demographic characteristics that were analyzed in this research are beyond those of interest. All

baseline variable data were categorical and, therefore, Chi-square and Fisher's exact tests were used to test for similarity between any of the two study groups in the three evaluations. The p-value of the Chi - square test was used if no more than 20% of cells had expected counts of less than five. However, if more than 20% of the expected counts were less than five, p-value of Fisher's exact test was used. Since all data were categorical, normality test was not required. All were calculated using an alpha of 0.05. Numerical and percentage measures were used to describe the categorical variables. Analyzing the effect of individual demographic characteristics as independent factors on the study outcomes is not an objective of this research.

3.2.8 Perspective

The economic modeling adopted the perspective of WH at HMC. Only direct medical costs for managing the RDS in mechanically ventilated neonates were assessed. Medical costs related to other underlying diseases (e.g. cost of medications to treat other medical disorders) and indirect hospital costs (e.g. staff salary) were not included. Intangible costs were also excluded from this study due to the retrospective nature of the observational cohort study.

Direct medical costs included were associated with:

- Sedative medications.
- Therapies to manage the ADRs associated with sedatives.
- Mechanical ventilator.
- Diagnostics, laboratory, and monitoring tests during the NICU stay.

- Length of NICU stay.

3.2.9 Model structure

The pharmacoeconomics analysis was performed based on the decision analytic model as designed to describe the patient management flow in the NICU, where possible sedation consequences of interest were considered as shown in the model trees in **Figures 3.2-3.4**. In any tree, for each of the sedatives, the model included seven possible treatment pathways depending on whether the initial sedation was successful, and on the causes and results of failures. Mechanically ventilated agitated neonates with RDS were initially assigned to one of the two sedatives; morphine monotherapy or fentanyl monotherapy. Patients who received morphine monotherapy continued sedation until therapy was considered successful, with or without ADRs, or considered a failure. Patients who failed to respond to the initial sedative, had increased the dose, switch to any other alternatives, sedation associated with withdrawal symptoms, death, or persistent agitation.

Based on tree structures, in addition to populated input model data on resources consumed and their monetary values, any model generated a weighted average cost for treating patients. As per the general decision analysis principles, this was calculated through multiplying the costs of treatment outcomes by their respective probabilities. The costs of managing a single episode of acute agitation were compared among the different therapies in evaluations.

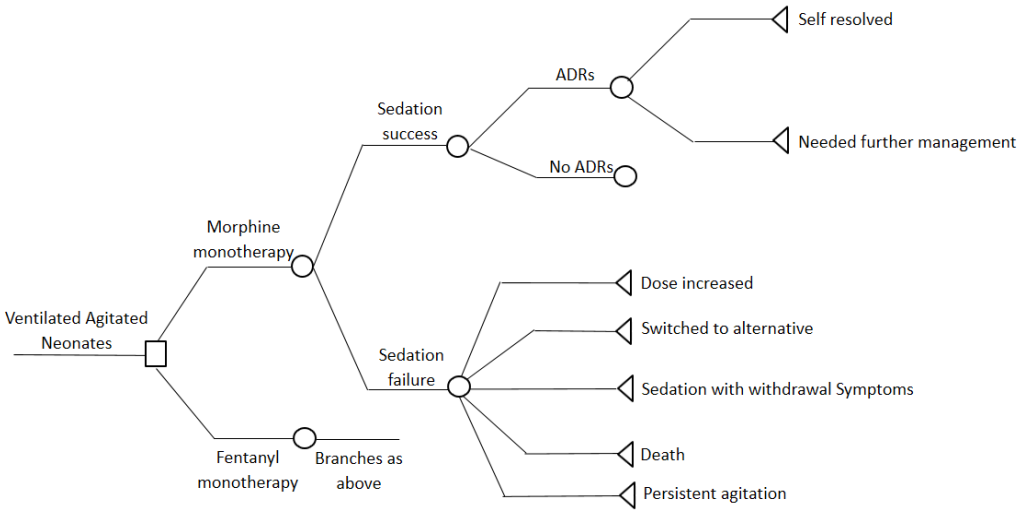


Figure 3.2 Decision tree model of morphine monotherapy vs. fentanyl monotherapy

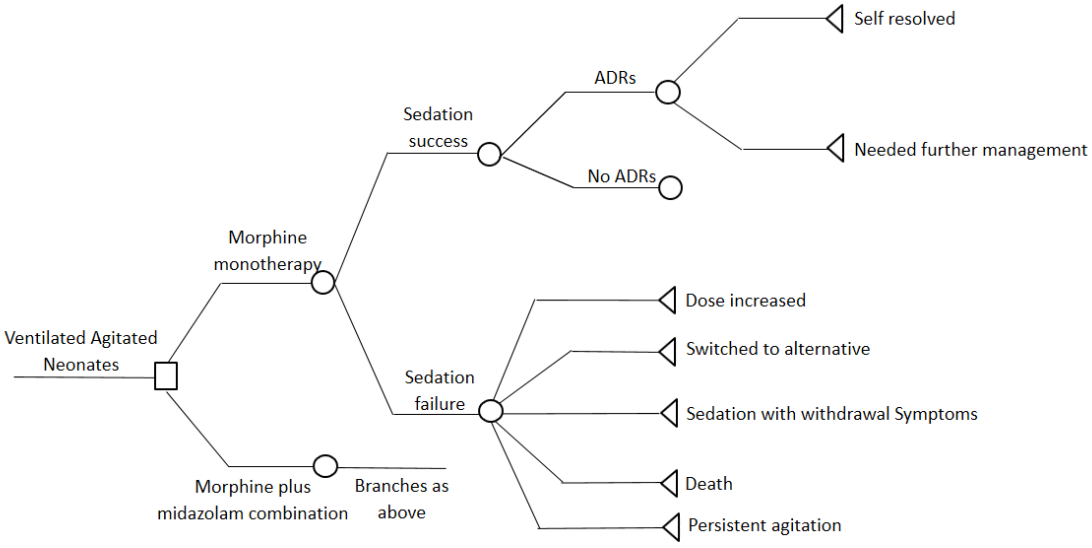


Figure 3.3 Decision tree model of morphine monotherapy vs. morphine plus midazolam

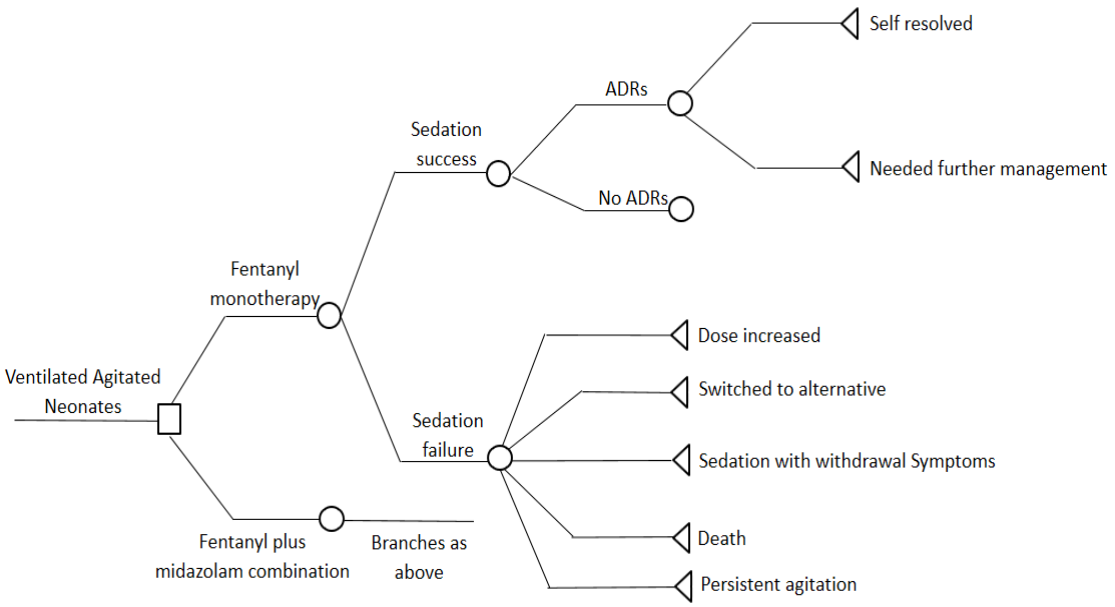


Figure 3.4 Decision tree model of fentanyl monotherapy vs. fentanyl plus midazolam

3.2.10 Model clinical inputs

Data inputs for the model in relation to the clinical outcomes and their probabilities were extracted from the review of WH medical records within the duration from October 2014 to January 2016.

3.2.11 Model cost inputs and calculations

All calculated costs were in the Qatari Riyal, adjusted for the financial year 2016-2017 using inflation rates as obtained from the Central Intelligence Agency (53). No discounting was applied given the short timeframe of the analysis. The cost of initial sedation was the cost associated with the initial sedative use until success or failure. The overall cost of each therapy outcome pathway included both, the primary costs of initial sedatives and their secondary costs as associated with patient management, including

that of failure. Medication costs involved in this study were based on drug wholesale prices, as paid by HMC. All resource costs included in the analysis were derived from the Accounting and Finance Department at HMC. The cost inputs used in the model are summarized in **Table 3.2**.

An assumption was made where cost data of resources were unavailable at HMC. Here, the costs of interest were obtained from the accounting system, extracted from Ministry of Public Health resources (74), at Al-Ahli Hospital (AH), a major private profit-based hospital in Qatar with 100 beds (75). These were then adjusted to their HMC estimated values. For any resource, this was based on the average relative difference between HMC and AH available prices in within the resources category that the resource belong to. The AH prices of interest are summarized in **Table 3.3**. Some input costs were not available (N/A) in both hospitals and were excluded from the study (**Table 3.4)**.

Table 3.2 Resource costs based on the NICU at HMC

Item / Name of test	Unit	Unit cost (QAR)
Morphine	15 mg/ml IV vial	1.97
Fentanyl	50 mcg/ml IV vial	6
Midazolam	1 mg/ml IV vial	3.29
Naloxone	0.4 mg/ml IV vial	2.75
Furosemide	10 mg/ml IV vial	0.6
Dobutamine	1 mg/ml IV vial	6.81
Phenobarbital	30 mg/ml IV vial	6.32
Complete blood count	1 test during NICU	30
Calcium	1 test during NICU	10
Bilirubin	1 test during NICU	10
Protein	1 test during NICU	10
Albumin	1 test during NICU	10
Alkaline phosphatase	1 test during NICU	10
Alanine aminotransferase	1 test during NICU	10
Aspartate aminotransferase	1 test during NICU	10
Glucose-6-phosphate dehydrogenase screen	1 test during NICU	20
Glucose	1 test during NICU	10
C-reactive protein	1 test during NICU	30
17 Hydroxyprogesterone, dried blood spot (DBS)	1 test during NICU	40
Amino acid and acy serum creatinine (Scr) DBS	1 test during NICU	360

Biotinidase DBS	1 test during NICU	30
Galactose-1-phosphate uridyltransferase	1 test during NICU	30
Thyroid stem hormone	1 test during NICU	40
Homocystine Scr	1 test during NICU	70
MRSA screening	1 test during NICU	130
Urine culture	1 test during NICU	50
PH	1 test during NICU	30
PO_2	1 test during NICU	10
Partial pressure of carbon dioxide (PCO_2)	1 test during NICU	10
Bicarbonate (HCO_3)	1 test during NICU	10
Base excess	1 test during NICU	10
Cytomegalovirus antibodies (CMV Ab) IgG	1 test during NICU	110
CMV Ab IgM	1 test during NICU	110
Herpes simplex type I IgG	1 test during NICU	30
Herpes simplex type I IgM	1 test during NICU	30
Herpes simplex type II IgG	1 test during NICU	30
Herpes simplex type II IgM	1 test during NICU	30
Rubella Ab IgG	1 test during NICU	110
Rubella Ab IgM	1 test during NICU	90
Toxoplasma Ab IgG	1 test during NICU	120
Toxoplasma Ab IgM	1 test during NICU	120

Table 3.3 Estimated resource costs based on the NICU at AH

Item / Name of test	**Unit**	**Unit cost (QAR)**
Urea	1 test during NICU	7.27
Creatinine	1 test during NICU	7.27
Sodium	1 test during NICU	10.91
Potassium	1 test during NICU	10.91
Chloride	1 test during NICU	10.91
Bicarbonate	1 test during NICU	8.48
Magnesium	1 test during NICU	9.7
Blood culture	1 test during NICU	125.18
Cerebrospinal fluid (CSF) culture	1 test during NICU	105.92
CSF analysis	1 test during NICU	120.37
Urinalysis tests	1 test during NICU	72.22
X-radiation (x-ray)	1 test during NICU	26.36
Computerized tomography scan (CT scan)	1 test during NICU	158.14
Ultrasound scan (US)	1 test during NICU	84.34
Magnetic resonance imaging (MRI)	1 test during NICU	263.57
Barium enema	1 test during NICU	71.69
Electrocardiogram-EKG	1 test during NICU	26.36
Water soluble contrast enema	1 test during NICU	15.81
Peripherally inserted central catheter (PICC line) insertion	1 test during NICU	21.08
Echocardiogram	1 test during NICU	115.97

Lumbar puncture	1 test during NICU	57.98
Oxygen therapy	1 test during NICU	211.54
NICU stay	Stay per day	527.14
Mechanical ventilator	1 machine	430.15

Table 3.4 Unavailable resource costs in HMC and AH

Item	**Unit**	**Unit cost (QAR)**
Respiratory secretion culture	1 test during NICU	N/A
Volume CSF	1 test during NICU	N/A
WBC CSF	1 test during NICU	N/A
RBC CSF	1 test during NICU	N/A
Lymphocyte CSF	1 test during NICU	N/A
Monocyte CSF	1 test during NICU	N/A
Fluoroscopy thorax	1 test during NICU	N/A
Pediatric surgery	1 test during NICU	N/A
NM blood pool scan	1 test during NICU	N/A
Loopogram gastrointestinal trace	1 test during NICU	N/A
Central catheter repositioning	1 test during NICU	N/A
Circumcision procedure	1 test during NICU	N/A
Urethrocystogram once	1 test during NICU	N/A
Hepatobiliary function scan and stim	1 test during NICU	N/A
Fluoroscopy esophagus	1 test during NICU	N/A
Cardiac catheterization-diagnostic	1 test during NICU	N/A

Pulmonary function studies	1 test during NICU	N/A
Bronchoscopy	1 test during NICU	N/A

3.2.12 Sensitivity analysis

The main goal of sensitivity analysis was, as previously discussed, to indicate the robustness of the evaluation conclusion against any potential variations in the model inputs

One-way sensitivity analyses. Variations in the duration of MV and NICU stay, loading and maintenance doses of initial medications, and estimated costs were investigated for their effect on the study outcomes. Uncertainty of ±3% was used for the duration of MV and NICU stay, and an uncertainly of ±5% was used for medication doses. A ±10% range was used to investigate the uncertainty associated with the estimated input prices in the model. All uncertainty analyses were run via Monte Carlo (see description in the following paragraph). Variables and their uncertainty ranges are shown in **Table 3.5.**

Probabilistic sensitivity analyses: Uncertainty analysis, by means of Monte Carlo simulation, was performed via the @Risk-7.5® analysis tool to investigate the likelihood (probability) of a therapy's economic advantage. Monte Carlo is a method whereby simulated input values, chosen randomly across a range of probability distributions of a model input, are added into the model. A triangular type of distribution and uncertainty of ±3%, based on 10,000 model simulations, was used. The model was run for each simulated input, resulting in a range of outputs characterizing the output uncertainty for

the input. Based on this, a distribution of “cost savings” or “cost-effectiveness” was generated, indicating the probability of one therapy having an economic advantage over another.

Table 3.5. Variation ranges of variables of interest in sensitivity analysis

Variable	**Base case**	**Variation range**	
		Low	**High**
Cost of urea	7.27 QAR	6.54	8
Cost of creatinine	7.27 QAR	6.54	8
Cost of sodium	10.91 QAR	9.82	12
Cost of potassium	10.91 QAR	9.82	12
Cost of chloride	10.91 QAR	9.82	11.9
Cost of bicarbonate	8.48 QAR	8.06	8.9
Cost of magnesium	9.7 QAR	8.73	10.67
Cost of blood culture	125.18 QAR	112.67	137.09
Cost of CSF culture	105.92 QAR	95.34	116.5
Cost of CSF analysis	120.37 QAR	95.32	116.52
Cost of urinalysis tests	72.22 QAR	65	79.44
Cost of x-ray	26.36 QAR	23.72	29
Cost of CT-scan	158.14 QAR	142.33	173.95
Cost of US-scan	84.34 QAR	75.91	92.77
Cost of MRI	263.57 QAR	237.31	289.83
Cost of barium enema	71.69 QAR	64.52	78.86

Cost of electrocardiogram-EKG	26.36 QAR	23.72	29
Cost of water soluble contrast enema	15.81 QAR	14.23	17.39
Cost of peripherally inserted central catheter (PICC line) insertion	21.08 QAR	18.98	23.2
Cost of echocardiogram	115.97 QAR	104.25	127.57
Cost of lumbar puncture	57.98 QAR	52.19	63.79
Cost of oxygen therapy	211.54 QAR	190.39	232.69
Cost of NICU stay	527.14 QAR	474.43	579.85
Cost of MV	430.15 QAR	387.14	473.17
Evaluation 1: Fentanyl monotherapy			
MV duration during sedation success	6 days	5.82	6.18
MV duration during sedation failure-high dose	4 days	3.88	4.12
MV duration during sedation failure-alternative	9.27 days	8.99	9.55
MV duration during sedation failure-death	6 days	5.82	6.18
MV duration during sedation failure-persistent agitation	1 day	0.97	1.03
NICU duration during sedation success	45 days	43.65	46.35
NICU duration during sedation failure-high dose	27 days	26.19	27.81
NICU duration during sedation failure-alternative	33 days	32.01	33.99
NICU duration during sedation failure-death	11 days	10.67	11.33
NICU duration during sedation failure-persistent agitation	9 days	8.73	9.27
Loading dose of fentanyl during sedation success	2.11 mcg/kg	2	2.22

Loading dose of fentanyl during sedation failure-high dose	5.32 mcg/kg	5.05	5.59
Loading dose of fentanyl during sedation failure-alternative	3 mcg/kg	2.85	3.15
Loading dose of morphine during sedation failure-alternative	100 mcg/kg	95	105
Loading dose of fentanyl during sedation failure-death	1 mcg/kg	0.95	1.05
Loading dose of fentanyl during sedation failure-persistent agitation	N/A	N/A	N/A
Maintenance dose of fentanyl during sedation success	4.57 mcg/kg	4.34	4.8
Maintenance dose of fentanyl during sedation failure-high dose	4.3 mcg/kg	4.09	4.52
Maintenance dose of fentanyl during sedation failure-alternative	3.33 mcg/kg	3.17	3.5
Maintenance dose of morphine during sedation failure-alternative	13.33 mcg/kg	12.66	14
Maintenance dose of fentanyl during sedation failure-death	N/A	N/A	N/A
Maintenance dose of fentanyl during sedation failure-persistent agitation	N/A	N/A	N/A
Evaluation 1: Morphine monotherapy			
MV duration during sedation success	6 days	5.82	6.18
MV duration during sedation failure-high dose	27 days	26.19	27.81
MV duration during sedation failure-alternative	66 days	64.02	67.98
MV duration during sedation failure-withdrawal symptoms	1 day	0.97	1.03
MV duration during sedation failure-death	16 days	15.52	16.48

MV duration during sedation failure-persistent agitation	1 day	0.97	1.03
NICU duration during sedation success	47 days	45.9	48.41
NICU duration during sedation failure-high dose	54 days	52.38	55.62
NICU duration during sedation failure-alternative	83 days	80.51	85.49
NICU duration during sedation failure-withdrawal symptoms	15 days	14.55	15.45
NICU duration during sedation failure-death	20 days	19.4	20.6
NICU duration during sedation failure-persistent agitation	16 days	15.52	16.48
Loading dose of morphine during sedation success	125 mcg/kg	118.75	131.25
Loading dose of morphine during sedation failure-high dose	292.5 mcg/kg	277.88	307.13
Loading dose of morphine during sedation failure-alternative	120 mcg/kg	114	126
Loading dose of fentanyl during sedation failure-alternative	3.73 mcg/kg	3.54	3.92
Loading dose of morphine during sedation failure-withdrawal symptoms	N/A	N/A	N/A
Loading dose of morphine during sedation failure-death	127.5 mcg/kg	121.13	133.89
Loading dose of morphine during sedation failure-persistent agitation	N/A	N/A	N/A
Maintenance dose of morphine during sedation success	12.27 mcg/kg	11.66	12.88
Maintenance dose of morphine during sedation failure-high dose	15 mcg/kg	14.25	15.75
Maintenance dose of morphine during sedation failure-alternative	10 mcg/kg	9.5	10.5

Maintenance dose of fentanyl during sedation failure-alternative	10 mcg/kg	9.5	10.5
Maintenance dose of morphine during sedation failure-withdrawal symptoms	15 mcg/kg	14.25	15.75
Maintenance dose of morphine during sedation failure-death	11.67 mcg/kg	11.09	12.25
Maintenance dose of morphine during sedation failure-persistent agitation	5 mcg/kg	4.25	5.75
Evaluation 2: Morphine monotherapy			
MV duration during sedation success	7 days	6.79	7.21
MV duration during sedation failure-withdrawal symptoms	25 days	24.25	25.75
MV duration during sedation failure-death	15 days	14.55	15.45
NICU duration during sedation success	51 days	49.47	52.53
NICU duration during sedation failure-withdrawal symptoms	27 days	26.19	27.81
NICU duration during sedation failure-death	16 days	15.52	16.48
Loading dose of morphine during sedation success	175 mcg/kg	166.25	183.75
Loading dose of morphine during sedation failure-withdrawal symptoms	N/A	N/A	N/A
Loading dose of morphine during sedation failure-death	108.25 mcg/kg	102.84	113.66
Maintenance dose of morphine during sedation success	16.1 mcg/kg	15.3	16.91
Maintenance dose of morphine during sedation failure-withdrawal symptoms	11.8 mcg/kg	11.21	12.39
Maintenance dose of morphine during sedation failure-death	15 mcg/kg	14.25	15.75

Evaluation 2: Morphine plus midazolam			
MV duration during sedation success	29 days	28.13	29.87
MV duration during sedation failure-high dose	27 days	26.19	27.81
MV duration during sedation failure-alternative	28 days	27.16	28.84
MV duration during sedation failure-withdrawal symptoms	11 days	10.67	11.33
MV duration during sedation failure-death	18 days	17.46	18.54
MV duration during sedation failure-persistent agitation	6 days	5.82	6.18
NICU duration during sedation success	77 days	72.75	77.25
NICU duration during sedation failure-high dose	63 days	61.11	64.89
NICU duration during sedation failure-alternative	47 days	45.59	48.41
NICU duration during sedation failure-withdrawal symptoms	12 days	11.64	12.36
NICU duration during sedation failure-death	54 days	53.38	55.62
NICU duration during sedation failure-persistent agitation	6 days	5.82	6.18
Loading dose of morphine during sedation success	102 mcg/kg	96.9	107.1
Loading dose of midazolam during sedation success	N/A	N/A	N/A
Loading dose of morphine during sedation failure-high dose	207.6 mcg/kg	197.22	217.98
Loading dose of midazolam during sedation failure-high dose	100 mcg/kg	95	105

Loading dose of morphine during sedation failure-alternative	160 mcg/kg	152	168
Loading dose of midazolam during sedation failure-alternative	100 mcg/kg	95	105
Loading dose of fentanyl during sedation failure-alternative	5.2 mcg/kg	5.04	5.36
Loading dose of morphine during sedation failure-withdrawal symptoms	N/A	N/A	N/A
Loading dose of midazolam during sedation failure-withdrawal symptoms	N/A	N/A	N/A
Loading dose of morphine during sedation failure-death	97 mcg/kg	92.15	101.85
Loading dose of midazolam during sedation failure-death	100 mcg/kg	95	105
Loading dose of morphine during sedation failure-persistent agitation	50 mcg/kg	47.5	52.5
Loading dose of midazolam during sedation failure-persistent agitation	200 mcg/kg	190	210
Maintenance dose of morphine during sedation success	10 mcg/kg	9.5	10.5
Maintenance dose of midazolam during sedation success	20.88 mcg/kg	16.44	18.17
Maintenance dose of morphine during sedation failure-high dose	16.1 mcg/kg	15.3	16.91
Maintenance dose of midazolam during sedation failure-high dose	47.5 mcg/kg	45.13	49.88
Maintenance dose of morphine during sedation failure-alternative	160 mcg/kg	152	168
Maintenance dose of midazolam during sedation failure-alternative	100 mcg/kg	95	105
Maintenance dose of fentanyl during sedation failure-alternative	5.2 mcg/kg	4.94	5.46

Maintenance dose of morphine during sedation failure-withdrawal symptoms	18.5 mcg/kg	17.58	19.43
Maintenance dose of midazolam during sedation failure-withdrawal symptoms	30 mcg/kg	28.5	31.5
Maintenance dose of morphine during sedation failure-death	14.5 mcg/kg	13.78	15.23
Maintenance dose of midazolam during sedation failure-death	N/A	N/A	N/A
Maintenance dose of morphine during sedation failure-persistent agitation	20 mcg/kg	19	21
Maintenance dose of midazolam during sedation failure-persistent agitation	N/A	N/A	N/A
Evaluation 3: Fentanyl monotherapy			
MV duration during sedation success	3 days	2.91	3.09
MV duration during sedation failure-high dose	3 days	2.91	3.09
MV duration during sedation failure-alternative	7 days	6.79	7.21
MV duration during sedation failure-withdrawal symptoms	6 days	5.82	6.18
MV duration during sedation failure-death	12 days	11.64	12.36
MV duration during sedation failure-persistent agitation	8 days	7.76	8.24
NICU duration during sedation success	41 days	39.77	42.23
NICU duration during sedation failure-high dose	19 days	18.43	19.57
NICU duration during sedation failure-alternative	25 days	24.25	25.75
NICU duration during sedation failure-withdrawal symptoms	12 days	11.64	12.36

NICU duration during sedation failure-death	12 days	11.64	12.36
NICU duration during sedation failure-persistent agitation	27 days	26.19	27.81
Loading dose of fentanyl during sedation success	2.6 mcg/kg	2.47	2.73
Loading dose of fentanyl during sedation failure-high dose	5.4 mcg/kg	5.13	5.67
Loading dose of fentanyl during sedation failure-alternative	5.86 mcg/kg	5.57	6.16
Loading dose of morphine during sedation failure-alternative	280 mcg/kg	266	294
Loading dose of fentanyl during sedation failure-withdrawal symptoms	N/A	N/A	N/A
Loading dose of fentanyl during sedation failure-death	N/A	N/A	N/A
Loading dose of fentanyl during sedation failure-persistent agitation	2 mcg/kg	1.9	2.1
Maintenance dose of fentanyl during sedation success	4.5 mcg/kg	4.28	4.73
Maintenance dose of fentanyl during sedation failure-high dose	6.4 mcg/kg	6.08	6.72
Maintenance dose of fentanyl during sedation failure-alternative	3 mcg/kg	2.85	3.15
Maintenance dose of morphine during sedation failure-alternative	28.3 mcg/kg	26.89	29.72
Maintenance dose of fentanyl during sedation failure-withdrawal symptoms	3.5 mcg/kg	3.33	3.68
Maintenance dose of fentanyl during sedation failure-death	5 mcg/kg	4.75	5.25
Maintenance dose of fentanyl during sedation failure-persistent agitation	3.88 mcg/kg	3.69	4.07

Evaluation 3: Fentanyl plus midazolam			
MV duration during sedation success	13 days	12.61	13.39
MV duration during sedation failure-high dose	30 days	29.1	31.9
MV duration during sedation failure-alternative	54 days	52.38	55.62
NICU duration during sedation success	43 days	41.71	44.29
NICU duration during sedation failure-high dose	61 days	59.17	62.83
NICU duration during sedation failure-alternative	79 days	76.63	81.37
Loading dose of fentanyl during sedation success	3 mcg/kg	2.85	3.15
Loading dose of midazolam during sedation success	95 mcg/kg	90.25	99.75
Loading dose of fentanyl during sedation failure-high dose	2.25 mcg/kg	2.14	2.36
Loading dose of midazolam during sedation failure-high dose	116.6 mcg/kg	110.2	121.8
Loading dose of fentanyl during sedation failure-alternative	5.1 mcg/kg	4.85	5.36
Loading dose of morphine during sedation failure-alternative	210 mcg/kg	199.5	220.5
Loading dose of midazolam during sedation failure- alternative	200 mcg/kg	190	210
Maintenance dose of fentanyl during sedation success	2.6 mcg/kg	2.47	2.73
Maintenance dose of midazolam during sedation success	20 mcg/kg	19	21
Maintenance dose of fentanyl during sedation failure-high dose	9.1 mcg/kg	8.65	9.56

Maintenance dose of midazolam during sedation failure-high dose	15 mcg/kg	14.25	15.75
Maintenance dose of fentanyl during sedation failure-alternative	10 mcg/kg	9.5	10.5
Maintenance dose of morphine during sedation failure-alternative	12.2 mcg/kg	11.59	12.81
Maintenance dose of midazolam during sedation failure- alternative	19 mcg/kg	18.05	19.95

*N/A: Not applicable

Alternative scenario: In this study, we investigated the scenario of performing the cost-effectiveness evaluation of morphine, fentanyl, morphine plus midazolam, and fentanyl plus midazolam from the perspective of the private health section in Qatar, i.e. solely based on AH prices. This is to generalize the relative sedation outcomes to the neonates who are not covered by governmental subsidies, such as those of visitors and/or those looking for the five star services in the private sector.

Chapter 4: Results

4.1 Phase 1*: Systematic review of literature methods*

4.1.1 Study selection and study description

The search of literature generated 33 eligible articles for analysis (**Figure 4.1**). A summary description of the included studies is in **Table 4.1**. The studies were conducted between 1989-2014. Twelve studies were conducted in the US (63, 76-86), whereas nine reported data from five countries within Europe (58, 61, 62, 87-92), two from Asia (93, 94), three in Canada (60, 95, 96), two in Brazil (80, 97), and no name of country was specified in the remaining studies (n= 5) (59, 98-101).

4.1.2 Study population

Of the 33 included studies, 22 were conducted in a population of adults, eight in neonates, and three in pediatrics. In about half of the studies (n= 14), patients had mixed conditions where respiratory disorders were identified as one of several other underlying conditions. In eight studies, the respiratory disorder was identified as the underlying condition of interest. Eleven studies did not report the underlying disorder of the patients. All studies are summarized in **Appendix 5**. Four of the studies that primarily identified an underlying respiratory disorder were in adults (80, 95, 96, 100) and four were in neonates (61-64).

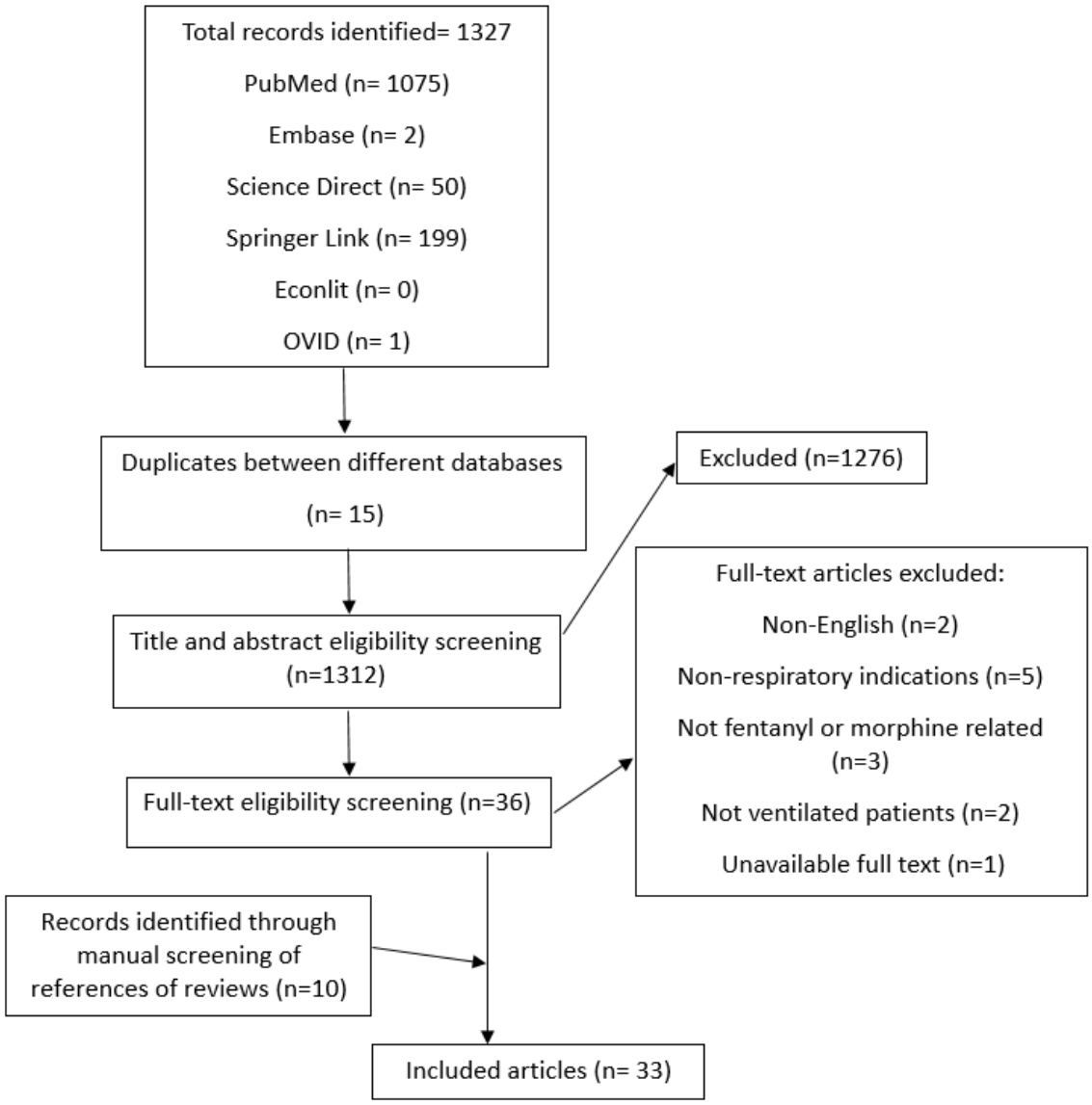


Figure 4.1 Flow diagram of literature search results

Table 4.1. Summary of the characteristics of the included studies

N	Subject	Author, Year, Country	Study Design	Interventions vs. Comparators	Duration of Therapy	Economics Methods	Primary Outcome	Definition of Primary Outcome	Secondary Outcome	Definition of Secondary Outcome	Main Findings
1	Adult	Carrasco et al, 1993, USA (76)	RCT	Propofol + morphine vs. midazolam	NA	CBA, NA	Treatment success based on the desired level of sedation using RSS and GCS	Adequate sedation (if sedation level was grade 2, 3, 4, or 5 on RSS or degree of reactivity was maintained between 8-13 points on GCSC	Sedatives cost and Hypotension episodes	NA	Propofol and morphine provided significantly adequate sedation, more hypotension cases with higher short term cost and lower medium and long term cost
2	Adult	Al MJ et al, 2010, Netherlands (87)	RCT	Remifentanyl + propofol vs. fentanyl or morphine + midazolam, propofol or lorazepam	10 days maximum	CCA, Markov	Sedatives cost	NA	NA	NA	Remifentanyl + propofol was less costly
3	Adult	Zhou et al, 2014, China (93)	RCT	Midazolam + fentanyl vs. propofol vs. sequential use of midazolam + propofol	More than 72 hours	CA, NA	Recovery and extubation time	NA	Sedatives and ICU costs hypotension episodes	Hypotension defined as reduce in systolic blood pressure	Sequential use of propofol + midazolam was better in relation to earlier

										more than 20%	extubation, less sedation and total ICU costs, and less hypotension cases compared the other groups
4	Adult	Barrientos et al, 1997, NA (98)	RCT	Midazolam + morphine vs. propofol + morphine	More than 24 hour	CA, Predictive	Weaning time and cost	NA	Tachyphyl axis, treatment failures associated with sedatives	Treatment failures (patients needing >12 mL/hour of study medication)	Propofol + morphine reduced the weaning time, cost, and therapeutic failure
5	Adult	Swart et al, 1999, USA (77)	RCT	lorazepam + fentanyl vs. midazolam + fentanyl	NA	CA, NA	Treatment success based on the desired level of sedation using Addenobroke Scale	Adequate sedation level was considered as lightly asleep but easily roused by voice	Total cost of sedation	NA	Lorazepam provided easier management of the sedation level and offered a significant cost-savings
6	Adult	Mehta et al, 2008, Canada (95)	RCT	Midazolam + morphine (PS+DIS) vs. midazolam + morphine (PS only)	NA	NA, NA	Treatment success based on the desired level of sedation using SAS	Adequate sedation level was scored as level 3 and 4	Duration of MV, ICU and hospital stay, and mortality rate	Duration of MV from the time of intubation to extubation for 2 days	PS achieveed better desired SAS score No difference was observed in the duration of

											MV, ICU and hospital stay, and mortality
7	Adult	Rozendaal et al, 2009, Netherlands (88)	RCT	Remifentanyl + propofol vs. fentanyl or morphine + midazolam, propofol or lorazepam	10 days maximum	NA, NA	Duration of MV	NA	Weaning time and ICU-LOS	NA	Duration of MV, weaning time and ICU stay was statistically lower in the remifentanyl + propofol
8	Adult	Breen et al, 2005, NA (99)	RCT	Remifentanyl vs. midazolam + morphine or fentanyl	10 days	NA, NA	Extubation time	NA	Weaning time, ICU stay, and treatment success based on the desired level of sedation based on SAS	Adequate sedation was considered as level 3 or 4 ICU stay until discharge	Extubation and weaning time and ICU stay were lower in remifentanyl with same sedation score
9	Adult	Karir et al, 2012, USA (78)	Observational	Morphine vs. fentanyl	14 days	NA, NA	Cumulative 14 days dose	NA	NA	NA	The median dose of fentanyl was higher during the 14 days
10	Adult	Watling et al, 1996, Canada (96)	Observational	Lorazepam with/out morphine	NA	NA, NA	Apnea and respiratory effort	NA	NA	NA	Lorazepam and morphine combination caused apnea

											and reduced the respiratory effort during 2 to 50 days of sedation
11	Adult	Strom et al, 2010, Denmark (89)	RCT	Morphine vs. morphine + propofol	28 days	NA, NA	MV free days ICU and hospital stay, mortality	MV free days in 28 days period	The need for CT or MRI brain scans, accidental removal of endotracheal tube, and VAP	VAP: new lung parenchymal opacity on a chest radiograph of a patient who had been intubated for > 48 hours, and simultaneous presentation of 2 or more of: temperature of <36°C or >38°C; white blood cell count of $<4\times10^9$/L or $>10\times10^9$/L; or purulent secretions from the endotracheal	MV free days was statistically lower in the morphine + propofol group LOS in ICU and hospital, tracheostomy, VAP and mortality were less but not significant in morphine monotherapy

										tube	
12	Adult	Jarman et al, 2013, USA (79)	Observational	Morphine + propofol vs. midazolam	NA	NA, NA	MV free days, ICU LOS, mortality rate	NA	NA	NA	MV free days was significantly lower in midazolam ICU LOS was significantly lower in propofol + morphine No difference between both in relation mortality
13	Adult	Tedders et al, 2014, USA (86)	Observational	Fentanyl vs. propofol	NA	NA, NA	Duration of MV	NA	ICU stay, the percentage of the desired level of pain and sedation and frequency of hypotension	Hypotension defined as reduce in the systolic blood pressure to less than 90 mmHg at two repeated periods or reduce in systolic blood pressure to more than	Duration of MV was significantly lower in the fentanyl group No difference was associated between both groups in ICU stay, hypotension, and desired RASS score

										40 mmHg	
14	Adult	Riker et al, 2009, USA, brazil, Australia, Argentina, New Zealand (80)	RCT	Dexmedetomidine + fentanyl vs. midazolam + fentanyl	30 days maximum	NA, NA	Time to reach the desired RASS score	Target sedation range (RASS score −2 to 1)	The duration and free days of delirium	Delirium free days were calculated as days alive and free of delirium during study drug exposure	Time to reach the desired RASS score was not significantly lower in the midazolam and fentanyl group Delirium free days were significantly lower in midazolam group
15	Adult	Junior et al, 2014, Brazil (97)	RCT	Intermittent sedation (fentanyl) vs. daily interruption (fentanyl)	28 days	NA, NA	MV-free days	In a 28 day period	ICU and hospital mortality, ICU and hospital LOS, incidence of delirium, time to reach the desired SAS score	Target SAS (level 3 or 4) Delirium within 7 days	MV free days and time to reach desired SAS score were higher in the intermittent group ICU and hospital mortality and delirium happened less in the intermittent group
16	Adult	Shehabi et al,	RCT	Lightly vs.	NA	NA, NA	Treatment	Target	Delirium	Delirium was	Median target

		2013, Malaysia (94)		deeply sedation of (midazolam, propofol, morphine, fentanyl, dexmedetomidine)			success based on the level of sedation using RASS	sedation range (RASS score −2 to 1)	and free days of delirium	defined if patients had positive results using the confusion assessment methods for intensive care Subjects were considered delirium free if they had a RASS above 3	RASS scores and delirium-free days were higher in the lightly sedated group after 48 hours
17	Adult	Aitkenhead et al, 1989, NA (100)	RCT	Propofol + morphine vs. midazolam + morphine	Less than 24 hours	NA, NA	Treatment success based on the desired level of sedation using RSS	Desired level was defined as cooperative, oriented, and tranquil, responding to command only, or showing a brisk response to light glabellar tap or a loud	Weaning time, mortality and hypotension episodes	NA	Higher desired RSS score and lower weaning time were in the propofol and morphine group Mortality and hypotension happened more frequently in the propofol and morphine

								auditory stimulus			group
18	Adult	Cox et al, 2008, Denmark (90)	RCT	Propofol vs. lorazepam vs. morphine	NA	CEA, Decision analysis	MV- free days	Within 28 days from intubation	Cost	NA	Propofol dominated lorazepam due to its lower overall costs and greater MV free days
19	Neonate	Anand et al, 1999, NA (59)	RCT	Morphine vs. midazolam vs. placebo	14 days maximum	NA, NA	Severity of illness using PIPP scale and level of sedation using COMFORT scale	PIPP defined as no or mild pain if the score was between 0-6, moderate pain if the score was between 7-12, and severe pain if the score was above 12 COMFORT score defined as target range of sedation between 17 and 26	Poor neurological outcomes (neonatal death, IVH grade 3 or 4, PVL) MV free days, ICU stay, tolerance of enteral feeds	Neonatal death occurring at 0 to 28 days of age without discharge from NICU	Only morphine had elevated COMFORT score which decreased significantly the level of sedation Morphine and midazolam groups reduced significantly the pain score Three deaths; two in placebo, one in midazolam, and none in morphine Poor

											neurological outcomes occurred more frequently in placebo group and least in the morphine group No difference between both groups in MV free days and ICU stay
20	Neonate	Saarenmaa et al, 1999, Finland (58)	RCT	Fentanyl vs. morphine	2 days	NA, NA	Severity of illness using behavioral pain scale	NA	Decreased gastrointestinal motility, necrotizing enterocolitis, urinary retention	Decreased gastrointestinal motility through daily meconium passage assessment Urinary retention defined as the inability to urinate spontaneously with bladder enlargement or reversible hydro	No difference was observed in the pain score response between both groups except in the b-Endorphin in favor of fentanyl Decreased gastrointestinal motility occurred significantly less frequently in fentanyl group

										nephrosis	Necrotizing enterocolitis and urinary retention were more diagnosed in the fentanyl group
21	Neonate	Wood et al, 1998, UK (61)	RCT	Diamorphine vs. morphine	25 hours	NA, NA	Treatment success based on desired level of sedation using a study specific scale	NA	Duration of MV and mortality, IVH	NA	No difference was seen after 24 hour of optimum sedation score, duration of MV, and mortality Incidence of IVH was higher in diamorphine
22	Neonate	Quinn et al, 1992, Ireland (62)	RCT	Morphine vs. pancuronium vs. Morphine+ pancuronium	Until O_2 concentration fell below 45%	NA, NA	Duration of MV and mortality, IVH	NA	NA	NA	No difference among the groups in terms of MV reduction and mortality IVH happened least in pancuronium
23	Pediatric	Tobias et al, 1999, NA (101)	Observational	Fentanyl+ midazolam vs. midazolam	3-7 days	NA, NA	Withdrawal symptoms prevention	NA	NA	NA	No subjects developed withdrawal symptoms in

											both groups
24	Pediatric	Tobias et al, 2004, USA (81)	RCT	Midazolam + morphine vs. dexmedetomidine + morphine	NA	NA, NA	Treatment success based on desired level of sedation using RSS	Adequate sedation level was grade 2, 3, 4, or 5 on the RSS	Blood pressure and heart rate	NA	No difference was seen between groups in relation to all the measured outcomes
25	Adult	Kress et al, 2000, USA (82)	RCT	Midazolam + morphine vs. propofol + morphine	NA	NA, NA	Duration of MV, ICU and hospital stay	NA	The need for CT, MRI scan	NA	Duration of MV and ICU stay and need for diagnostic tests were significantly lower in the midazolam+ morphine group The hospital stay did not differ between the groups
26	Adult	Carson et al, 2006, USA (83)	RCT	Lorazepam + morphine vs. propofol + morphine	NA	NA, NA	Duration of MV	From the time of intubation to the first time of extubation for ≥ 3 days	MV free days, ICU and hospital stay, and mortality	NA	Lorazepam + morphine reduced significantly the MV duration No difference between the groups in the

											MV free days, ICU and hospital stay, and mortality
27	Adult	Barrientos et al, 2001, Spain (91)	Observational	Propofol 2% + morphine vs. propofol 1% + morphine vs. midazolam +morphine	14 days maximum	CBA, Predictive	Treatment failure and the ability to reach the desired sedation using RSS	NA	ICU cost	ICU cost for duration of MV, sedative cost depending on dose used, and ICU cost during weaning	No difference was seen in the ability to reach the desired sedation score and the treatment failure between propofol 1% and 2% Lowest ICU cost in propofol 2% and highest in the midazolam group
28	Neonate	Simons et al, 2003, Netherland (92)	RCT	Morphine vs. placebo	7 days	NA, NA	Level of pain using VAS, NIPS, PIPP	VAS defined as scores range between 0-10, low scores indicates low pain, while high scores indicates severe pain NIPS defined	Poor neurological outcomes	Poor neurologic outcome defined as severe IVH, PVL, or death within 28 days and the incidence of all grades of IVH	No significant differences between groups in pain scores Poor neurological outcome happened in the lower ages but not associated with

								as scores range between 0-above 4, 0 indicate no or mild pain and above 4 means severe pain PIPP as defined by Anand et al study			sedative
29	Neonate	Grunau et al, 2009, Canada (60)	RCT	Morphine vs. placebo	NA	NA, NA	Neurodevelopmental outcomes	MDI measures cognitive and language function and includes eye-hand items such as stacking blocks, concrete problem solving tasks, receptive and expressive vocabulary items; PDI measures the gross	NA	NA	Morphine was associated with poor neurodevelopmental outcome at 8 months only after sedation

								motor development			
30	Neonate	Orsini et al, 1996, USA (63)	RCT	Fentanyl vs. placebo	5 days	NA, NA	Behaviors' of infants using behavioral state score	Low score reflects sedated neonate while high score indicates not well sedated	Duration of ventilation use, incidence of IVH	NA	Fentanyl showed significantly lower behavioral state score compared with placebo No difference was seen in relation to other outcomes
31	Neonate	Guinsburg et al, 1998, Brazil (64)	RCT	Fentanyl vs. placebo	NA	NA, NA	Behaviors' of infants using NFCS and MPC Scores	NA	Blood pressure and heart rate	NA	Lower behavioral state score in fentanyl Fentanyl reduced heart rate and blood pressure
32	Adult	Richman et al, 2006, USA (84)	RCT	Midazolam vs. midazolam + fentanyl	NA	NA, NA	The number of hour /day that patients' RSS deviated from the	NA	Number of patient-ventilator asynchronous events/ day	Number of times/day the chest wall respiratory rate exceeds the measured	Midazolam and fentanyl reduced significantly the off target RSS score and number of patient-

							target value			ventilator rate by 3/min	ventilator asynchronous
33	Pediatric	Anand et al, 2013, USA (85)	Observational	Morphine vs. fentanyl	NA	NA, NA	Increased in opioid dose	NA	NA	NA	Doubling the dose of opioids was more likely to happen after opioid infusion for 7 days or longer More dose doubling happened when morphine was used as the initial opioid or if the child had prior PICU admission

*RCT = randomized controlled trial; CBA = cost-benefit analysis; NA = not available; RSS = Ramsey Sedation Scale
†GCS = Glasgow Coma Scale; CCA = cost consequence analysis; CA = cost analysis; ICU = intensive care unit
‡PS = protocol sedation; DIS = daily interruption sedation; MV = mechanical ventilation; SAS = Sedation-Agitation Scale
§LOS = length of stay; CT = computer tomography; MRI = magnetic resonance imaging; VAP = ventilator-associated pneumonia
|| RASS = Richmond Agitation and Sedation Scale; CEA = cost-effectiveness analysis; PIPP = Premature Infant Pain Profile
¶ IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; NICU = neonatal intensive care unit; VAS = Visual Analogue Scale
** NIPS = Neonatal Infant Pain Scale; MDI = Mental Development Index; PDI = Psychomotor Development Index
††NFCS = Neonatal Facial Coding System; MPC = Modified Postoperative Comfort; PICU = pediatric intensive care unit

4.1.3 Study comparators

Only six studies compared between morphine and fentanyl in a head to head comparison (58, 78, 85, 87, 88, 99). In 23 studies, morphine was evaluated as monotherapy (n= 9) and/or combined with other agents, including propofol, midazolam, or lorazepam (n= 16) (58-62, 76, 78, 79, 81-83, 85, 87-92, 94-96, 98-100). Comparators were fentanyl, midazolam, propofol, lorazepam, diamorphine, pancuronium, or placebo. In contrast, fentanyl was evaluated in fifteen of the 33 studies, given alone (n= 7) or in combination with midazolam, propofol, lorazepam, or dexmedetomidine (n= 8) (58, 63, 64, 77, 78, 80, 84, 86-88, 93, 94, 97, 99, 101). Comparators were morphine, remifentanyl, propofol, midazolam, lorazepam, or placebo. Study interventions and comparators are as shown in **Table 4.1** and **Appendices 6 and 7.**

4.1.4 Adult patients

The age range of adult subjects was between fourteen and eighty years. The doses of morphine and fentanyl varied between (0.08-5 mg/kg/hr) and (0.5-2 mcg/kg/hr), respectively. The majority of the 22 adult studies were RCTs (n= 17) and the remaining were observational studies (n= 5) (**Table 4.1**).

Comparison of morphine and fentanyl was identified in four studies, two of which compared between remifentanyl plus propofol and fentanyl or morphine plus either midazolam, propofol or lorazepam while the third study compared between remifentanil and morphine or fentanyl in addition to midazolam (87, 88, 99). Two studies evaluated only the use of both sedatives without a direct comparison (78, 94).

The primary endpoint measured in the majority of the studies was the optimum level of sedation (n= 8). Studies by Richamn et al, Carrasco et al, Barrientos et al and Aitkenhead et al utilized Ramsay Sedation Scale (RSS) score to evaluate optimum sedation (76, 84, 91, 100), which is defined as "cooperative, oriented, and tranquil, responding to command only, or showing a brisk response to light glabellar tap or a loud auditory stimulus". The Addenobrook scale, however, was used in the Swart et al study (77). This is defined as "lightly asleep, but easily roused by voice". Other studies, by Riker et al and Shehabi et al (80, 94), used the Richmond Agitation-Sedation Scale (RASS), which is defined as achieving target RASS score range of (-2 to +1), "briefly awakens with eye opening, not fully alert, anxious with movements". Sedation Agitation Scale (SAS) which is defined as "calm, cooperative, and sedated" was used by Mehta et al (95).

Only the study by Riker at al included study populations that were based on sample size calculations (80).

All the scales were utilized differently without any specification in relation to the outcome of the study or the type of sedative as illustrated in **Table 4.1**.

The duration of the MV was evaluated in seven different studies as another primary outcome by Rozendaal et al, Strom et al, Jarman et al, Tedders et al, Junior et al, Cox et al, Kress et al, and Carson et al (79, 82, 83, 88-90, 97). This was reported as mean or median days/hrs, in addition to ranges in all studies and was defined as MV free days in a 28 day period in Strom et al, Junior et al, and Cox et al studies and as from the time of intubation to the first time of extubation for equal to or more than three days in Carson

et al study. The other studies did not provide definitions for the duration of MV. Only in the studies by Rozendaal et al, Strom et al, Jarman et al, Tedders et al, Junior et al, Kress et al, and Carson et al, the statistical difference in outcome between comparators was reported.

The optimum level of sedation was assessed as a secondary outcome in Breen et al and Junior et al studies (97, 99) where SAS was used and defined similar to the Mehta et al study. Mehta et al study used the duration of MV as their secondary outcome and defined it as from the time of intubation to extubation (95). The most identified secondary outcome measures were the length of stay in ICU (83, 86, 88, 95, 97, 99), adverse events, weaning time (88, 99, 100), delirium events and free days of delirium (80, 94, 97), and mortality (83, 95, 97, 100).

The ICU length of stay was reported as mean/median days in addition to a range in all studies. Only Breen et al study defined this outcome as patients' stay in the ICU until discharge. Others only followed up stay during sedation. The statistical difference in relation to the duration of ICU stay was reported in the studies by Carson et al, Junior et al, Rozendaal et al, Tedders et al, Mehta et al, and Breen et al. Mortality events were defined as ICU mortality, but without any clarification if this is sedation related, in Mehta et al and Junior et al studies (95, 97), while Carson et al measured the mortality during hospital stay (83) and were reported as total number of cases. In Aitkenhead et al study, mortality was not defined. The statistical difference in the mortality was reported in the Mehta et al, Junior et al, and Carson et al studies.

With respect to adverse events, these were hypotension episodes (76, 86, 93, 100), and ventilator-associated pneumonia (VAP) (89). These were reported as total number of cases occurred during the sedation. Resources used to manage these events were not reported in any of the studies.

In relation to delirium events, these were reported in the studies by Riker et al, Junior et al, and Shehabi et al (80, 94, 97) and were defined as the number of days without delirium during sedation by Riker et al study, delirium within seven days by Junior et al, and, by Shehabi et al, as a RASS score of more than -3 or if the patients had positive results using the confusion assessment methods for intensive care. Measurement of delirium was assessed via the confusion assessment methods in Shehabi et al study only.

How statistically different secondary outcomes are among alternatives was only reported in the studies by Zhou et al, Tedders et al, Strom et al, Shehabi et al, and Riker et al.

4.1.5 Neonatal patients

Only one study of the eight neonatal studies involved direct comparison of fentanyl with morphine (58). The doses of morphine and fentanyl varied as 0.01-0.1 mg/kg/hr and 0.5-1 mcg/kg/hr, respectively. Seven studies were RCTs, and only one was an observational study.

Similar to studies in adults, the desired level of sedation was the most common primary endpoint measured in the majority of the studies (n= 6). This was measured in the study

by Anand et al, via the PIPP score, which is defined as neonate who has no or mild pain if the score is between 0 and 6, moderate pain if the score is between 7 and 12, and severe pain if the score is above 12, which indicates the need for sedation (59). Both COMFORT score and the PIPP score were used in one study to compare the same medications by Anand et al. Optimal sedation is defined as a COMFORT score between 17 and 26. Simons et al measured the level of sedation using three tools; VAS (defined as scores range between 0 and 10, with lower scores indicating low pain, while high scores indicating severe pain), NIPS (defined as scores range between 0 and above 4, with 0 indicating no or mild pain, and above 4 meaning severe pain), and PIPP as defined by Anand et al study. In the study by Guinsburg et al, two scales were used to assess the behavior of the neonates, being NFCS and PCS which were not clearly defined (64). In the studies by Saarenmaa et al and Orsini et al, the outcome of sedation was measured by looking at the behavioral state of the neonates, low score reflects sedated neonate while high score indicates not well sedated neonates, as defined by Orsini et al study only (58, 63).

Only in the Saarenmaa et al study, the studied population was based on sample size and power calculations. Outcomes in the study by Anand et al were of a pilot trial.

Duration of MV and mortality were other primary endpoints measured in the Quinn et al study. This was reported as median days, and total number of cases, respectively. The definitions of these outcomes however were not provided.

As another primary outcome, the neurodevelopmental function was measured in the study by Grunau et al. This was performed through measuring the cognitive and language function using the MDI and the gross motor development using the PDI.

Only in the study by Saarenmaa et al, the statistical difference between comparators' outcomes was identified.

The main secondary endpoints reported in the included studies were the duration of MV (59, 61), length of NICU stay (59), Gastrointestinal motility (58), urinary retention (58), poor neurological outcomes (59), and mortality (61).

The duration MV and NICU stay was defined and reported as in the adult studies, so does the mortality. For the gastrointestinal motility and urinary retention, these were reported through measuring the daily meconium passage and inability to urinate spontaneously with bladder enlargement or reversible hydronephrosis.

The neurological outcomes were defined as occurrence of cases of death, IVH grade 3 or 4, or PVL.

The statistical difference in secondary outcomes among alternatives was only reported in the studies by Saarenmaa et al and Wood et al.

4.1.6 Pediatric patients

Of the three eligible studies, two did not specify the respiratory disorder of patients. Direct comparison of morphine versus fentanyl was identified in one study by

Anand et al (85). The age range of children was 2 to 9 years old. The doses of morphine and fentanyl varied between 0.08-0.1 mg/kg/hr and 11-19 mcg/kg/hr, respectively.

Two of the studies, by Anand et al and Tobias et al, were observational studies (85, 101), and one was RCT, also by Tobias et al (81). Tobias et al compared between fentanyl and midazolam as per their association with withdrawal symptoms after prolonged sedation (101). This was not defined, and is reported as mean. In a different study, Tobias et al measured the level of sedation using three different scales, i.e. RSS, Pediatric Intensive Care Unit (PICU) scale, and tracheal suctioning scale, in subjects receiving morphine with either midazolam or dexmedetomidine. The definitions of optimum sedation were not identified. Fentanyl and morphine were compared by Anand et al in a multicenter study that only measured the increase in opioids use to attain the level of sedation as seen at the beginning of management.

In none of the three studies, study outcomes were based on power and sample size calculations. Also in none of the studies, efforts to report the power of outcomes were made.

Secondary outcomes were only measured in one of the Tobias et al studies (81), in which the HR was comparatively reported. This was measured during receiving therapy. Despite the non-powered study population, statistical significance of the outcome was reported by Tobias et al and Anand et al studies (81, 85).

4.1.7 Economics evaluations

Economic outcomes were evaluated in seven of the included studies; all in the adult population. Four studies used cost analysis (77, 91, 93, 98), one used CEA (90), one used CBA (76), and one used CCA (87). All the studies employed a hospital perspective, including medications, ICU stay, and hospital stay costs. Only one study, by Carrasco et al, reported the additional/marginal costs in which the subject needed a special care after sedation, such as nursing, respiratory or physiotherapy care (76). Only four studies used modeling approaches in this review, one was described as having a Markov structure (87), one used basic decision model (90), and two were described as predictive models (91, 98).

The Markov model by Al MJ et al, in their cost consequence study, defined a variety of health states: MV (maintenance); MV (eligible to start weaning); MV (weaning started); MV (eligible to extubate); post-extubation; post-extubation (eligible for discharge ICU); discharged from ICU (final state); and death (final state). The time horizon of follow up was 28 days and the cycle length was one hr. Probabilistic sensitivity analysis was performed in the study, and an outcome probability was reported (87).

In the predictive cost analysis models (77, 98), which only were cost analysis based, similar elements were considered throughout all studies for cost of medication calculations. Here, the total cost was depended on death, therapeutic failures, sedation time, medication cost, and length of stay in ICU during sedation and weaning cost.

Resources that were included in the cost analysis are medication costs and medication costs during MV. Both predictive models were based on simple linear regression.

The remaining two studies that conducted cost analysis, by Zhou et al and Barrientos et al (91, 93), did not use a modeling approach. The comparative cost in both studies was the total ICU stay, including therapy and ICU management cost.

A CBA was conducted by Carrasco et al who evaluated both the sedation and post sedation costs of the same therapies in three different sedation subgroups (76). These are short term 24 hr sedation, medium term 24 hrs up to one week sedation, and long term over one week sedation. While the duration of follow up differed among these, the outcomes and resources that were accounted for in cost calculations were similar, including medication costs, special therapy care costs such as physiotherapy and tracheal aspiration, and nursing care costs. Final outcomes were reported as the cost to benefit ratio.

Cox et al compared among three therapies based on a cost-effectiveness basic decision model analysis. The model was for a follow up duration of 28 days, and included the cost of resources, such as costs of medication, MV, hospital stay, physicians, and laboratory tests. The ICER evaluation was the cost per additional MV-free days. The decision analytic model included nine possible treatment pathways depending on whether (the patient tolerated the medication with survival or death in the ICU or hospital ward and whether the patient was on or off MV) or (the patient developed ADRs due to inadequate sedation, hypertriglyceridemia, hemodynamic changes or

metabolic acidosis). As in the study by Al MJ et al, a probabilistic sensitivity analysis was conducted in this study.

In none of the studies a deterministic, one-way or multivariate, analysis was conducted to investigate uncertain inputs.

4.1.8 Quality assessment of the studies

Results of the quality assessment of included studies can be summarized as in **Tables 4.2, 4.3, and 4.**

Table 4.2. Quality assessment of the randomized controlled trials based on CONSORT criteria

	Questions	Studies – Part 1								
		Anand et al	Saarenmaa et al	Wood et al	Quinn et al	Simons et al	Orsini et al	Guinsburg et al	Mehta et al	Richman et al
1a	Identification as a randomized trial in the title	NA	A	A	NA	A	NA	NA	A	NA
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	A	A	A	A	A	A	A	A	A
2a	Scientific background and explanation of rationale	A	A	A	A	A	A	A	A	A
2b	Specific objectives or hypotheses	A	A	A	A	A	A	A	A	A
3a	Description of trial design (such as parallel, factorial) including allocation ratio	A	A	A	A	A	A	A	A	A
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA

4a	Eligibility criteria for participants	A	A	A	A	A	A	A	A	A
4b	Settings and locations where the data were collected	A	A	NA	NA	A	A	A	A	A
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	A	A	A	A	A	A	A	A	A
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	A	A	A	A	A	A	A	A	A
6b	Any changes to trial outcomes after the trial commenced, with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA
7a	How sample size was determined	NA	A	NA	A	A	NA	NA	NA	NA
7b	When applicable, explanation of any interim analyses and stopping guidelines	NA	NA	NA	NA	NA	NA	NA	NA	NA
8a	Method used to generate the random allocation sequence	A	A	A	A	NA	A	A	A	NA

8b	Type of randomization; details of any restriction (such as blocking and block size)	A	A	NA	A	NA	A	A	A	NA
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	A	A	NA	NA	NA	A	A	A	NA
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to Interventions	A	A	A	A	NA	NA	NA	A	NA
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	A	A	A	A	A	A	A	A	NA
11b	If relevant, description of the similarity of interventions	A	A	A	NA	A	A	A	A	A
12a	Statistical methods used to compare groups for primary and secondary outcomes	A	A	A	A	A	A	A	A	A

12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	A	NA	NA	NA	NA	NA	NA	NA	NA
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	A	A	A	A	A	A	A	A	A
13b	For each group, losses and exclusions after randomization, together with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA
14a	Dates defining the periods of recruitment and follow-up	NA	A	NA	A	A	NA	A	A	A
14b	Why the trial ended or was stopped	NA	NA	NA	NA	NA	NA	NA	NA	NA
15	A table showing baseline demographic and clinical characteristics for each group	A	A	A	NA	A	A	A	A	A
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned	A	A	A	A	A	A	A	A	A

	groups								
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	A	A	A	A	A	A	A	A	A
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	A	NA	A	A	NA	NA	NA	A	NA
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	A	NA	NA	NA	NA	NA	NA	NA	NA
19	All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	A	A	A	A	A	A	NA	A	A
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	A	A	A	N/A	A	NA	NA	A	A
21	Generalizability (external validity, applicability) of the trial findings	NA	NA	NA	NA	NA	NA	NA	A	NA

22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	A	A	A	A	A	A	A	A	A
23	Registration number and name of trial registry	NA	NA	NA	NA	NA	NA	NA	NA	NA
24	Where the full trial protocol can be accessed, if available	NA	NA	NA	NA	NA	NA	NA	NA	NA
25	Sources of funding and other support (such as supply of drugs), role of funders	NA	NA	NA	NA	A	NA	NA	NA	NA

	Questions	**Studies – Part 2**								
		Rozenda et al	Breen et al	Strom et al	Riker et al	Junior et al	Aitkenhead et al	Kress et al	Tobias et al	Carson et al
1a	Identification as a randomized trial in the title	A	A	A	A	A	NA	NA	NA	A
1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	A	A	A	A	A	A	A	A	A
2a	Scientific background and explanation of rationale	A	A	A	A	A	A	A	A	A

2b	Specific objectives or hypotheses	A	A	A	A	A	A	A	A	A
3a	Description of trial design (such as parallel, factorial) including allocation ratio	A	A	A	A	A	A	A	A	A
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA
4a	Eligibility criteria for participants	A	A	A	A	A	A	A	A	A
4b	Settings and locations where the data were collected	A	A	A	A	A	A	A	A	A
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	A	A	A	A	A	A	A	A	A
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	A	A	A	A	A	A	A	A	A
6b	Any changes to trial outcomes after the trial	NA	NA	NA	NA	NA	NA	NA	NA	NA

	commenced, with reasons									
7a	How sample size was determined	A	N/A	A	A	A	NA	NA	NA	A
7b	When applicable, explanation of any interim analyses and stopping guidelines	NA	NA	NA	A	A	NA	A	A	A
8a	Method used to generate the random allocation sequence	A	A	A	A	A	A	A	A	A
8b	Type of randomization; details of any restriction (such as blocking and block size)	A	A	A	A	A	A	A	NA	A
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	A	A	A	A	A	A	A	A	A
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to Interventions	NA	A	A	A	A	A	A	A	A
11a	If done, who was blinded	A	A	A	A	A	A	A	NA	A

	after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how									
11b	If relevant, description of the similarity of interventions	A	A	A	A	A	A	A	A	A
12a	Statistical methods used to compare groups for primary and secondary outcomes	A	A	A	A	A	NA	A	A	A
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA	NA	NA	NA	NA	A	A	NA	NA
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	A	A	A	A	A	A	A	A	A
13b	For each group, losses and exclusions after randomization, together with reasons	NA	NA	NA	NA	NA	NA	NA	NA	NA
14a	Dates defining the periods of recruitment and follow-	NA	NA	NA	A	A	NA	NA	NA	A

	up									
14b	Why the trial ended or was stopped	NA	NA	NA	NA	A	NA	NA	NA	NA
15	A table showing baseline demographic and clinical characteristics for each group	A	A	A	A	A	A	A	A	A
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	A	A	A	A	A	A	A	A	A
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	A	A	A	A	A	A	A	A	A
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA	NA	NA	NA	A	NA	NA	NA	A
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified	NA	NA	NA	NA	NA	A	A	NA	NA

	from exploratory									
19	All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	A	A	A	A	A	A	A	A	A
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	A	NA	A	A	A	NA	A	A	A
21	Generalizability (external validity, applicability) of the trial findings	NA	NA	A	NA	A	NA	NA	NA	A
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	A	A	A	A	A	A	A	A	A
23	Registration number and name of trial registry	NA	NA	A	A	A	NA	NA	NA	NA
24	Where the full trial protocol can be accessed, if available	NA	NA	NA	NA	NA	NA	NA	NA	NA
25	Sources of funding and other support (such as supply of drugs), role of funders	NA	NA	A	A	NA	NA	NA	NA	NA

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented but it was suggested)

NA: Not adequate (No information about the matter was available in the text)

Table 4.3. Cohort evaluations according to STROBE instrument

	Questions	**Studies**							
		Tedder et al	Walting et al	Karir et al	Jarman et al	Shehabi et al	Tobias et al	Anand et al	Grunanu et al
1	(a) Indicate the study's design with a commonly used term in the title or the abstract	NA	NA	NA	NA	NA	NA	NA	NA
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found	A	A	A	A	A	A	A	A
2	Explain the scientific background and rationale for the investigation being reported	A	A	A	A	A	A	A	A
3	State specific objectives, including any prespecified hypotheses	A	A	A	A	A	A	A	A
4	Present key elements of study design early in the paper	A	NA	A	A	A	A	A	A
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	A	A	A	A	A	NA	A	A
6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	A	A	A	A	A	A	A	A
	(b) For matched studies, give matching criteria	A	A	A	A	A	A	A	A

	and number of exposed and unexposed								
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	A	A	A	A	A	A	A	A
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	A	NA	A	A	NA	A	A	A
9	Describe any efforts to address potential sources of bias	NA	NA	NA	A	NA	NA	NA	NA
10	Explain how the study size was arrived at	NA	NA	NA	NA	A	NA	NA	NA
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	A	NA	A	NA	A	NA	A	A
12	(a) Describe all statistical methods, including those used to control for confounding	A	NA	A	A	A	NA	A	A
	(b) Describe any methods used to examine subgroups and interactions	NA	NA	NA	NA	NA	NA	NA	NA
	(c) Explain how missing data were addressed	NA	NA	NA	NA	NA	NA	NA	NA
	(d) If applicable, explain how loss to follow-up was addressed	NA	NA	NA	NA	A	NA	NA	NA
	(e) Describe any sensitivity analyses	NA	NA	NA	NA	NA	NA	NA	NA
13	(a) Report numbers of individuals at each stage of study—eg numbers potentially	NA	NA	NA	A	A	NA	A	NA

	eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed								
	(b) Give reasons for non-participation at each stage	NA	NA	NA	A	NA	NA	A	NA
	(c) Consider use of a flow diagram	NA	NA	NA	A	NA	NA	A	NA
14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	A	A	A	A	A	A	A	NA
	(b) Indicate number of participants with missing data for each variable of interest	NA	NA	NA	NA	NA	NA	NA	NA
	(c) Summarise follow-up time (eg, average and total amount)	NA	NA	NA	NA	NA	NA	NA	NA
15	Report numbers of outcome events or summary measures over time	A	A	A	A	A	NA	A	A
16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	A	A	A	A	A	NA	A	A
	(b) Report category boundaries when continuous variables were categorized	NA	NA	NA	NA	NA	NA	NA	NA
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA	NA	NA	NA	NA	NA	NA
17	Report other analyses done—eg analyses of	NA	NA	NA	NA	NA	NA	NA	NA

	subgroups and interactions, and sensitivity analyses								
18	Summarise key results with reference to study objectives	A	A	A	A	A	A	A	A
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	A	NA	A	A	A	NA	A	A
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	A	A	A	A	A	A	A	A
21	Discuss the generalizability (external validity) of the study results	NA	NA	NA	NA	916	NA	NA	NA
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA	NA	NA	NA	N/A	NA	NA	NA
	A: Adequate (information was explicitly presented in the text) PA: Partially adequate (information was NOT explicitly presented but it was suggested) NA: Not adequate (No information about the matter was available in the text)								

Table 4.4. Quality assessment of the pharmacoeconomics evaluations based on CHEERS criteria

Section/Items	**Studies**						
	Carrasco et al	Al MJ et al	Barrientos et al	Swart et al	Barrientos et al	Zhou et al	Cox et al
Title/Abstract/Introduction							
Title	A	A	A	A	A	A	A
Abstract	A	A	A	A	A	A	A
Background/objectives	A	A	A	A	A	A	A
Methods							
Population/subgroups	PA	PA	A	PA	A	A	PA
Setting/location	PA	A	NA	A	A	A	A
Study perspective	A	A	A	A	A	A	A
Comparators	A	A	A	A	A	A	A
Time horizon	NA	A	NA	NA	NA	NA	A
Choice of health outcomes	A	NA	A	A	A	A	A
Measurement of effectiveness	A	NA	A	A	A	A	A

Estimating resources and costs	NA	A	NA	A	NA	NA	A
Currency, price date, conversion	NA	A	PA	PA	PA	PA	A
Choice of model	NA	A	NA	NA	NA	NA	A
Assumptions	NA	A	NA	NA	A	NA	A
Analytical model	NA	A	NA	NA	NA	NA	A
Results							
Study parameters	A	A	A	A	A	A	A
Incremental costs and outcomes	NA	PA	NA	NA	NA	NA	A
Characterizing uncertainty	NA	A	NA	NA	NA	NA	A
Characterizing heterogeneity	NA	A	NA	NA	NA	NA	A
Discussions/others							
Study findings, limitations, generalizability, current knowledge	A	A	PA	PA	PA	A	A
Source of funding							
Conflict of interests	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented but it was suggested)
NA: Not adequate (No information about the matter was available in the text)

4.2 Phase 2: ***Evaluation 1: morphine monotherapy versus fentanyl monotherapy***

4.2.1 Demographic characteristics of the study participants

Out of total 126 neonates included in the study, 63 received morphine and 63 received fentanyl. All baseline demographic characteristics were not significantly different (P <0.05) between both groups (**Table 4.5**).

Table 4.5. Main baseline patient demographics

Characteristic	**Morphine (n= 63)**	**Fentanyl (n= 63)**	**p-Value**
	No (%)	No (%)	
Gender			0.59
Male	34 (53.97)	38 (60.32)	
Female	29 (46.03)	25 (39.68)	
Gestational Age (weeks)			0.34
Pre-term (<37 weeks)	55 (87.30)	50 (79.37)	
Full-term (≥37 weeks)	8 (12.70)	13 (20.63)	
Birth Weight (g)			0.15
≥2500 g	19 (30.16)	21 (33.33)	
<2500 g and ≥ 1500 g	8 (12.70)	17 (26.98)	
<1500 g and ≥ 1000 g	17 (26.98)	12 (19.05)	
<1000 g	19 (30.16)	13 (20.64)	
Nationality			0.32
Qatari	19 (30.16)	26 (41.27)	
Arab	25 (39.68)	25 (39.68)	
Non-Arab	19 (30.16)	12 (19.05)	

Type of Delivery			0.2
Vaginal	28 (44.44)	20 (31.75)	
Caesarean	35 (55.56)	43 (68.25)	
Received Vecuronium			1
Yes	11 (17.46)	11 (17.46)	
No	52 (82.54)	52 (82.54)	

4.2.2 Neonates with sedation success with or without ADRs

The number of neonates who were successfully sedated was significantly higher in the morphine group compared with the fentanyl group [43 (68%) versus 27 (43%)], risk ratio (RR) = 1.72, 95% confidence interval (CI) = (1.16 – 2.56), (P= 0.0075)]. The average loading and maintenance doses of fentanyl were 2.11 mcg/kg (range, 0.4 to 3) and 4.57 mcg/kg/hr (range, 2 to 10), respectively. Whereas, they were 125 mcg/kg (range, 100 to 150) and 10.27 mcg/kg/hr (range, 10 to 20) with morphine. The average duration of fentanyl given as the first sedative was shorter compared with morphine; 24 hrs (range, 1 to 96) versus 120 hrs (range, 1 to 864). Six patients successfully responded to the fentanyl treatment; this was observed through a reduction in their PIPP scores after initiating the sedative and 21 patients maintained their PIPP scores below 7. In patients who were given morphine, nine successfully responded to the sedation and 34 maintained their sedation scores. The average duration of MV was similar in the two groups; 144 hrs (range, 5 to 1374) with fentanyl and 144 hrs (range, 5 to 1405) with morphine. The average duration of NICU stay was also almost similar between the two groups; 45 days (range, 6 to 96) with fentanyl and 47 days (range, 1 to 132) with

morphine. The ranges of vital signs for morphine were 36.4 to 38.70 Celsius (°C), 9 to 202 bpm (HR), 13 to 233 bpm (respiratory rate, RR), and 17.30 to 83 mmHg (mean blood pressure, MAP). For fentanyl, these were 36.2 to 37.5 °C, 90 to 222 bpm (HR), 10 to 100 bpm (RR), and 17.3 to 84 mmHg. All patients in the two groups experienced ADRs, whether self-resolved or needing further management (**Table 4.6**).

4.2.3 Neonates with sedation failure due to receiving an increased dose

Out of patients who failed sedation, more patients received high doses of fentanyl compared with morphine (27 out of 36 versus 4 out of 20). In the fentanyl group twelve patients had increases in doses above the normal range and fifteen patients received higher doses within the therapeutic range. In the morphine monotherapy group, only four patients were given higher doses above the normal range. The average loading and maintenance doses of fentanyl were 5.32 mcg/kg (range, 2 to 10) and 4.30 mcg/kg/hr (range, 1 to 10), respectively. In patients receiving morphine, the average loading and maintenance doses were 292.5 mcg/kg (range, 270 to 300) and 15 mcg/kg/hr (range, 10 to 20), respectively. The duration of sedation was 48 hrs (range, 1 to 480) with fentanyl and 48 hrs (range, 1 to 69) with morphine. The average duration of the MV and NICU stay were shorter in patients sedated with fentanyl compared with morphine; 96 hrs (range, 1 to 674) versus 648 hrs (range, 39 to 2340), and 27 days (range, 7 to 130) versus 54 days (range, 4 to 162), respectively. In relation to the vital signs of patients in both groups, the temperature was between 36.1 and 38 °C, HR was between 91 to 198 bpm, RR was between 14 and 100 bpm, and MAP

was between 23.3 and 121 mmHg in the fentanyl group, while in the morphine group, the temperature was between 36.5 and 37.4 °C, HR was between 110 and 234 bpm, RR was between 13 and 96 bpm, and MAP was between 25 and 66.3 mmHg.

4.2.4 Neonates with sedation failure due to receiving alternative sedative

Under sedation failure, neonates who received alternative therapy in the fentanyl group was double the number of patients in the morphine group (6 out of 36 versus 3 out of 20). The average initial loading and continuous infusion doses of fentanyl were 3 mcg/kg (range, 1 to 5) and 3.33 mcg/kg/hr (1 to 5), respectively, with an average duration of 48 hrs (range, 1 to 73), and 120 mcg/kg (range, 60 to 180) and 10 mcg/kg/hr (range, 10 to 20), respectively, with an average duration of 864 hrs (range, 24 to 1562), with morphine. In relation to the alternative sedation of morphine in patients who received initial fentanyl, the average loading and maintenance doses of morphine were 100 mcg/kg and 12.5 mcg/kg/hr (range, 10 to 20) with an average duration of 96 hrs (range 12 to 216). For the patients receiving initially morphine, the average loading and maintenance doses of fentanyl as an alternative were 3.73 mcg/kg (range, 2.08 to 5.12) and 10 mcg/kg/hr with 24 hrs duration of sedation (range, 1 to 73). Similar to the failure due to increased dose pathway, the MV duration and NICU stay were shorter in the fentanyl group compared with morphine with 216 hrs (range, 19 to 774) and 33 days (range, 13 to 70 days) versus 1584 hrs (range, 144 to 2731) and 83 days (range, 49 to 123 days), respectively. The ranges of vital signs in patients receiving morphine were 36.5 to 38.7 °C for temperature, 62 to 191 bpm for HR, 21 to 153 bpm for RR, and 28 to

56.6 mmHg for MAP, respectively. For those who received fentanyl, the temperature, HR, RR, and MAP were between 36.3 and 38.1 °C, 72 and 209 bpm, 13 and 98 bpm, and 17 and 121 mmHg, respectively.

4.2.5 Neonates with sedation failure due to withdrawal symptoms

While one patient experienced withdrawal symptom in the morphine group, none was found in the fentanyl group. That patient only received continuous infusion of morphine (15 mcg/kg) for one day and conventional MV for one day. Additionally, the stay at the NICU was 15 days. In relation to the vital signs, the patient had temperatures between 36.2 and 37.4 °C, HR between 16 and 186 bpm, RR between 51 and 97 bpm, and MAP between 34 and 57.3 mmHg.

4.2.6 Neonates with sedation failure due to death

Although the sedation success was higher in neonates sedated with morphine, eleven patients died in the morphine group compared with one patient only in the fentanyl group. The average loading and maintenance doses were 127.5 mcg/kg (range, 65 to 180) and 11.67 mcg/kg/hr (range, 10 to 20) with morphine versus one mcg/kg loading dose and 0 mcg/kg/hr maintenance dose with fentanyl group. Longer duration of sedation, MV, and NICU stay were noticed in the morphine group compared with the fentanyl group; 312 hrs (range, 48 to 1562), 384 hrs (range, 52 to 1806 hr), and 20 days (range, 6 to 75 days), versus 24 hrs, 216 hrs and 11 days, respectively. In the morphine group, the ranges of vital signs of the patients were between 36 and 38 °C, 106 and 213 bpm for HR, 27 and 96 bpm for RR, and 14.6 and 66.3 mmHg for MAP. While in the

fentanyl group, the patient's vital signs were between 36.5 and 37.4 °C, 48 and 196 bpm for HR, 31 and 65 bpm for RR, and 29.3 and 59.3 mmHg for MAP.

4.2.7 Neonates with sedation failure due to persistent agitation

Only one patient in the morphine group had persistent agitation compared with two patients in the fentanyl group. The average loading dose of fentanyl was 2.5 mcg/kg (range, 2 to 3) with 1 hr duration and none received continuous infusion. With respect to the morphine group, the patient received only maintenance dose (5 mcg/kg) with a duration of six days. Both groups had about similar average duration of MV (1 day in each group), however, the average duration of NICU stay was higher in the morphine group; 16 days versus 9 days (range, 3 to 14 days). The ranges of vital signs were: 32 to 37.3 °C for temperature, 49 to 164 bpm for HR, 13 to 88 bpm for RR, 33 to 76.6 mmHg for MAP in patients sedated by morphine, and were 36.6 to 37.3 °C for temperature, 139 to 189 bpm for HR, 41 to 94 for RR, and 27 to 44.6 mmHg for MAP in patients receiving fentanyl, respectively.

Baseline clinical and probability outcomes are summarized in (**Table 4.7**).

Table 4.6 Summary of the ADRs associated with sedation success

The ADRs associated with sedation success	**Morphine**		**Fentanyl**	
	Total number of patients	Cost per patient (QAR)	Total number of patients	Cost per patient (QAR)
Desaturation	23	38,440.17	21	36,207.61
Desaturation and urinary retention	1	38,450.17	2	36,217.61
Desaturation, urinary retention, MV adjustment and edema	1	38,485.17	0	N/A
Desaturation and MV adjustment	7	38,440.17	0	N/A
Desaturation, MV adjustment, and urinary retention	1	38,450.17	1	36,217.61
Desaturation, MV adjustment, and edema	3	38,263.63	0	N/A
Desaturation and edema	6	38,263.63	0	N/A
Desaturation and respiratory depression	1	38,441.61	0	N/A
Desaturation, MV adjustment, and joint stiffness	0	N/A	1	36,215.95
MV adjustment	0	N/A	2	35,996.07

*N/A: Not applicable

Table 4.7. Clinical outcomes and probabilities of morphine monotherapy vs. fentanyl monotherapy

Study clinical outcome	**Probability with morphine monotherapy (n= 63)**	**Probability with fentanyl monotherapy (n= 63)**
Sedation success	0.68 (n= 43)	0.43 (n= 27)
With ADRs	0.68 (n= 43)	0.43 (n= 27)
Without ADRs	0 (n= 0)	0 (n= 0)
Sedation failure	0.32 (n= 20)	0.57 (n= 36)
Increased dose	0.2 (n= 4)	0.75 (n= 27)
Therapy switch to alternatives	0.15 (n= 3)	0.17 (n= 6)
Withdrawal symptoms	0.05 (n= 1)	0 (n= 0)
Death	0.55 (n= 11)	0.03 (n= 1)
Persistent agitation	0.05 (n= 1)	0.05 (n= 2)

4.2.8 Cost of sedation

Morphine monotherapy achieved successful sedation in 68% of patients, compared to 43% with fentanyl monotherapy, with an ICER of QAR 490.36 per extra case of sedation success compared to fentanyl. Sedation success with ADRs (**Table 4.6**) was the major clinical outcome that had an impact on the total therapeutic cost of morphine and fentanyl, as shown in **Table 4.8,** where the weighted probabilities and costs for therapy outcomes are also given in **Table 4.8**. Cost components of the overall therapy are shown in **Table 4.9.**

4.2.9 Sensitivity analysis

One-way sensitivity analyses. The model was insensitive to the changes in the majority of the variables in the morphine and fentanyl monotherapy groups. The result was sensitive to the changes in the cost of MV. When the cost of MV decreased to from QAR 430.15 to QAR 404.35, fentanyl became more expensive that morphine (**Figure 4.2**). The result was also sensitive to the changes in the NICU stay in the fentanyl's successful sedation pathway and in the fentanyl's increased dose pathway. When these decreased from 45 and 27 days to 44.65 and 26 days, respectively, cost saving shifted in the favor of morphine (**Figures 4.3-4.4)**. The results were also sensitive to changes in the NICU stay in patients sedated successfully with morphine. Fentanyl became more expensive than morphine when the NICU stay of successful patients decreased from 47 to 46.6 days (**Figure 4.5).**

Table 4.8. The weighted probabilities and costs of morphine monotherapy and fentanyl monotherapy

Therapy outcome	**Morphine**			**Fentanyl**		
	Probability	Cost per patient (QAR)	Proportional cost (QAR)	Probability	Cost per patient (QAR)	Proportional cost (QAR)
Sedation success with ADRs	0.68	56,477.59	38,404.76	0.43	84,170.60	36,193.36
Sedation success without ADRs	0	N/A	N/A	0	N/A	N/A
Sedation failure						
Sedation failure due to increased dose	0.06	49,990.06	3,173.97	0.43	25,304.46	10,844.77
Sedation failure due to need for alternatives (fentanyl or morphine)	0.05	85,375.86	4,065.52	0.1	31,137.43	2,965.47
Sedation failure due to withdrawal symptoms	0.02	13,126.36	208.35	0	N/A	N/A
Sedation failure due to death	0.17	25,941.17	4,529.41	0.02	14,690.98	233.19
Sedation failure due to persistent agitation	0.02	16,059.43	254.91	0.03	8,681.53	275.60
Total cost per patient			**50,636.93**			**50,512.39**

*N/A: Not applicable

Table 4.9. Cost components of the overall therapy

	Cost (QAR)	**Cost (QAR)**
Cost component	**Morphine**	**Fentanyl**
Sedation success with ADRs		
Initial sedation	19.7	12
MV	2,580.89	2,580.89
NICU stay	24,775.72	23,721.44
Hematological tests	240	180
Chemistry tests	1,759.09	2,736.36
Metabolic tests	1,140	1,140
Microbiology tests	1,644.44	1,233.33
Blood gases tests	2,940	2,310
Virology tests	1,560	780
Urinalysis tests	N/A	N/A
Diagnostic tests	1,568.78	1,302.04
Oxygen therapy	211.54	211.54
Catheter	10	10
Medications to treat ADRs	36.45	8.34
Sedation failure due to increased dose		
Initial sedation	41.37	18
MV	11,614.02	1,720.59
NICU stay	28,465.72	14,232.86
Hematological tests	210	N/A

Chemistry tests	2,345.45	2,540.91
Metabolic tests	1,140	1,140
Microbiology tests	822.22	1,233.33
Blood gases tests	2,310	1,750
Virology tests	1,560	780
Urinalysis tests	N/A	216.67
Diagnostic tests	1,481.27	1,672.1
Medications to treat ADRs	N/A	N/A
Sedation failure due to receiving alternative		
Initial sedation	17.73	12
Alternative sedation	4.76	102.03
MV	28,389.82	3,871.34
NICU stay	43,752.87	17,395.72
Hematological tests	510	180
Chemistry tests	3,713.64	3,127.27
Metabolic tests	1,710	1,140
Microbiology tests	2,466.67	1,233.33
Blood gases tests	2,800	3,220
Virology tests	N/A	N/A
Urinalysis tests	N/A	72.22
Diagnostic tests	2,003.14	869.79
Medications to treat ADRs	N/A	N/A
Sedation failure due to withdrawal symptoms		

Initial sedation	1.97	N/A
MV	430.15	N/A
NICU stay	7,907.15	N/A
Hematological tests	120	N/A
Chemistry tests	586.36	N/A
Metabolic tests	570	N/A
Microbiology tests	1,644.44	N/A
Blood gases tests	770	N/A
Virology tests	780	N/A
Urinalysis tests	0	N/A
Diagnostic tests	316.29	N/A
Medications to treat ADRs	N/A	N/A
Sedation failure due to death		
Initial sedation	19.7	6
MV	6,882.38	2,580.89
NICU stay	10,542.86	5,798.57
Hematological tests	210	60
Chemistry tests	1,563.64	1,954.55
Metabolic tests	1,140	570
Microbiology tests	1,233.33	411.11
Blood gases tests	2,030	2,730
Virology tests	780	N/A
Urinalysis tests	N/A	N/A

Diagnostic tests	1,539.26	579.86
Medications to treat ADRs	N/A	N/A
Sedation failure due to persistent agitation		
Initial sedation	1.97	6
MV	430.15	430.15
NICU stay	8,434.29	4,744.29
Hematological tests	120	60
Chemistry tests	1,172.73	781.82
Metabolic tests	570	1,140
Microbiology tests	822.22	822.22
Blood gases tests	4,060	560
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A
Diagnostic tests	448.07	137.06
Medications to treat ADRs	N/A	N/A

*N/A: Not applicable

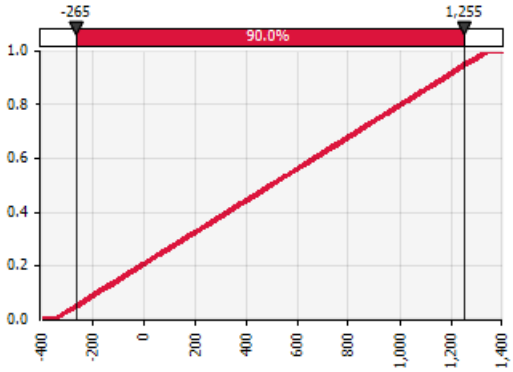


Figure 4.2. ICER probability curve of morphine with the variable “cost of MV”

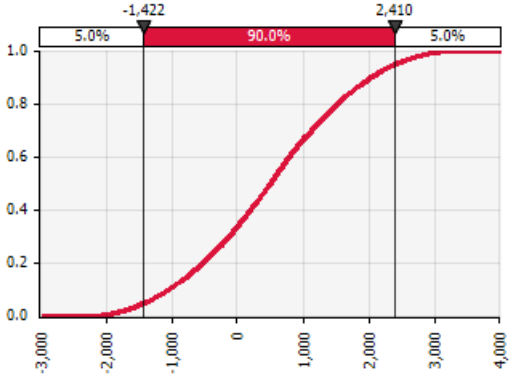


Figure 4.3. ICER probability curve of morphine with the variable “NICU stay in patients successfully sedated by fentanyl”

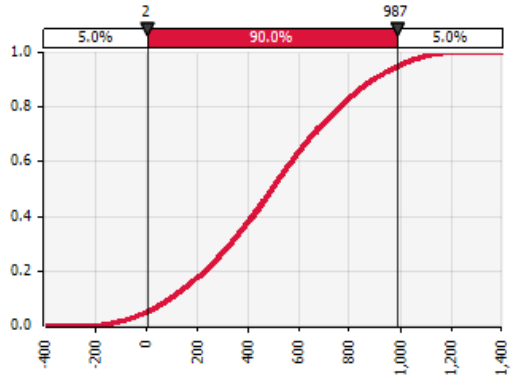


Figure 4.4. ICER probability curve of morphine with the variable “NICU stay in patients receiving increased doses of fentanyl”

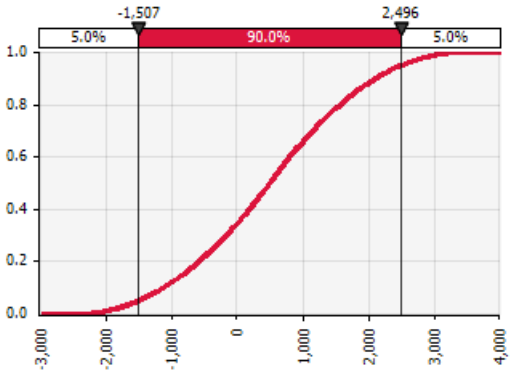


Figure 4.5. ICER probability curve of morphine with the variable "NICU stay in patients successfully sedated by morphine"

Probabilistic sensitivity analyses. **Figure 4.6** shows the tornado diagram that illustrates the ranking of the clinical variables as per impact on the model outcome. Here, the sedation failure due to receiving higher doses in the fentanyl group had the highest uncertainty that influenced the outcome and the sedation success in the fentanyl group had the lowest uncertainty that affected the outcome.

The cost of all variables remained unchanged in favor of fentanyl. Morphine had a 98% probability of having an economic advantage over fentanyl. An ICER probability curve is shown in **Figure 4.7.**

Alternative scenario: The total management cost of morphine and fentanyl were QAR 420,375.99 and QAR 418,398.61, respectively. Morphine monotherapy had an ICER of QAR 7,785.96 per extra case of sedation success compared to fentanyl monotherapy.

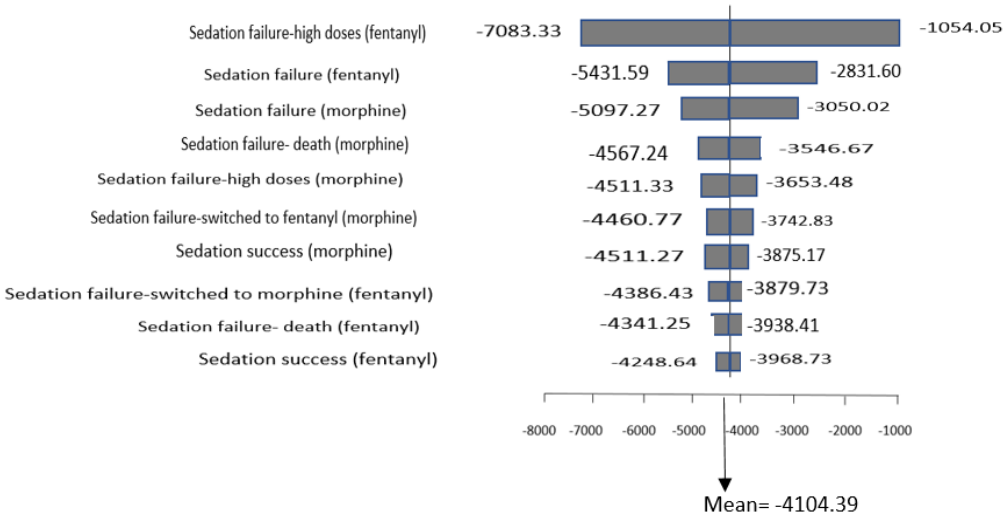


Figure 4.6. Tornado diagram of the variables as per their influence on the outcome of the Monte Carlo simulation

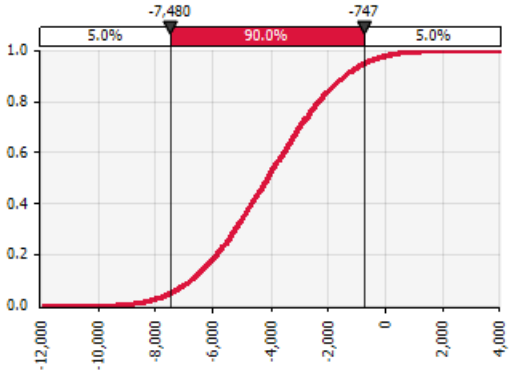


Figure 4.7. ICER with morphine probability curve

4.3 Phase 2: ***Evaluation 2: morphine monotherapy versus morphine plus midazolam***

4.3.1 Demographic characteristics of the study participants

Out of total 64 patients included in the analysis, 32 were in the morphine group and 32 were in the morphine plus midazolam combination group. All baseline

characteristics were not significantly different between the two groups except in the use of vecuronium (**Table 4.10**)**.**

Table 4.10. Main baseline patient demographics

Characteristic	**Morphine Monotherapy (n = 32)**	**Morphine Plus midazolam (n= 32)**	**p-Value**
	No (%)	No (%)	
Gender			0.77
Male	25 (78.12)	23 (71.88)	
Female	7 (21.88)	9 (28.12)	
Gestational Age (weeks)			1
Pre-term (<37 weeks)	24 (75)	23 (71.88)	
Full-term (≥37 weeks)	8 (25)	9 (28.12)	
Birth Weight (g)			0.41
≥2500 g	10 (31.25)	8 (25)	
< 2500 g and ≥1500 g	3 (9.38)	3 (9.38)	
<1500 g and ≥1000 g	7 (21.87)	3 (9.38)	
<1000 g	12 (37.50)	18 (56.25)	
Nationality			0.8
Qatari	13 (40.63)	12 (37.5)	
Arab	15 (46.87)	14 (43.75)	
Non-Arab	4 (12.5)	6 (18.75)	
Type of Delivery			0.8
Vaginal	14 (43.75)	16 (50)	
Caesarean	18 (56.25)	16 (50)	

Received Vecuronium			0.004
Yes	6 (18.75)	18 (56.25)	
No	26 (81.25)	14 (43.75)	

4.3.2 Neonates with sedation success with or without ADRs

Successful sedation was significantly achieved in 66% (n= 21) and 34% (n= 11) in the morphine monotherapy group and combination of morphine and midazolam group, respectively, with an RR of 1.91, 95% CI= (1.11 to 3.28), (P= 0.019). Hundred percent of patients (n= 21) who were successfully sedated with morphine monotherapy were during the maintenance stage of therapy, whereas 91% of patients (n= 10) maintaining their sedation scores in the combination regimen and 9% (n= 1) successfully responding to the therapy. In the monotherapy group, the average loading and maintenance doses of morphine were 175 mcg/kg (range, 150 to 200) and 16.1 mcg/kg/hr (range, 10 to 30), respectively. In the combination regimen, doses were 102 mcg/kg (range, 70 to 270) and 10 mcg/kg/hr (range, 10 to 25) for morphine and 20.88 mcg/kg/hr (range, 8 to 30) for midazolam. Longer duration of sedation was observed with the combination therapy; 144 hrs (range, 1 to 744) versus 504 hrs (range, 24 to 1824). Moreover, both of the average of the duration of MV and stay at the intensive unit were longer in the combination regimen; 696 hrs (range, 35 to 1926) and 75 days (range, 3 to 192) versus 168 hrs (range, 1 to 797) and 51 days (range, 6 to 210). The HR and MAP vital signs ranges were 60 to 207 bpm and 21 to 100 mmHg in the monotherapy group, respectively, and 70 to 219 bpm and 20 to 100 mmHg in the combination group,

respectively. The temperature and RR ranges were 33 to 38 °C and 6 to 202 bpm, and 33.8 to 39.4 °C and 13 to 105 bpm for the two groups, respectively. All sedated neonates in both groups had ADRs, self-resolving or needing further management (**Table 4.11**).

4.3.3 Neonates with sedation failure due to receiving an increased dose

None of the neonates who were sedated by morphine monotherapy required high administration of doses compared with midazolam and morphine together (0 versus 8 neonates). Out of the eight, one had an increase in the morphine dose, two had an increase in the midazolam dose above the normal range, and five received higher doses within the therapeutic range. The average loading and continuous infusion doses were: 207.6 mcg/kg (range, 150 to 273) and 16.1 mcg/kg/hr (range, 10 to 25) for morphine and 100 mcg/kg followed by 47.5 mcg/kg/hr (range, 5 to 85) for midazolam. The average sedation duration of morphine and midazolam regimen was 432 hrs (range, 1 to 1848). With respect to the average duration of the MV and NICU stay, patients needed 648 hrs (range, 34 to 2568) and 63 days (range, 11 to 180), respectively. The vital signs ranges were a temperature of 33.4 to 39.9 °C, an HR of 70 to 246 bpm, a RR of 4 to 140 bpm, and a MAP of 23 to 119 mmHg.

4.3.4 Neonates with sedation failure due to receiving alternatives

Similar to the failure due to increased dose pathway, only neonates who were sedated by the combination regimen were switched to alternative (n= 5). The average initial loading and continuous infusion doses of morphine were 160 mcg/kg (range, 100

to 270) and 15.6 mcg/kg/hr (10 to 25), respectively, while the average doses of midazolam were 100 mcg/kg and 61.67 mcg/kg/hr (range, 20 to 85), with an average duration of 648 hrs (range, 1 to 1848), respectively. Fentanyl was used as an alternative sedative to morphine with an average loading and maintenance dose of 5.2 mcg/kg (range, 2 to 8.4) and 12.5 mcg/kg/hr (range, 10 to 20), for average 144 hrs (range, 1 to 912), respectively. The average MV duration and NICU stay were 504 hrs (range, 81 to 2568) and 128 days (range, 11 to 180), respectively. The vital signs were 33.8 to 38.5 °C, 70 to 197 bpm, 4 to 14 bmp, and 24 to 82.6 mmHg for temperature, HR, RR, and MAP respectively.

4.3.5 Neonates with sedation failure due to withdrawal symptoms

Two neonates had withdrawal symptoms in the morphine monotherapy group compared with only one case in the combination regimen. In both groups, none received loading doses of morphine, however the continuous infusion doses were 11.6 mcg/kg (range, 10 to 15) and 18.5 mcg/kg/hr (range, 10 to 29), respectively, in addition to 30 mcg/kg/hr of midazolam in the combination group. The average duration of monotherapy sedation was almost half of the combination therapy's duration (12 days versus 22 days). However, the monotherapy group has longer average duration of MV (25 days versus 11 days) and NICU stay (27 days versus 12 days). Values of main vital signs were as follows: temperature (36.3 to 37.5 °C versus 26 to 37.6°C), HR (28 to 196 bpm versus 0 to 218 bpm), RR (22 to 75 bpm versus 38 to 90 bpm), and MAP (14.6 to

59.3 mmHg versus 20 to 82.6 mmHg) in the monotherapy and combination groups, respectively.

4.3.6 Neonates with sedation failure due to death

The mortality rate was higher in neonates managed by morphine alone compared with the combination (9 out of 11 versus 6 out of 21). The average loading and maintenance doses of the monotherapy were 108.3 mcg/kg (range, 100 to 128) and 15 mcg/kg/hr (range, 10 to 40) with 192 hrs duration (range, 1 to 916), respectively. With the combination, these are 97 mcg/kg followed by 14.5 mcg/kg/hr (range, 10 to 20) of morphine plus 7 mcg/kg (range, 4 to 10) loading dose of midazolam, with longer duration of sedation, 1176 hrs (range, 1 to 2918). Add to this, the need for MV and ICU stay was less in the monotherapy group compared with the combination regimen; 360 hrs (range, 5.00 to 1892) and 16 days (range, 1 to 89) versus 432 hrs (range, 77 to 1144) and 54 days (range, 31 to 138), respectively. The temperature and HR were of ranges of 34 to 38.5 °C, 70 to 246 bpm, 36 to 40.4 °C, and 63 to 214 bpm, for the monotherapy and combination regimens, respectively. The RR and MAP were 4 to 147 bpm and 10 to 82.3 mmHg and 6 to 91 bpm and 18.6 to 67.3 mmHg, respectively.

4.3.7 Neonates with sedation failure due to persistent agitation

With similar trend to the increased doses and alternative sedative failure pathways, none experienced persistent agitation in the morphine monotherapy group. Only one case was seen in the combination group. The patient received 50 mcg/kg loading dose of morphine, 20 mcg/kg/hr maintenance dose of morphine and 200

mcg/kg loading dose of midazolam. The durations of sedation and MV, and the NICU stay were 5, 6, and 6 days, respectively. Patient's temperature, HR, RR, and MAPs were 32 to 37.4 °C, 0 to 192 bpm, 46 to 74 bpm, and 34 to 43.3 mmHg, respectively.

Baseline clinical and probabilities inputs are summarized in **Table 4.12**.

Table 4.11. Summary of the ADRs associated with sedation success

The ADRs associated with sedation success	**Morphine monotherapy**		**Morphine plus midazolam**	
	Total number of patients	Cost per patient (QAR)	Total number of patients	Cost per patient (QAR)
Desaturation	13	42,711.49	4	7,426.81
Desaturation and urinary retention	3	42,721.49	1	7,437.17
Desaturation and MV adjustment	2	42,711.49	2	7,462.81
Desaturation, MV adjustment, and urinary retention	1	42,721.49	0	N/A
Desaturation and edema	1	42,847.7	2	7,426.81
Desaturation and joint stiffness	1	42,712.89	0	N/A
Desaturation, MV adjustment, and edema	0	N/A	2	7,428.75

*N/A: Not applicable

Table 4.12. Clinical and probability of outcomes of the morphine monotherapy vs. morphine plus midazolam combination

Study clinical outcome	**Probability with morphine monotherapy (n= 32)**	**Probability with morphine plus midazolam (n= 32)**
Sedation success	0.66 (n= 21)	0.34 (n= 11)
With ADRs	0.66 (n= 21)	0.34 (n= 11)
Without ADRs	0 (n= 0)	0 (n= 0)
Sedation failure	0.34 (n= 11)	0.66 (n= 21)
Increased dose	0 (n= 0)	0.38 (n= 8)
Therapy switch to alternatives	0 (n= 0)	0.24 (n= 5)
Withdrawal symptoms	0.18 (n= 2)	0.05 (n= 1)
Death	0.82 (n= 9)	0.28 (n= 6)
Persistent agitation	0 (n= 0)	0.05 (n= 1)

4.3.8 Cost of sedation

The base case analysis demonstrated that the morphine monotherapy was associated with a successful sedation level of 66%, compared to 34% with the combination, with an ICER of QAR 21,206.85 per additional case of sedation success. For those who received the morphine monotherapy, sedation success with ADRs (**Table 4.11**) was the main clinical outcome that influenced the total cost, and with the combination, it was the sedation failure due to increased doses that prevailed (**Table 4.13**). The weighted probabilities and costs for therapy outcomes are also given in **Table 4.13**. Cost components of the overall drug therapies are shown in **Table 4.14.**

Table 4.13. The weighted probabilities and costs of morphine monotherapy and morphine plus midazolam regimen

Therapy outcome	**Morphine monotherapy**			**Morphine plus midazolam**		
	Probability	Cost per patient (QAR)	Proportional cost (QAR)	Probability	Cost per patient (QAR)	Proportional cost (QAR)
Sedation success with ADRs	0.66	64,718.42	42,714.16	0.34	21847.35	7,428.10
Sedation success without ADRs	0	N/A	N/A	0	N/A	N/A
Sedation failure						
Sedation failure due to increased dose	0	N/A	N/A	0.25	66,254.51	18,634.08
Sedation failure due to need for alternatives	0	N/A	N/A	0.16	52,012.83	8,127.01
Sedation failure due to withdrawal symptoms	0.06	39,930.42	2,495.65	0.03	18,562.82	580.09
Sedation failure due to death	0.28	25,184.45	7,083.13	0.19	56,252.23	10,547.29
Sedation failure due to persistent agitation	0	N/A	N/A	0.03	11,175.32	349.23
Total cost per patient			**52,292.94**			**45,665.80**

*N/A: Not applicable

Table 4.14. Cost components of the overall therapy

	Cost (QAR)	**Cost (QAR)**
Cost component	**Morphine monotherapy**	**Morphine plus midazolam**
Sedation success with ADRs		
Initial sedation	27.58	19.05
MV	3,011.04	12,474.31
NICU stay	26,884.3	39,535.73
Hematological tests	210	390
Chemistry tests	3,127.27	4,300.00
Metabolic tests	1,140	1,140
Microbiology tests	1,644.44	1644.44
Blood gases tests	3,080	3,990
Virology tests	2,340	780
Urinalysis tests	144.44	N/A
Diagnostic tests	890.87	2,229.82
Oxygen therapy	211.54	211.54
Catheter	10	10
Medications to treat ADRs	16.19	1.94
Sedation failure due to increased dose		
Initial sedation	N/A	131.64
MV	N/A	11,614.02
NICU stay	N/A	33,210.01

Hematological tests	N/A	510
Chemistry tests	N/A	5,668.18
Metabolic tests	N/A	1,140
Microbiology tests	N/A	1,233.33
Blood gases tests	N/A	8,190
Virology tests	N/A	1,560
Urinalysis tests	N/A	N/A
Diagnostic tests	N/A	2,997.34
Medications to treat ADRs	N/A	N/A
Sedation failure due to receiving alternative		
Initial sedation	N/A	32.19
Alternative sedation	N/A	25.34
MV	N/A	12,044.16
NICU stay	N/A	24,775.72
Hematological tests	N/A	390
Chemistry tests	N/A	4,104.55
Metabolic tests	N/A	1,140
Microbiology tests	N/A	1,233.33
Blood gases tests	N/A	5,600
Virology tests	N/A	780
Urinalysis tests	N/A	N/A
Diagnostic tests	N/A	1,900.88
Medications to treat ADRs	N/A	N/A

Sedation failure due to withdrawal symptoms		
Initial sedation	1.97	3.94
MV	10,753.72	4,731.64
NICU stay	14,232.86	6,325.72
Hematological tests	300	210
Chemistry tests	5,472.73	1,368.18
Metabolic tests	570	570
Microbiology tests	2,055.56	1,233.33
Blood gases tests	5,600	2,660
Virology tests	N/A	780
Urinalysis tests	N/A	N/A
Diagnostic tests	943.59	680.01
Medications to treat ADRs	N/A	N/A
Sedation failure due to death		
Initial sedation	17.73	19.05
MV	6,452.23	7,742.68
NICU stay	8,434.29	28,465.72
Hematological tests	120	570
Chemistry tests	1,954.55	4,886.36
Metabolic tests	1,140	1,140
Microbiology tests	822.22	1,233.33
Blood gases tests	4,620	8,400
Virology tests	780	1,560

Urinalysis tests	N/A	N/A
Diagnostic tests	843.43	2,235.09
Medications to treat ADRs	N/A	N/A
Sedation failure due to persistent agitation		
Initial sedation	N/A	15.11
MV	N/A	2,580.89
NICU stay	N/A	3,162.86
Hematological tests	N/A	120
Chemistry tests	N/A	781.82
Metabolic tests	N/A	570
Microbiology tests	N/A	822.22
Blood gases tests	N/A	2,590
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A
Diagnostic tests	N/A	532.41
Medications to treat ADRs	N/A	N/A

*N/A: Not applicable

4.3.9 Sensitivity analysis

One-way sensitivity analyses. The model was insensitive to the changes in all the variables in the both groups.

Probabilistic sensitivity analyses: Tornado diagram is given in (**Figure 4.8**) which shows that the uncertainty in the sedation failure outcome in the morphine plus midazolam

group had the highest potential impact on the study outcome, while the sedation failure due to withdrawal symptoms in the combination group was the outcome that had the lowest influence the study outcome. Monto Carlo simulation illustrated that morphine remained more costly over the combination of morphine plus midazolam in 100% of cases, with 0% probability of having an economic advantage over the combination therapy. An "ICER" probability curve is shown in (**Figure 4.9**) as well.

Alternative scenario: A total of QAR 424,864.17 and QAR 890,817.09 resulted from the management of morphine monotherapy and the morphine and midazolam combination, respectively. Unlike in the HMC perspective scenario, morphine monotherapy dominated the combination of morphine plus midazolam combination with an economic saving of QAR 465,952.91 per patient.

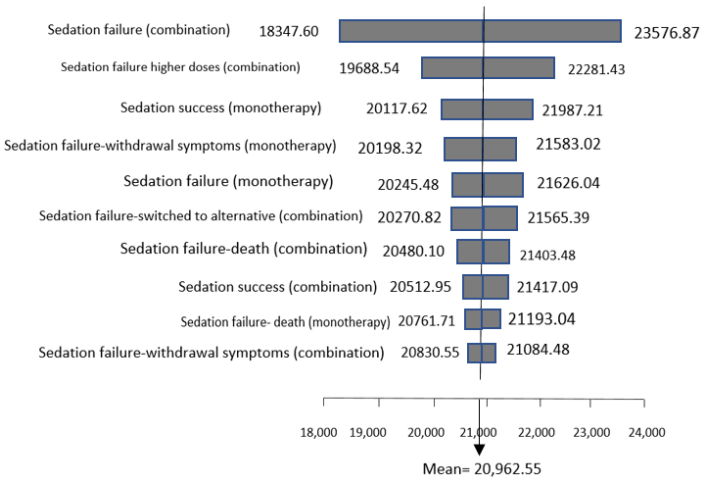


Figure 4.8. Tornado diagram of the variables as per their influence on the outcome of the Monte Carlo simulation

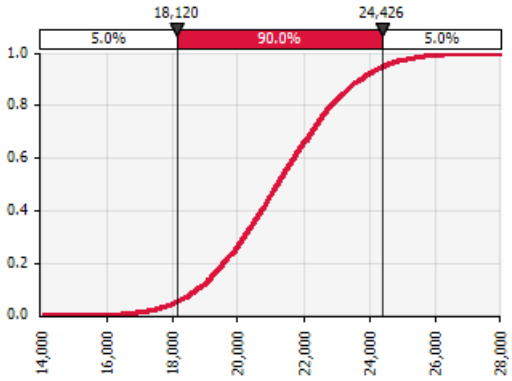


Figure 4.9. ICER probability curve with morphine monotherapy

4.4 Phase 2: Evaluation *3: fentanyl monotherapy versus fentanyl plus midazolam*

4.4.1 Demographic characteristics of the study participants

Out of 54 neonates included in the study, 39 received fentanyl monotherapy and 15 received fentanyl based analgesia using midazolam. Due to the small number of neonates with RDS admitted to the NICU, the sample size was not met. Both groups did not show any significant difference in terms of the baseline demographic characteristics (**Table 4.15**).

Table 4.15. Main baseline patient demographics

Characteristic	**Fentanyl Monotherapy (n= 39)**	**Fentanyl Plus midazolam (n= 15)**	**p-Value**
	No (%)	No (%)	
Gender			0.55
Male	19 (48.72)	9 (60)	
Female	20 (51.28)	6 (40)	
Gestational Age (weeks)			1
Pre-term (<37 weeks)	26 (66.67)	10 (66.67)	
Full-term (≥37 weeks)	13 (33.33)	5 (33.33)	
Birth Weight (g)			0.72
≥2500 g	16 (41.03)	5 (33.33)	
<2500 g and ≥1500 g	9 (23.08)	2 (13.34)	
<1500 g and ≥1000 g	6 (15.38)	3 (20)	
<1000 g	8 (20.51)	5 (33.33)	
Nationality			0.86
Qatari	17 (43.59)	7 (46.66)	
Arab	13 (33.33)	4 (26.67)	
Non-Arab	9 (23.08)	4 (26.67)	
			0.23
Type of delivery	21 (53.85)	5 (33.33)	
Vaginal	18 (46.15)	10 (66.67)	
Caesarean			
Received Vecuronium			0.19
Yes	10 (25.64)	7 (46.67)	
No	29 (74.36)	8 (53.33)	

4.4.2 Neonates with sedation success with or without ADRs

About 51% of neonates managed by fentanyl as a sole agent were successfully sedated (n= 7, responded with a reduced PIPP score and an= 13, maintained their scores) compared to 33% by fentanyl and midazolam regimen (n= 1 responded with reduced PIPP score and n= 4, maintained their scores) with RR of 1.22, 95% CI= (0.88-1.70), (P= 0.24). For those who received fentanyl monotherapy, the average loading and maintenance doses were 2.6 mcg/kg (range, 0.5 to 10) and 4.5 mcg/kg/hr (range, 0.6 to 10), respectively. On the other hand, the regimen of fentanyl and midazolam consisted of 3 mcg/kg (range, 2 to 5) followed by 2.6 mcg/kg/hr (range, 2 to 4) fentanyl and 95 mcg/kg (range, 30 to 160) followed by 20 mcg/kg/hr midazolam. Neonates sedated by fentanyl only needed shorter period of sedation compared to the combination regimen (48 hrs, range 1 to 150, versus 264 hrs, range 1 to 720). Also, the duration of MV was shorter in the monotherapy group (72 hrs, range 1 to 320, versus 312 hrs, range 51 to 936). Both groups had almost similar average duration of NICU stay (41 days, range 2 to 102, versus 43 days, range 16 to 66). The patients who were managed with the combination of fentanyl and midazolam, had vital signs ranges between 34.2 and 37.8 °C, 107 and 180 bpm, 22 and 187 bpm and 33 and 78.3 mmHg, of temperature, HR, RR, MAP, respectively. Respectively, these were between 36 and 39 °C, 95 and 196 bpm, 10 and 100 bpm, and 16.3 and 71 mmHg in patients treated by fentanyl only. The ADRs as self-resolved or requiring further management were noticed in both groups (**Table 4.16**).

4.4.3 Neonates with sedation failure due to receiving an increased dose

The majority of sedation failure was due to increased doses in the two groups (12 out of 19) in the monotherapy group versus (5 out of 10) in the combination group. In the fentanyl monotherapy, out of twelve patients, five patients received higher doses above the therapeutic range and the doses for the other seven patients remained within the normal range. All the five patients in the fentanyl plus the midazolam combination group received normal doses. The monotherapy management consisted of 5.4 mcg/kg (range, 3.50 to 12) followed by 6.40 mcg/kg/hr (range, 2 to 12) of fentanyl for 48 hrs (range, 1 to 168). Whereas, in the combination group, fentanyl was of initial 2.25 mcg/kg (range, 2 to 2.5) and a follow up 9.10 mcg/kg/hr (range, 2.50 to 20), combined with 117 mcg/kg (range, 50 to 200) followed by 15 mcg/kg/hr (range, 10 to 20) midazolam for 48 hrs (range, 2 to 170). Both the average duration of MV and stay at NICU were longer in the combination regimen compared with the sole therapy; 720 hrs (range, 82 to 2882) and 61 days (range, 12 to 151) versus 72 hrs (range, 4 to 148) and 19 days (range, 5 to 67 days), respectively. For fentanyl versus fentanyl based analgesia, the vital signs were about 36.5 to 38.7 °C, 76 to 202 bpm, 9 to 100 bpm, and 23.6 to 75.3 mmHg, versus 35.7 to 38.5 °C, 90 to 206 bpm, 6 to 100 bpm, and 25.3 to 92 mmHg, respectively, for the temperature, HR, RR and MAP.

4.4.4 Neonates with sedation failure due to receiving alternative

Five patients (50% of patients with sedation failure) in the combination group were switched to an alternative therapy after the initial fentanyl therapy, compared

with three patients (16%) in the monotherapy group. The average loading dose of fentanyl was 5.86 mcg/kg (range, 5 to 6.72), while the average maintenance dose was 3 mcg/kg/hr for 72 hrs (range, 1 to 124). In relation to the combination group, the patients were started on a loading fentanyl dose of 5.1 mcg/kg (range, 2 to 10) and continuous infusion of 10 mcg/kg/hr, and then received midazolam with 200 mcg/kg (range, 150 to 300) as loading dose followed by 19 mcg/kg/hr (range, 5 to 20) for 264 hrs (range, 1 to 1224). Patients in the monotherapy group received morphine (280 mcg/kg followed by 28.30 mcg/kg/hr, range 5 to 60) for 48 hrs (range, 15 to 70) as an alternative therapy. However, the duration of the alternative sedation was higher in the combination group (336 hrs, range 2 to 1128) using 210 mcg/kg (range, 120 to 300) followed by 12.2 mcg/kg (range, 5 to 30) of morphine. Both the MV duration and NICU stay were longer in the combination group with 1296 hrs (range, 27 to 4368) and 79 days (range, 8 to 153) versus 168 hrs (range, 36 to 354) and 25 days (range 7 to 48). The vital signs were 36.5 to 37.5 °C, 75 to 191 bpm (HR), 20 to 91 bpm (RR), 35 to 74.6 mmHg (MAP) with the monotherapy, and 36.5 to 38.6 °C, 68 to 208 bpm, 15 to 171 bpm and 20 to 100 mmHg, respectively, with the combination therapy.

4.4.5 Neonates with sedation failure due to withdrawal symptoms

Withdrawal symptoms were only developed in one patient in the fentanyl group who was given two doses of continuous infusions ranging from 3 to 4 mcg/kg/hr for an average 2 days. The duration of NICU stay was 12 days, and the duration of the MV was

6 days. The patient's vital signs were as follows: (36.5 to 37.4 °C), HR (110 to 195 bpm), RR (0 to 80 bpm), and MAP (15.6 to 62.3 mmHg).

4.4.6 Neonates with sedation failure due to death

No one in the combination therapy group died, while two cases of mortality were seen in the monotherapy group. These two patients received only maintenance dose of 5 mcg/kg/hr for an average of 10 days. The average duration of MV and NICU stay were equal to 12 days each. The ranges of vital signs while on sedation for the two patients were 36.5 to 37.6 °C (temperature), 0 to 195 bpm (HR), 24 to 65 bpm (RR), and 21.6 to 75.3 mmHg (MAP).

4.4.7 Neonates with sedation failure due to persistent agitation

The persistent agitation occurred only in one neonate sedated by fentanyl alone using 2 mcg/kg followed by 3.89 mcg/kg/hr for seven days. That patient received MV for about 8 days and stayed in the ICU for about 27 days. The patient had a temperature range of 36.4 to 37.3 °C, HR of 139 to 181 bpm, RR of 34 to 84 bpm, and MAP of 66 to 18.6 mmHg.

Baseline clinical and probabilities inputs are summarized in **Table 4.17**.

Table 4.16 Summary of the ADRs associated with sedation success

The ADRs associated with sedation success	Fentanyl monotherapy		Fentanyl plus midazolam	
	Total number of patients	Cost per patient (QAR)	Total number of patients	Cost per patient (QAR)
Desaturation	13	35,039.15	4	40,691.29
Desaturation and urinary retention	1	35,049.15	0	N/A
Desaturation and MV adjustment	2	35,039.15	0	N/A
Desaturation and edema	1	35,041.49	0	N/A
Desaturation, MV adjustment, and edema	3	35,041.49	1	40,481.72

*N/A: Not applicable

Table 4.17. Clinical outcomes and probabilities of fentanyl monotherapy vs. fentanyl plus midazolam combination used in the model

Study clinical outcome	Probability with fentanyl monotherapy (n= 39)	Probability with fentanyl plus midazolam (n= 15)
Sedation success	0.51 (n= 20)	0.33 (n= 5)
With ADRs	0.51 (n= 20)	0.33 (n= 5)
Without ADRs	0 (n= 0)	0 (n= 0)
Sedation failure	0.49 (n= 19)	0.67 (n= 10)
Increased dose	0.63 (n= 12)	0.5 (n= 5)
Therapy switch to alternatives	0.16 (n= 3)	0.5 (n= 5)
Withdrawal symptoms	0.05 (n= 1)	0 (n= 0)
Death	0.11 (n= 2)	0 (n= 0)
Persistent agitation	0.05 (n= 1)	0 (n= 0)

4.4.8 Cost of sedation

Compared to the combination of fentanyl and midazolam, fentanyl monotherapy had an economic advantage of QAR 43,811.83 per patient and a 51% successful sedation rate, compared to 33%. In the fentanyl monotherapy group, the sedation success associated with ADRs (**Table 4.16**) had the most impact on the total therapeutic cost, while the sedation failure due to receiving alternative mostly influenced the total cost of the combination regimen as shown in **Table 4.18**, where the weighted probabilities and costs for therapy outcomes are also given. Cost components of the overall therapy as summarized in **Table 4.19**.

Table 4.18. The proportional cost of fentanyl monotherapy and fentanyl plus midazolam regimen

Therapy outcome	**Fentanyl monotherapy**			**Fentanyl plus midazolam**		
	Probability	Cost per patient (QAR)	Proportional cost (QAR)	Probability	Cost per patient (QAR)	Proportional cost (QAR)
Sedation success with ADRs	0.51	68,706.12	35,040.12	0.33	123,179.94	40,649.38
Sedation success without ADRs	0	N/A	N/A	0	N/A	N/A
Sedation failure						
Sedation failure due to dose increased	0.31	20,600.71	6,338.68	0.33	71,778.10	23,926.03
Sedation failure due to switch to alternative (morphine)	0.08	21,991.79	1,691.68	0.33	73,534.35	24,511.45
Sedation failure due to possibility of withdrawal symptoms	0.03	10,874.15	278.82	0	N/A	N/A
Sedation failure due to death	0.05	18,762.99	962.20	0	N/A	N/A
Sedation failure due to persistent agitation	0.03	37,577.38	963.52	0	N/A	N/A
Total cost per patient			**45,275.03**			**89,086.86**

*N/A: Not applicable

Table 4.19. Cost components of the overall therapy

	Cost (QAR)	**Cost (QAR)**
Cost component	**Fentanyl monotherapy**	**Fentanyl plus midazolam**
Sedation success with ADRs		
Initial sedation	12	18.58
MV	1,290.45	5,591.93
NICU stay	21,612.86	22,667.15
Hematological tests	150	210
Chemistry tests	6,254.55	4,104.55
Metabolic tests	1,140	1,140
Microbiology tests	1,644.44	822.22
Blood gases tests	840	3,430
Virology tests	780	780
Urinalysis tests	72.22	N/A
Diagnostic tests	1,031.09	1,715.32
Oxygen therapy	211.54	211.54
Catheter	10	N/A
Medications to treat ADRs	2.34	1.97
Sedation failure due to increased dose		
Initial sedation	12.00	18.58
MV	1,290.45	12,904.46
NICU stay	10,015.72	32,155.73
Hematological tests	90	750

Chemistry tests	4,104.55	12,900
Metabolic tests	1,140	2,280
Microbiology tests	1,233.33	2,055.56
Blood gases tests	1,750	5,530
Virology tests	N/A	780
Urinalysis tests	N/A	144.44
Diagnostic tests	964.67	2,259.34
Medications to treat ADRs	N/A	N/A
Sedation failure due to receiving alternative		
Initial sedation	12	18.58
Alternative sedation	1,127.49	53.21
MV	3,011.04	23,228.03
NICU stay	13,178.58	41,644.30
Hematological tests	90	390
Chemistry tests	2,540.91	3,127.27
Metabolic tests	1,140	1,140
Microbiology tests	822.22	1,644.44
Blood gases tests	560	910
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A
Diagnostic tests	595.67	1,431.72
Medications to treat ADRs	N/A	N/A
Sedation failure due to withdrawal symptoms		

Initial sedation	6	N/A
MV	2,580.89	N/A
NICU stay	6,325.72	N/A
Hematological tests	N/A	N/A
Chemistry tests	N/A	N/A
Metabolic tests	570	N/A
Microbiology tests	822.22	N/A
Blood gases tests	N/A	N/A
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A
Diagnostic tests	569.31	N/A
Medications to treat ADRs	N/A	N/A
Sedation failure due to death		
Initial sedation	6	N/A
MV	5,161.78	N/A
NICU stay	6,325.72	N/A
Hematological tests	150	N/A
Chemistry tests	1172.73	N/A
Metabolic tests	1,140	N/A
Microbiology tests	1,233.33	N/A
Blood gases tests	2,730	N/A
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A

Diagnostic tests	843.43	N/A
Medications to treat ADRs	N/A	N/A
Sedation failure due to persistent agitation		
Initial sedation	12	N/A
MV	3,441.19	N/A
NICU stay	14,232.86	N/A
Hematological tests	N/A	N/A
Chemistry tests	13,095.45	N/A
Metabolic tests	3,990	N/A
Microbiology tests	N/A	N/A
Blood gases tests	70	N/A
Virology tests	N/A	N/A
Urinalysis tests	N/A	N/A
Diagnostic tests	2,735.87	N/A
Medications to treat ADRs	N/A	N/A

*N/A: Not applicable

4.4.9 Sensitivity analysis

One-way sensitivity analyses. The model was insensitive to the changes in all the variables in the both groups.

Probabilistic sensitivity analyses. The tornado diagram in **Figure 4.10** shows that the study outcome was mostly influenced by the uncertainty in sedation success in the

fentanyl plus midazolam. In the monotherapy regimen, however, the uncertainty in the sedation failure due to persistent agitation had the lowest impact on the outcome. The probabilistic curve illustrates that fentanyl alone achieves cost saving over the combination regimen in 100% of cases, as seen in **Figure 4.11**.

Alternative scenario. A net saving of QAR 380,871.79 per patient was associated with fentanyl monotherapy compared with the fentanyl and midazolam combination. The total cost of management for both groups were QAR 381,876.67 and QAR 762,748.45, respectively.

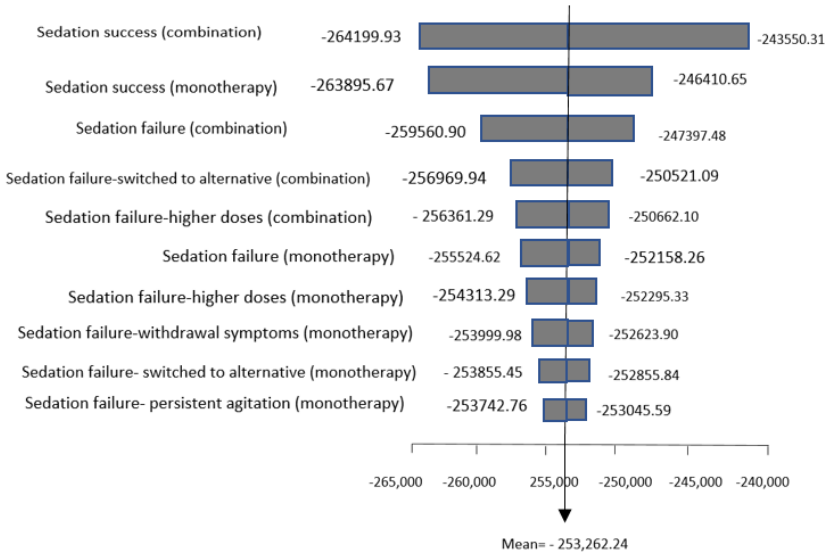


Figure 4.10. Tornado diagram of the variables as per their influence on the outcome of the Monte Carlo simulation

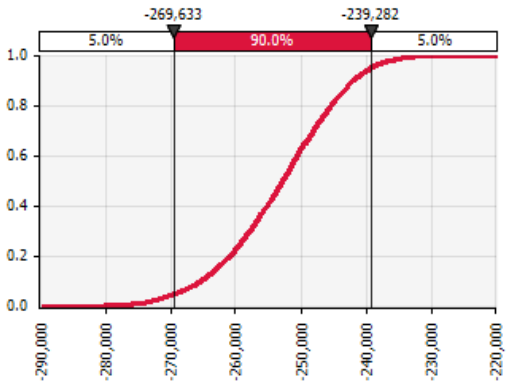


Figure 4.11. ICER probability curve with fentanyl plus midazolam

Chapter 5: Discussion

5.1 Phase 1: ***Systematic review of literature methods***

The first phase was a comprehensive systematic review of the literature designs and methods used in the evaluations of morphine and fentanyl in critically ill patients who are on MV due to respiratory diseases, especially in relation to the economic aspect of research. This guides future research, including, to the best possible, the current one, in relation to these two medications. This review assessed the quality of 33 publications, including RCTs, observational studies, and economic evaluations, with none published after 2014. Studies were characterized by a number of weaknesses and variations in the methodological strategies used, especially in relation to the economic evaluations. A medication performed differently in different studies with similar populations, providing a very limited aggregate evidence to guide decision makers in other settings.

In adult patients, the studies differed in their clinical outcome measures. While some only looked at sedation based on scales, others looked at the duration of MV. Here, while most studies used the optimal sedation level as the primary study outcome, some incorporated duration of therapy when made their conclusions. These variations in endpoint measures make it difficult to compare the results of the studies. Different types of scales were used, including RSS, RASS, Addenobrook, and SAS. In one 1993 study, the RSS scale of sedation was used, despite that this was not validated until the year 2000 (102, 103). In addition, the majority of studies in the review did not define the duration of sedation, which raises a concern in relation to the proper time of management. Findings of studies performed with short term follow up, for example,

cannot be applied to patients in need for over 24 hrs sedation since these may not reflect the routine clinical practice in ICU settings. As another example, remifentanyl was found to have similar sedation efficacy compared with morphine or fentanyl, except for the purpose of a shorter ICU stay. Generalizability was also limited because of the very high heterogeneity in the approaches used to evaluate similar medications as first-line sedatives for similar indications. Sedatives were different in the doses administered and in the comparators they were evaluated against. While most of these were within therapeutic range of dose, some were not. For example, Strom et al reported doses given as a range, including higher than 4 mg/kg/hr dose of propofol for more than 48 hrs. This dose however was found to be problematic as it increases the risk of propofol infusion syndrome without switching to alternatives (89). All of such methods variability, and the lack of justification of methods, raise the concern in relation to the validity and reliability of results and their interpretation.

In the neonate population, similar to the adults, different studies also made different conclusions in relation to the same drugs because of targeting different types of primary and secondary outcomes, though the level of sedation was a more common outcome here than in adults. Additional primary outcomes were duration of sedation, death and the neurodevelopmental functions. A variety of scales were used to assess sedation in studies, including PIPP, NIPS, COMFORT, NFCS, PCS and VAS, with the former two being more specific for pain than agitation. NFCS and PCS scales were not defined in the study in relation to targeted score levels, limiting the ability to know if the standard measures were used.

In the pediatric patients, each of the different studies used a different primary outcome, which included withdrawal symptoms and increased dosing. The level of sedation was measured via RSS, PICU and tracheal suctioning scales.

In all age groups, the intention to treat analysis in the RCT studies was not conducted in the majority of the studies (n= 23), especially where cases of subjects receiving alternatives after initial treatments existed, in one study which was RCT design (80). This is a confounder that affects the interpretation in clinical practices and should be considered. Also, the majority of the studies (n= 16) was not conducted specifically in patients with respiratory disorders, which were among patients with a variety of underlying diseases, such as congenital anomalies, cardiac disorders, neurological diseases, gastrointestinal diseases, infectious diseases, post operation patients, and respiratory disorders. Such studies, therefore, may not be representative of patients with pure respiratory disorders, seeing that different medical conditions may require different types of assessments due to differences in clinical outcomes. In all populations, the majority of studies were RCTs, which is best for achieving internal validity. When RCTs are infeasible due to ethical or resource availability, observational studies are a useful, efficient source of effectiveness data, especially due to the associated savings in time, effort and expenses. An observation of interest is the limited number of economic evaluations in studies. The pharmacoeconomics evaluation strengthens the multidimensional evidence in promoting the rational use of medications, and is now an integral type of research in practices. Less than a quarter of reviewed studies included any form of these.

The CONSORT checklist does not allow a quantitative overall quality scoring of RCTs. Threats to quality/validity, however, occurred in 0-100% of studies in relation to several items of validity (out of a total 18) measured. Especially high were problems in relation to important changes to methods after trial commencement (such as eligibility criteria), any changes to trial outcomes after the trial commenced, losses and exclusions after randomization for each group, and where the full trial protocol can be accessed, which were reported in none of the studies. To lesser extent, studies did poorly in relation to several items; how sample size was determined, with 44% of trials reporting this; explanation of any interim analyses and stopping guidelines (when applicable), with 28% reporting in studies; methods for additional analyses, such as subgroup analyses and adjusted analyses (only reported in 17% of studies); for binary outcomes, presentation of both absolute and relative effect sizes (only in 33% of studies); results of other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory (only in 17%); generalizability (external validity, applicability) of the trial findings (only discussed in 22% of studies); registration number, sources of funding and other support (in 17% of studies). These are mostly methods and results related topics, and while example weaknesses in relation to the sample size calculations and the outcome effect size estimations can limit the reliability and interpretability of results, the results of research will also less likely be generalizable beyond study populations due to the limitations in discussing the external validity of findings.

The quality of observational studies was less than ideal in 0-100% of studies with studies' scoring out of total 8 in several items of validity measured. All publications were lacking in relation to power analysis, any methods used to assess subgroups and interactions, explanation of how missing data were addressed, sensitivity analyses, the number of patients with missing data, follow-up time, category boundaries for continuous variables, translation of relative risk to absolute risk, other analyses (subgroups/interactions/sensitivity), and funding for studies. To a lesser extent, studies performed poorly in relation to the validity items relating to follow-up time, define all outcomes, exposures, predictors, potential confounders, and effect modifiers, and number of patients at each stage of study for example patients possibly eligible and confirmed eligible, with around 38% of studies reporting these; define potential confounders, how bias addressed, how quantitative variables addressed and how loss to follow up addressed, and directions or magnitude of bias and generalizability (only 13% of studies reported these); diagnostic criteria and use of a flow diagram (only found in 25% of studies). As with clinical trials, these weaknesses are mostly methods and results related, which in addition to translating to major problems in relation to reliability, validity of interpretation and the generalizability to other settings, also especially representing a problem in relation to controlling for selection, confounding and channeling bias.

The relatively limited pharmacoeconomics research is mostly due to the lack of proven treatments, where the utility of pharmacoeconomics becomes questionable, unless there is an advantage due to reduced adverse events. Of the seven economic

evaluations included in this review, four did not identify the exact respiratory disorder in the population for which they received MV, and none was conducted in neonates or pediatrics. Overall, the CHEERS checklist indicated that all of the included pharmacoeconomics evaluations were about poor in quality. The main shortcomings identified through the tool, to a large extent in the majority of studies, were related to the time horizon, analytical model, incremental costs and outcomes, characterizing uncertainty, the choice of model and characterizing heterogeneity, with 71% of the studies not reporting these; estimating resources and costs and assumptions (57% of trials did not report these); source of funding and conflict of interests (100% of studies did not report this).

Modeling analysis in economic evaluations simplifies the understanding of the effect and cost of the intervention. Out of the seven economic evaluations, however, only four included modeling. Out of these only one included the Markov modeling. This is anticipated as the Markov modeling is ideal for pharmacoeconomics evaluations in recurrent diseases, which the agitation due to MV is not. Markov extends the results of clinical studies and extrapolate intermediate endpoints into final outcomes, which was not necessary in the included studies. While variable in different studies, as discussed above, outcomes were mostly clinically relevant and short term in nature, which is not surprising due to the acute nature of the ICU setting. Except for a single study that did not clarify the type of setting (104), the included studies were evaluated from the perspective of hospital, including the direct medical type of costs. This is anticipated and is appropriate given that the non-health resources use and the work productivity are

minimally affected as a result of sedatives use in the ICU setting. An issue to discuss is the lack of clarity of costing methodology and components. Unclear description of cost methods and components leads to difficulty in having different settings benefiting from (and applying) results. Only the Barrientos et al and Cox et al studies provided detailed definitions of the costing methods. None of the studies, for instance, differentiated hospital charges from costs. This is as hospital charges are not ideal estimations of cost in the hospital setting as the latter uses it to compensate for the cost of other services in the setting, producing less robust conclusions. Another example is that only two studies reported the currency along with the financial year of cost values as part of analysis and modeling (87, 90), making it difficult to judge the need and appropriateness of time adjustment of cost. In one study, as another example, cost terminologies were misused, whereby the marginal or indirect cost were referred to as a secondary medical cost to include under the hospital perspective (76).

Further in relation to economic evaluations, while the sensitivity analysis, where uncertain input values are systematically changed to investigate robustness of study conclusions, is a corner stone in any economic evaluation, sensitivity analysis was conducted in only the Al MJ et al and Cox et al studies of the seven studies, which cannot be acceptable. And though conducted sensitivity analyses indicated studies robustness, in none of the studies justifications for the changes made were provided. This is added to the limited variability in the types of sensitivity analysis conducted. Most studies conducted one-way sensitivity analyses only. This, in the absence of

multivariate analyses, and even if interpreted correctly, can underestimate uncertainty (105).

To add, while studies included the analysis of adverse event costs, none of the studies modelled the discontinuations associated with adverse events. The impact of discontinuation is not clear in studies, which was also not part of sensitivity analyses conducted. Quantifying the side effects that are associated with discontinuations as equivalent to those that are not is not ideal when guiding decision making.

While it is attractive and easily acceptable to transfer findings from one setting to another, given the observed weaknesses and limited consistency in methodological approaches observed in the included studies, decision makers should maintain caution when making decisions based on the current available body of clinical and economic evidence in relation to the use of morphine and/or fentanyl with MV in ICUs. It seems that health outcomes and costs have limited transferability across settings in relation to ICU practices.

Based on observations in the current study, several priority recommendations can be made for the purpose of enhancing the quality of future research and evidence.

- Economic evaluations should more often be incorporated in studies, especially in neonates and pediatrics. Future work needs to ensure the availability of relevant research experiences and a better cost data, including secondary costs of interventions. Further to this, economic evaluations should more rely on the cost-effectiveness type of research as compared to the cost and cost-consequence

analyses, which is because, unlike with the latter two, the cost-effectiveness research does not only identify and measure outcomes and costs, but also compare among them. This is ideal for decision making as it enables conclusions in relation to whether an intervention's outcome justifies its cost.

- Details of studies should be better identified and presented, including in relation to RCTs, observational and economic evaluations. Main details include sample size and power analysis, follow up, generalizability, missing data, effect size, sensitivity analyses, cost and costing methods, and funding. There are several quality assessment checklists that can be used to guide methods reporting. These include CONSORT and JADAD for RCTs, and STROBE and GRACE for observational studies, Quality of Health Economic Studies and CHEERS for economic evaluations.
- Future work should include a head to head comparison of morphine with fentanyl in subjects with respiratory disorders, making it difficult to determine which agent is more efficacious. Current differences in design, reporting, assumptions, definitions, and estimations limit the ability to make head-to-head conclusions between these two medications.
- Adherence to methodological standards should be enhanced. Researchers should better follow good practice guidelines in relation to RCTs, observational studies, economic evaluations, and the clinically relevant. This relates to increasing the utilization of power and sample size calculations in studies and better controlling for systematic errors within study designs, in addition to eliminating errors that would affect generalizability to other settings. Also, to use reliable outcome

measures to evaluate sedation as well as justified tools for the assessing of these measures. This will improve uniformity among tools, i.e. scales, used in similar comparisons in literature. Also of relevance is to minimize the attrition rate, where data analyzed and reported are based on a sample size that is lower than that initially calculated to achieve power, which limits the validity of study results. In relation to economic evaluations, uncertainty will need to be accounted for in future research, which is by incorporating comprehensive sensitivity analyses in studies, in addition to incorporating (when meaningful) correlation effects of variables. Furthermore, future studies need to evaluate adverse events that results in discontinuation in isolation from those that do not, better guiding decision making based on secondary consequences and costs.

- Long-term outcomes should be incorporated more often, especially in the neonatal and pediatric populations. For example, out of all studies, only one looked at the neurodevelopmental function as an outcome. This however requires the better availability of long-term data, including cost, and the use of analytical models adopting longer term horizons. Here, future research should map beyond-ICU effects as well as associations between intermediate and final outcomes.
- Finally, the narrow scope of most study questions limit the ability of decision makers when trying to prioritize sedatives. Studies have mostly focused on how a drug performs based on an outcome or two at a time. Methods to better synthesize evidences that are multidimensional in nature should be developed and tested into the decision making. The multi-criteria decision analysis, for example,

> enables comparative single numerical measures that are based on a wide variety of the drug's multiple criteria, which may include efficacy, safety, formulation and dosing, adverse events, drug interactions, ability to combine, and costs (106).

To the best of our knowledge, this is the first systematic review to assess the methodological quality of studies in relation to fentanyl and morphine with MV in the ICU setting, identifying priority aspects for improving the quality of future research. Limitations in the review include the possibility that relevant studies were not included in this study due to the English restricted search. Studies may exist in other less common languages, such as French, Chinese and German. Authors however do not have the resources to translate the non-English language literature. Moreover, despite the comprehensive search conducted via several search engines in the study, additional literature search terms and/or combinations among them are possible and, hence, we cannot exclude the possibility that we missed relevant studies. Also, while different journals have varying publication criteria, all journals were weighted equally in this study, which can be associated with bias.

5.2 Phase 2: ***Comparative evaluation of sedatives***

While the HMC, as a public provider, is regulated by the Supreme Council of Health in Qatar, the drug formulary selection at the hospitals within HMC is determined by pharmacy and therapeutic (P&T) committees within the corporation, and this is where the context of this research is most relevant. While the HMC P&T committees traditionally judged medications based on safety and efficacy considerations mostly, due

to the notion of economic wealth, these have also been increasingly looking at the economic considerations of medications in recent year. Indeed, while unrestricted formularies are powerful, they are not economically practical or efficient, including in a rich country like Qatar.

The study is the first to compare the pharmacoeconomics of fentanyl monotherapy versus morphine monotherapy as sedatives in the management of mechanically ventilated neonates during the NICU stay worldwide. It is also the first study in the literature to evaluate each sedative alone against its combination therapy (morphine monotherapy versus morphine plus midazolam, and fentanyl monotherapy versus fentanyl plus midazolam) for the same population. All patients were followed up until NICU discharge. The study followed all the different patient pathways in the Qatari practice of managing the critically ill neonates who are on MV due to RDS.

Morphine monotherapy improved sedation and agitation levels over fentanyl monotherapy and the morphine plus midazolam combination, with relatively enhanced sedation success by a significant 36.76 % and 48.48% in favor to morphine, respectively. These corresponded to ICERs of QAR 490.36 and QAR 21,206.85 with morphine per the additional case of sedation success over the two comparators, respectively.

For the purpose of the current research, the evaluation of fentanyl versus its combination with midazolam is considered a pilot study as required sample size was not achieved in the study. As discussed above in section “3.2.6” of the methods, it is difficult to obtain records of WH patients from the period prior to October 2014, and due to the

fact that the first-line use of fentanyl was stopped in WH in December 2015, it is not possible to obtain patients sedated by fentanyl from any period afterwards.

Fentanyl monotherapy was found superior to its combination with midazolam, giving higher clinical effectiveness by 35.29% and a cost saving of QAR 43,535.89. The patient baseline characteristics did not differ between comparators in each of the evaluations except in the use of vecuronium in the morphine monotherapy and morphine plus midazolam combination (107, 108). In the Qatari NICU at WH, vecuronium is potentially administered in addition to sedatives prior to intubation to paralyze the critically ill neonates. This raises the concern that vecuronium can bias the sedation effect of sedatives. Nevertheless, while in the evaluations of the fentanyl versus its combination more patients in the combination regimen received the vecuronium, the outcome was in favor of the fentanyl monotherapy. Adjusting for the difference will only add to the advantage of the monotherapy.

For the purpose of the main clinical endpoint in this study, the PIPP score was used to reflect the sedation status of the patient in the Qatari NICU. It has been previously validated and used by studies to reflect the clinical and agitation status of the patient and neonate's need of sedation (70). There is a clear cut off criteria in relation to the PIPP score or the agitation level and the use of sedatives, which the current practice at the Qatari NICU follows.

The only study that directly compared between morphine and fentanyl as sole sedatives was conducted by Saarenmaa et al, who reported no significant difference between the

sedatives (58). In this study, however, morphine and fentanyl were evaluated in neonates with different disorders, including RDS, infection, persistent pulmonary hypertension (PPHN), NEC, and IVH. Since the study was not purely conducted in neonates with RDS, and stratification by underlying medical conditions was not performed, generalizability of the results to all population is limited. Patients with PPHN, for example, do not respond to the conventional type of ventilation, and they require high frequency ventilation in addition to inhaled nitric oxide with different range of doses of sedation (109). In another study, by Anand et al, morphine was compared to midazolam and placebo in which both morphine and midazolam reduced the level of pain compared to the placebo. Nevertheless, this was a pilot study, where the underlying diseases were not specified, with patients who would benefit from the study not identified (59).

Additional limitation in the studies by Saarenmaa et al, Wood et al, and Quinn et al (58, 61, 62), which were conducted in preterm infants, is that the level of sedation was based on measuring the hormonal response levels of adrenaline and noradrenaline. However, these are not applicable or accurate indicators of sedation in preterm neonates as the level of them changes with maturity, where with the increase in age the adrenaline level is increased as the noradrenaline is converted to it. The level is also not specific to the pain, they can be affected by other factors such as the RDS itself (62). For instance, in the included studies by Saarenmaa et al and Quinn et al no change in the levels of these hormones was observed in any of the treated groups, except the noradrenaline level in the morphine monotherapy group in the Quinn et al study (58,

62), while in the Wood et al study the adrenaline level was reduced in neonates sedated with morphine and diamorphine, and noradrenaline was only reduced in the morphine group (61).

In our study, neonates who received morphine monotherapy or fentanyl monotherapy experienced greater success compared to the combination regimen with either of them. The addition of midazolam to either morphine or fentanyl did not show any advantages in terms of achieving better sedation, instead longer duration of sedation, extended NICU stay and longer MV were required compared to the monotherapy regimens. The results of this study indicate the limitation of the HMC practices regarding the addition of a combination therapy to enhance sedation, which is based on personal points of views, clinical judgment, and individual experiences. Pain management in neonates that is not evidence based is not an issue only in Qatar but also in most of the clinical NICU practices, where limited consensus on the use of opioids as sedatives is common, including the combination with other sedatives (110).

An important clinical endpoint was the evaluation of the sedation and non-sedation related mortality associated with the study sedatives. The mortality rate was higher in patients managed with morphine monotherapy compared to fentanyl monotherapy or the morphine plus midazolam combination. Large differences in the duration of sedation were noticed among the groups (12 days with morphine over fentanyl, and 41 days with morphine over its combination). In the third study, none died in the midazolam plus fentanyl group while two cases were reported in the fentanyl

monotherapy group. One may suggest that mortality increases with longer durations of therapy or decreases with the use of midazolam. The confirmation of this however, is not feasible is this study. This is especially when one looks at the RCT by Anand et al, for example, where mortality rate was found to be comparable based on similar durations of sedation between study groups. To note however, while death was reported by Anand et al in two cases with placebo, one with midazolam, and none with morphine, no doses of sedatives were specified in the study (59). In another RCT by Quinn et al, mortality among study groups, i.e. morphine alone, pancuronium alone, morphine plus pancuronium, was also measured based on equal duration of sedation, where no significant differences were observed. Important, is that the mortality was not clearly defined in this study (62).

The withdrawal symptoms outcome measure in the current study was not measured in any of the previous neonatal studies. The interest in this was based on the fact that withdrawal symptoms from an opioid are considered one of the most important factors that cause abnormalities in release of noradrenaline in the brain that is responsible for controlling the alertness, respiration, and muscle tone, which lead to opioid's dependence (111). In our study, this was seen in patients receiving morphine monotherapy, while none experienced it in the fentanyl monotherapy group. Although one day of sedation by morphine may not be considered prolonged enough to cause withdrawal symptoms, other associated etiologies cannot be ruled out. Also in this study, withdrawal symptoms were higher with the monotherapies compared to their

combinations. This is expected since midazolam has proven to be effective in treatment of seizure and agitation (112).

Persistent agitation was found to be more associated with fentanyl monotherapy than with the morphine monotherapy. While the addition of midazolam to fentanyl seemed to prevent the agitation in all patients, the midazolam plus morphine was associated with persistent agitation in one patient. The reason behinds this could be that midazolam, which is indicated to treat agitation, was only given to the patient as loading dose (with no follow up maintenance doses), despite that the patient was on maintenance doses of morphine for 5 days.

The total cost of morphine monotherapy was higher compared to that with the fentanyl monotherapy. Looking at the factors that contributed to the overall cost management of morphine monotherapy, sedation success that is associated with ADRs was the most influential, followed by sedation failure due to death. With fentanyl, these were the success that is associated with ADR, followed by sedation failure due to receiving increased doses. Out of all of these, the success associated with ADRs was associated with the highest cost per patient. Taking this into consideration, and that morphine was associated with more of the success associated with ADRs than fentanyl, translated into a higher cost with morphine. The justification of the higher ADRs with morphine is mostly the longer duration of sedation, MV, and NICU stay in the morphine monotherapy group. This surely contributes to the increased total cost of therapy,

especially as the MV and NICU stay durations were found to be more expensive (QAR 430.15 and QAR 527.14 per day, respectively) compared to the other variables.

Although the morphine plus midazolam regimen was associated with longer durations of MV, NICU stay and sedation compared to the morphine alone, the total cost of the former was lower. However, the cost per patient in the success with ADRs pathway was over five times higher with morphine versus the morphine plus midazolam combination, in addition to that the probability of success with ADRs is higher with morphine than with its combination regimen. It seems that this led to a higher morphine cost that surpassed the high cost of the longer duration of MV, NICU and sedation with the combination.

With improved agitation and better cost saving (QAR 45,275.03 versus QAR 89,086.86) fentanyl monotherapy demonstrated dominance over its combination with midazolam, keeping in consideration that this imporved agitation connot be confirmed due to limited sample size. Success with ADRs and the failure due to switching to alternatives were the most two contributing outcomes in the total cost of both fentanyl and fentanyl plus midazolam. But while the proportional cost of the success with ADRs was about QAR 4,400 more with fentanyl per patient, the proportional cost of the failure due to a switch to an alternative was about QAR 22,819 higher with the combination. This, taking in consideration the effect of a longer duration in the combination therapy, which allows for more utilization of MV that leads to the longer stay at the NICU, justifies the overall cost saving associated with the fentanyl monotherapy.

Based on the above, it seems that the addition of midazolam was associated with reduced incidence of ADRs associated with morphine or fentanyl. This finding is supported by RCT studies by Kim et al and Mahajan et al that suggested that treatment with midazolam did not yield desaturation (113, 114). As demonstrated in our study, desaturation contributes the most to the ADRs in the monotherapy groups.

The sensitivity analyses demonstrated robustness of the all the economic outcomes of evaluations to all variables, except in the morphine versus fentanyl monotherapies, where sensitivity was demonstrated to the cost of MV, NICU stay during sedation success, and NICU stay during receiving increased doses in the fentanyl monotherapy. The variability in these variables therefor, will need to be taken in consideration by decision makers when anticipating outcomes, including for the purpose of generalizability to other settings.

Also, it seems that doses of administered therapies were occasionally below or above the therapeutic range. As in many other practices, in the Qatari NICU, the sedatives are first ordered through the physicians. Then, the dose, frequency and preparation are verified by the inpatient pharmacy, followed by administration and signing the patient's medication record on Cerner by nurses. Sensitivity analysis, however, did not demonstrate major influences on economic results by the dosing variability.

Interestingly, not one patient in all the study groups reported sedation success without ADRs, at least experiencing one self-managed ADR which did not require further management. Sedation success associated with ADRs that required further management

was the clinical outcome that influenced the total therapeutic cost the most for each of the different therapies in all of the evaluations, except the morphine plus midazolam combination. This is not unexpected as all the patients who were successfully sedated by the study sedatives developed at least one ADR that needed further management. The outcome that contributed the most towards the cost of the morphine and midazolam combination was the failure due to receiving the increased dose, which particularly was prevalent with the combination.

The cost of the alternative therapy was higher in the morphine monotherapy group when compared to the fentanyl therapy. This was as few number of patients switched to fentanyl in the morphine group as compared to those who switched to the more expensive morphine in the fentanyl group. As compared to the morphine combination, none in the morphine monotherapy group switched to an alternative therapy, making the cost of alternative therapy higher in the combination therapy. As compared to the fentanyl monotherapy, up to half the patients who received its combination with midazolam failed therapy due to receiving alternative therapies, leading to a higher cost with the combination. While it is important for decision makers to not only consider the initial medication costs, but also the cost of alternatives, in the current evaluations, it seems that the costs of the initial therapies were high enough to minimize the influence of alternative therapies on the comparative overall cost of therapies.

The RCTs are considered an ideal source of evidence for pharmacoeconomics evaluations due to well established methodology and internally valid data, including due

to random assignments of patients, blinding assessment, and controlling confounding factors that minimize bias (115). Nonetheless, RCTs have several drawbacks which limit their use in pharmacoeconomics evaluations. RCTs have limited external validity and, hence, limited generalizability of results to other settings due to the controlled design of studies in relation to the patients' criteria and medication regimens (116). Also, they can be limited by a pre-defined specific duration that might not include important, though maybe infrequent, consequences of therapies in real life, which are associated with cost. Such consequences and outcomes can include mortality, needs for higher doses, switching to alternatives, and possibility of withdrawal symptoms. Such limitations have generally led researchers to also depend on the observational cohort retrospective studies, which are also considered relatively inexpensive and require less time, effort and resource consumption. Also important, is that cohort studies are better suited to measure effectiveness as per real practices when compared to RCTs. All this is particularly important to consider for the purpose of the current research, where the objective is to enhance decision making that is especially based on local evidence and practices with the study sedatives, in addition to following patients up until NICU discharge, which represent more realistic NICU costs in relation to medications and/or procedures.

Another strength in the current study relates to the fact that the decision analytic modeling used is the most comprehensive in the literature so far, reflecting all the possible endpoints of sedatives which accurately represented the overall cost of sedation. None of previous studies performed in the adult population, where all

sedation-based economic evaluations were conducted, assessed the impact of sedatives in mechanically ventilated patients. Cox et al, for example, who conducted a CEA in the adult population, performed a modeling that only looked at survival/mortality in the ICU and specific ADRs, which consequently affected the total cost of sedatives in the ICU (90). Sedative regimens are not only associated with adjusted agitation status, but also adverse reactions, adjusted dosing, alternatives, withdrawal symptoms, and death, added to the duration of therapies. The latter is particularly important in affecting the overall resource utilization, relating to sedation duration, MV, and NICU stay. Such outcomes of sedation were all considered in the current model.

Clinicians, including consultants, physicians, and clinical pharmacists target sedatives that decrease the overall resources. The results of this study are important for stakeholders and policy makers given an anticipated increase in the ICU expenditures over the coming years (117). This is particularly of value due to the limited number of high quality CEA studies in literature in relation to guiding the management of sedation in the ICU patients (118). Through the alternative scenario analysis, the study results do not only represent the perspective of the governmental HMC setting but also the Qatari private setting, which is of additional strength to the study. Furthermore, it is common that the strength of retrospective studies is jeopardized by missing data in records. This was not an issue faced in this study, especially in relation to the PIPP scores, doses, duration and ADRs, further adding to the study strength.

The main limitation is this research was extracting the costs of several variables for the HMC sources. Due to the nature of this governmental corporation, the costs for few resources were not available and, thus, had to be extracted from alternative external sources, i.e. AH, the major private hospital in Qatar. The costs, however, were to the best possible adjusted as discussed in the methods section of this thesis. Another major limitation was the limited number of patients who were sedated by fentanyl within the study duration compared to morphine as its first-line use stopped in 2015. Hence, power was not attained for the purpose of the evaluation of it against its combination.

Follow up studies are needed to evaluate the effect of morphine with or without midazolam on the neurological outcomes in mechanically ventilated patients with RDS after NICU discharge, to assess the fine, gross, social, and cognitive motor as clarified in previous studies (58, 60). Due to time limits in the current research, the study did not measure these long-term outcomes, especially as these will need to include patients with RDS in the neonatal clinic at Al-Rumila Hospital in Qatar, to which neonates who have HIE or those less than 32 weeks are transferred, in which the fine and gross motor should be evaluated over two years, followed by assessment of the social and cognitive motor after another two years. Also, future clinical studies are highly recommended to measure associations of interest in relation to the sedation use and its consequences. These include the sedation-related mortality and the duration of sedation, the gestational age and the birth weight with the sedation use in neonatal patients. For example, Saarenmaa et al and Thummel et al found that the plasma clearance of

fentanyl and morphine increases with the progress of gestational age (107, 108).

Chapter 6: Conclusion

The current research is the first CEA in the literature to evaluate the economic and clinical outcomes of morphine and fentanyl as standalone or in combination with midazolam in mechanical ventilation due to RDS in neonates. The research also includes the first systematic review to assess the methodological quality of studies, including the pharmacoeconomics, evaluating the use of morphine and fentanyl in all populations undergoing MV. The control of agitation in RDS neonates was statistically significantly higher with morphine monotherapy than with either fentanyl monotherapy or the morphine plus midazolam combination. The clinical advantage of morphine, however, comes at a comparatively higher cost, in only 2% cases. Associated with higher effectiveness and lower therapy cost, fentanyl monotherapy demonstrated dominance over its combination with midazolam. The higher effectiveness of fentanyl over its combination however cannot be robustly interpreted as this was not based on power and sample size calculations.

The current research confirms the appropriateness of recent switching from sedative fentanyl to morphine monotherapies in NICU settings of HMC, taking in consideration local decision making and budget limits. The study, however, contradicts the current Qatari practice of utilizing the midazolam combination, especially with morphine, where the addition of midazolam is commonly believed to enhance effectiveness.

References

1. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. American Journal of Respiratory and Critical Care Medicine. 1994;149(3Pt1):818-24.
2. Frutos-Vivar F, Ferguson ND, Esteban A. Epidemiology of acute lung injury and acute respiratory distress syndrome. Seminars in Respiratory and Critical Care Medicine. 2006;27(4):327-36.
3. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. The Journal of the American Medical Association. 2012;307(23):2526-33.
4. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deboisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. The New England Journal of Medicine. 2006;354(24):2564-75.
5. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. American Journal of Respiratory Cell and Molecular Biology. 2005;33(4):319-27.
6. Villar J. What is the acute respiratory distress syndrome? Respiratory Care. 2011;56(10):1539-45.
7. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, Aramburu JA, Nájera L, Ferguson ND, et al. Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Annals of Internal Medicine. 2004;141(6):440-5.
8. Bachofen M, Weibel ER. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. The American Review of Respiratory Disease. 1977;116(4):589-615.
9. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319-23.
10. Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, et al. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. Critical Care Medicine. 2007;35(12):2755-61.
11. Matthay MA, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. Annual Review of Pathology. 2011;6:147-63.
12. Pubmed Health. *Respiratory distress syndrome*. 2014 [updated June 11, 2014; cited 2017 February 13]. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0062982/.
13. Battisti O, Bertrand J-M, Rouatbi H, Escandar G. Lung compliance and airways resistance in healthy neonates. Pediatrics & Therapeutics. 2012;2(2):1-4.
14. Martin R. *Pathophysiology, clinical manifestations, and diagnosis of respiratory distress syndrome in the newborn*. 2016 [cited 2017 February 13]. Available from: https://0-www.uptodate.com.mylibrary.qu.edu.qa/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-respiratory-distress-syndrome-in-the-newborn?source=search_result&search=RDS%20newborn&selectedTitle=1~150.
15. Jobe AH, Ikegami M. Biology of surfactant. Clinics in Perinatology. 2001;28(3):655-69.
16. Frank L, Sosenko RI. Development of lung antioxidant enzyme system in late gestation: possible implications for the prematurely born infant. The Journal of Pediatrics. 1987;110(1):9-14.

17. Turunen R, Nupponen I, Siitonen S, Repo H, Andersson S. Onset of mechanical ventilation is associated with rapid activation of circulating phagocytes in preterm infants. Pediatrics. 2006;117(2):448-54.
18. Jobe AH, Hillman N, Polglase G, Kramer BW, Kallapur S, Pillow J. Injury and inflammation from resuscitation of the preterm infant. Neonatology. 2008;94(3):190-6.
19. Carlton DP, Albertine KH, Cho SC, Lont M, Bland RD. Role of neutrophils in lung vascular injury and edema after premature birth in lambs. Journal of Applied Physiology. 1997;83(4):1307-17.
20. Brus F, van Oeveren W, Okken A, Oetomo SB. Number and activation of circulating polymorphonuclear leukocytes and platelets are associated with neonatal respiratory distress syndrome severity. Pediatrics. 1997;99(5):672-80.
21. Roumiantsev S. Invasive mechanical ventilation in premature infants: where do we stand today? Journal of Pulmonary & Respiratory Medicine. 2013;S13(002):1-8.
22. Saboute M, Kashaki M, Bordbar A, Khalessi N, Farahani Z. The incidence of respiratory distress syndrome among preterm infants admitted to neonatal intensive care unit: A retrospective study. Open Journal of Pediatrics. 2015;5(04):285.
23. World Health Organization. *Preterm birth*. 2016 [cited 2017 May 13]. Available from: http://www.who.int/mediacentre/factsheets/fs363/en/.
24. Wang C, Guo L, Chi C, Wang X, Guo L, Wang W, et al. Mechanical ventilation modes for respiratory distress syndrome in infants: a systematic review and network meta-analysis. Critical Care. 2015;19:108.
25. Hillberg RE, Johnson DC. Noninvasive ventilation. The New England Journal of Medicine. 1997;337(24):1746-52.
26. Mehta S, Hill NS. Noninvasive ventilation. American Journal of Respiratory and Critical Care Medicine. 2001;163(2):540-77.
27. Girou E, Schortgen F, Delclaux C, Brun-Buisson C, Blot F, Lefort Y, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. The Journal of the American Medical Association. 2000;284(18):2361-7.
28. Girou E, Brun-Buisson C, Taille S, Lemaire F, Brochard L. Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. The Journal of the American Medical Association. 2003;290(22):2985-91.
29. Meduri GU, Conoscenti CC, Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest. 1989;95(4):865-70.
30. Brochard L, Isabey D, Piquet J, Amaro P, Mancebo J, Messadi AA, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. The New England Journal of Medicine. 1990;323(22):1523-30.
31. Garpestad E, Brennan J, Hill NS. Noninvasive ventilation for critical care. Chest. 2007;132(2):711-20.
32. Sassoon CS. Intermittent mandatory ventilation. In: Tobin MJ, editor. Principles & practice of mechanical ventilation. 2nd ed. NY: McGraw-Hill; 2006.
33. PubChem. *Pancuronium bromide* [cited 2017 January 17]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/27350#section=Interactions.
34. Benyamin R, Trescot A, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11:S105-S20.
35. Aranda JV, Carlo W, Hummel P, Thomas R, Lehr VT, Anand KJ. Analgesia and sedation during mechanical ventilation in neonates. Clinical Therapeutics. 2005;27(6):877-99.

36. Hall RW, Boyle E, Young T. Do ventilated neonates require pain management?. Seminars in Perinatology. 2007;31(5):289-97.
37. Bootman JL, Townsend RJ, McGhan WF. Introduction to pharmacoeconomics. Principles of Pharmacoeconomics. OH: Harvey Whitney Books Company;1996.
38. *Opium, morphine and heroin* [cited 2017 February 10]. Available from: http://www.ch.ic.ac.uk/rzepa/mim/drugs/html/morphine_text.htm.
39. Walser D. *Midazolam. A short-acting hyponotic-sedative drug with anxiolytic and amnestic properties*. [cited 2017 February 10] Available from: https://newdrugapprovals.org/2014/01/10/midazolam/
40. DrugBank. *Fentanyl*. 2016 [Available from: https://www.drugbank.ca/drugs/DB00813.
41. Townsend RJ. Postmarketing drug research and development. Drug Intelligence & Clinical Pharmacy. 1987;21(2):134-6.
42. International Narcotics Control Board for 2014. *Analysis of the world situation*. 2014 [cited 2017 February 10] Available from: https://www.incb.org/documents/Publications/AnnualReports/AR2014/English/AR_2014.pdf.
43. PubChem. *Diacetylmorphine*. 2017 [cited 2017 January 17]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/5462328#section=Top.
44. Trask LS. Chapter 1. Pharmacoeconomics: principles, methods, and applications. 2016 [cited 2017 February 13] Available from: http://accesspharmacy.mhmedical.com/content.aspx?bookid=462&sectionid=41100767#7965069.
45. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig I-L, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Critical Care. 2005;9(3):R200-10.
46. McGhan WF, Rowland CR, Bootman JL. Cost-benefit and cost-effectiveness: methodologies for evaluating innovative pharmaceutical services. American Journal of Health-System Pharmacy. 1978;35(2):133-40.
47. Bootman JL, Wertheimer AI, Zaske D, Rowland C. Individualizing gentamicin dosage regimens in burn patients with gram-negative septicemia: A cost-benefit analysis. Journal of Pharmaceutical Sciences. 1979;68(3):267-72.
48. Bootman JL, Townsend RJ. Principles of pharmacoeconomics: Harvey Whitney Books; 1991.
49. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford University Press; 2015.
50. Arnold RJ. Pharmacoeconomics: from theory to practice. FL: CRC Press; 2016.
51. Pettiti D. Meta-analysis, decision analysis and cost-effectiveness analysis. Methods for quantitative synthesis in medicine. London: Oxford University Press; 1994.
52. Silbermann M. Current trends in opioid consumption globally and in Middle Eastern countries. Journal of Pediatric Hematology/Oncology. 2011;33 Suppl 1:S1-5.
53. Central Intelligence Agency. *The World Factbook*. 2017 [updated 12 January; cited 2017 February 14]. Available from: https://www.cia.gov/library/publications/the-world-factbook/geos/qa.html.
54. World Atlas. *Where Is Qatar?*. 2015 [cited 2017 February 14]. Available from: http://www.worldatlas.com/as/qa/where-is-qatar.html.
55. The World Bank. *Health expenditure, public (% of total health expenditure)*. 2016 [cited 2017 February 14]. Available from: http://data.worldbank.org/indicator/SH.XPD.PUBL.

56. Hamad Medical Corporation. *About US.* 2016 [cited 2016 November 20]. Available from: https://microsites.harveynash.com/hmc/about-us/.
57. World Health Organization. *Health System Profile Qatar* [cited 2017 May 15]. Available from: http://apps.who.int/medicinedocs/documents/s17307e/s17307e.pdf.
58. Saarenmaa E, Huttunen P, Leppaluoto J, Meretoja O, Fellman V. Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial. The Journal of Pediatrics. 1999;134(2):144-50.
59. Anand K, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Archives of Pediatrics & Adolescent Medicine. 1999;153(4):331-8.
60. Grunau RE, Whitfield MF, Petrie-Thomas J, Synnes AR, Cepeda IL, Keidar A, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18months in preterm infants. Pain. 2009;143(1):138-46.
61. Wood CM, Rushforth JA, Hartley R, Dean H, Wild J, Levene MI. Randomised double blind trial of morphine versus diamorphine for sedation of preterm neonates. Archives of Disease in Childhood Fetal and Neonatal Edition. 1998;79(1):F34-9.
62. Quinn MW, Otoo F, Rushforth JA, Dean HG, Puntis JW, Wild J, et al. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. Early Human Development. 1992;30(3):241-8.
63. Orsini AJ, Leef KH, Costarino A, Dettorre MD, Stefano JL. Routine use of fentanyl infusions for pain and stress reduction in infants with respiratory distress syndrome. The Journal of Pediatrics. 1996;129(1):140-5.
64. Guinsburg R, Kopelman BI, Anand KJ, de Almeida MF, Peres Cde A, Miyoshi MH. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. The Journal of Pediatrics. 1998;132(6):954-9.
65. Moerer O, Plock E, Mgbor U, Schmid A, Schneider H, Wischnewsky MB, et al. A German national prevalence study on the cost of intensive care: an evaluation from 51 intensive care units. Critical Care. 2007;11(3):R69.
66. Lorette G, Maruani A. [The CONSORT statement (Consolidated Standards Of Reporting Trials)]. Annales de Dermatologie et de Venereologie. 2013;140(6-7):431-5.
67. Noah N. The STROBE Initiative Strengthening the Reporting of Observational studies in Epidemiology (STROBE). Epidemiology and Infection. 2008;136(7):865.
68. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)-explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value in Health: the Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013;16(2):231-50.
69. Hamad Meical Corporation. *Neonatal Intensive Care Unit (NICU)*. 2016 [cited 2016 November 20]. Available from: https://www.hamad.qa/EN/hospitals-and-services/Womens-Hospital/Hospital-Services/Clinical-Departments/Neonatal-Intensive-Care-Unit-(NICU)/Pages/default.aspx.
70. Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. The Clinical Journal of Pain. 1996;12(1):13-22.
71. Arnold JH, Truog RD, Orav EJ, Scavone JM, Hershenson MB. Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. Anesthesiology. 1990;73(6):1136-40.

72. World Health Organization. *Infant, Newborn*. 2017 [cited 2017 February 20]. Available from: http://www.who.int/topics/infant_newborn/en/.
73. The United Nations Children's Fund. *The neonatal period is the most vulnerable time for a child* [updated January 2016; cited 2017 February 20]. Available from: https://data.unicef.org/topic/child-survival/neonatal-mortality/.
74. Ministry of Public Health, Qatar 2017 [cited 2017 Febraury 27]. Available from: http://eservices.moph.gov.qa/FARD/docs/293.pdf.
75. Al-Ahli Hospital. *History of Al-Ahli Hospital* [cited 2017 February 20]. Available from: http://www.ahlihospital.com/index.php/about-us/history-of-al-ahli-hospital/
76. Carrasco G, Molina R, Costa J, Soler JM, Cabre L. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis. Chest. 1993;103(2):557-64.
77. Swart EL, van Schijndel RJ, van Loenen AC, Thijs LG. Continuous infusion of lorazepam versus medazolam in patients in the intensive care unit: sedation with lorazepam is easier to manage and is more cost-effective. Critical Care Medicine. 1999;27(8):1461-5.
78. Karir V, Hough C, Daniel S, Caldwell E, Treggiari M. Sedation practices in a cohort of critically ill patients receiving prolonged mechanical ventilation. Minerva Anestesiologica. 2012;78(7):801-9.
79. Jarman A, Duke G, Reade M, Casamento A. The association between sedation practices and duration of mechanical ventilation in intensive care. Anaesthesia and Intensive Care. 2013;41(3):311-5.
80. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. The Journal of the American Medical Association. 2009;301(5):489-99.
81. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. Southern Medical Journal. 2004;97(5):451-6.
82. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. The New England Journal of Medicine. 2000;342(20):1471-7.
83. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Critical Care Medicine. 2006;34(5):1326-32.
84. Richman PS, Baram D, Varela M, Glass PS. Sedation during mechanical ventilation: a trial of benzodiazepine and opiate in combination. Critical Care Medicine. 2006;34(5):1395-401.
85. Anand KJS, Clark AE, Willson DF, Berger J, Meert KL, Zimmerman JJ, et al. Opioid Analgesia in Mechanically Ventilated Children: Results from the multicenter MOTIF study. Pediatric Critical Care Medicine: a Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2013;14(1):27-36.
86. Tedders KM, McNorton KN, Edwin SB. Efficacy and safety of analgosedation with fentanyl compared with traditional sedation with propofol. Pharmacotherapy. 2014;34(6):643-7.
87. Al MJ, Hakkaart L, Tan SS, Bakker J. Cost-consequence analysis of remifentanil-based analgo-sedation vs. conventional analgesia and sedation for patients on mechanical ventilation in the Netherlands. Critical Care . 2010;14(6):R195.
88. Rozendaal FW, Spronk PE, Snellen FF, Schoen A, van Zanten AR, Foudraine NA, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. Intensive Care Medicine. 2009;35(2):291-8.

89. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375(9713):475.
90. Cox CE, Reed SD, Govert JA, Rodgers JE, Campbell-Bright S, Kress JP, et al. Economic evaluation of propofol and lorazepam for critically ill patients undergoing mechanical ventilation. Critical Care Medicine. 2008;36(3):706-14.
91. Barrientos-Vega R, Sanchez-Soria MM, Morales-Garcia C, Cuena-Boy R, Castellano-Hernandez M. Pharmacoeconomic assessment of propofol 2% used for prolonged sedation. Critical Care Medicine. 2001;29(2):317-22.
92. Simons SH, van Dijk M, van Lingen RA, Roofthooft D, Duivenvoorden HJ, Jongeneel N, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. The Journal of the American Medical Association. 2003;290(18):2419-27.
93. Zhou Y, Jin X, Kang Y, Liang G, Liu T, Deng N. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: a prospective, randomized study. Critical Care. 2014;18(3):R122.
94. Shehabi Y, Chan L, Kadiman S, Alias A, Ismail WN, Tan MA, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Medicine. 2013;39(5):910-8.
95. Mehta S, Burry L, Martinez-Motta JC, Stewart TE, Hallett D, McDonald E, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Critical Care Medicine. 2008;36(7):2092-9.
96. Watling SM, Johnson M, Yanos J. A method to produce sedation in critically ill patients. The Annals of Pharmacotherapy. 1996;30(11):1227-31.
97. Nassar Junior AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Annals of Intensive Care. 2014.
98. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Critical Care Medicine. 1997;25(1):33-40.
99. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Critical Care. 2005;9(3):R200-10.
100. Aitkenhead AR, Pepperman ML, Willatts SM, Coates PD, Park GR, Bodenham AR, et al. Comparison of propofol and midazolam for sedation in critically ill patients. Lancet. 1989;2(8665):704-9.
101. Tobias JD. Subcutaneous administration of fentanyl and midazolam to prevent withdrawal after prolonged sedation in children. Critical Care Medicine. 1999;27(10):2262-5.
102. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. The Journal of the American Medical Association. 2000;283(11):1451-9.
103. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intensive Care Medicine. 2000;26(3):275-85.
104. Barrientos-Vega R, Mar S-SM, Morales-García C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Critical Care Medicine. 1997;25(1):33-40.

105. Claxton K. Exploring uncertainty in cost-effectiveness analysis. Pharmacoeconomics. 2008;26(9):781-98.
106. Al-Badriyeh D, Alabbadi I, Fahey M, Al-Khal A, Zaidan M. Multi-indication pharmacotherapeutic multicriteria decision analytic model for the comparative formulary inclusion of proton pump Inhibitors in Qatar. Clinical Therapeutics. 2016;38(5):1158-73.
107. Thummel KE, Shen DD, Isoherranen N, Smith H. Design and optimization of dosage regimens: pharmacokinetic data. Goodman and Gilman's the Pharmacological Basis of Therapeutics. NY: McGraw-Hill; 2001.
108. Saarenmaa E, Neuvonen PJ, Fellman V. Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. The Journal of Pediatrics. 2000;136(6):767-70.
109. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. The Journal of Pediatrics. 1997;131(1Pt1):55-62.
110. Kahn DJ, Richardson DK, Gray JE, Bednarek F, Rubin LP, Shah B, et al. Variation among neonatal intensive care units in narcotic administration. The Archives of Pediatrics & Adolescent Medicine. 1998;152(9):844-51.
111. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. Science & Practice Perspectives. 2002;1(1):13-20.
112. Marx J, Walls R, Hockberger R. Rosen's emergency medicine-concepts and clinical practice: Elsevier Health Sciences; 2013.
113. Mahajan R, Batra YK, Grover VK, Kajal J. A comparative study of caudal bupivacaine and midazolam-bupivacaine mixture for post-operative analgesia in children undergoing genitourinary surgery. International Journal of Clinical Pharmacology and Therapeutics. 2001;39(3):116-20.
114. Kim MH, Kim MS, Lee JH, Seo JH, Lee J-R. Can quality of recovery be enhanced by premedication with midazolam?: A prospective, randomized, double-blind study in females undergoing breast surgery. Medicine. 2017;96(7):e6107.
115. Stanley K. Design of randomized controlled trials. Circulation. 2007;115(9):1164-9.
116. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLoS Clinical Trials. 2006;1(1):e9.
117. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J, Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population?. The New England Journal of Medicine. 2000;284(21):2762-70.
118. Talmor D, Shapiro N, Greenberg D, Stone PW, Neumann PJ. When is critical care medicine cost-effective? A systematic review of the cost-effectiveness literature. Critical Care Medicine. 2006;34(11):2738-47.

Appendix 1. PubMed search strategy

#	Search History	Results
#1	"Morphine"[Mesh] OR "Fentanyl"[Mesh]	48504
#2	"Hypnotics and Sedatives"[Mesh]	25913
#3	#1 OR #2	73247
#4	Respiration, Artificial"[Mesh]	66155
#5	#3 AND #4	1511
#6	#5 AND "humans"[MeSH Terms]	1437
#7	#6 AND English[lang]	1202
#8	#7 AND (Clinical Conference[ptyp] OR Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Congresses OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH OR Controlled Clinical Trial OR Corrected and Republished Article[sb] OR Evaluation Studies[ptyp] OR Government Publications[ptyp] OR Guidelines[ptyp] OR Journal Article[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Practical Guideline[ptyp] OR Ranodmized Controlled Trials[ptyp] OR Review[ptyp] OR Systematic Reviews[sb])	1075

Appendix 2. PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Quality assessment of studies	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix 3: Ethics form from MRC

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH • EDUCATION • RESEARCH صحة • تعليم • بحوث

مركز البحوث الطبية
Medical Research Center

Ref No: MRC0272/2016
Date: 13 March 2016

Dr. Fouad Abounahia
Consultant
Clinical Pharmacy
Women's Hospital

Dear Dr. Fouad,

Proposal #16040/16: "Cost effectiveness Analysis of Sedatives in the management of Neonates undergoing mechanical ventilation inthe intensive care setting in Qatar"

This is in reference to your submission of the above titled proposal to the research center for review.

We would like to inform you that the Research Center has no objection for this Quality Improvement project to be conducted in HMC and published thereafter.

Yours sincerely,

Ms. Angela Ball,
Asst. Executive Director of Research and Business Development

Cc:
1. Dr. Daoud Al- Badriyeh, Qatar University
2. Ms. Dina Abushanab, Qatar University
3. Dr. Omar Alsoukhni, NICU, HMC

Tel: (+974) 4439 2440
Fax: (+974) 44395402
research@hmc.org.qa

P.O.Box 3050
Doha, Qatar
www.hmc.org.qa

Appendix 4: Data collection form

PLEASE RECORD:

Record number: ……

Date of collection: ……

Subject ID Code: ……

Active problems:

Gender: ☐ Male ☐ Female

Gestational age (weeks): ……

Weight: …… (g)

Type of delivery: ☐ Vaginal delivery ☐ Cesarean section

Date of birth: …… Date: …… Time: ……

☐ Monotherapy ☐ Combination

Sedative 1: …….

Loading dose: …… Received high dose (Yes/No): ……. Times of receiving high doses: ……

Maintenance dose: ……. Received high dose (Yes/No): ……. Times of receiving high doses: ……

Route of administration: …….

Duration of sedative: …….

Date of administration of sedative: …….

Time of administration of sedative: …… am / pm

Sedative 2: …….

Loading dose: …… Received high dose (Yes/No): ……. Times of receiving high doses: ……

Maintenance dose: …… Received high dose (Yes/No): ……. Times of receiving high doses: ……

Route of administration: …….

Duration of sedative: …….

Date of administration of sedative: …….

Time of administration of sedative: …… am / pm

Sedative 3: ……

Loading dose: ……. Received high dose (Yes/No): ……. Times of receiving high doses: ……

Maintenance dose: ……. Received high dose (Yes/No): ……. Times of receiving high doses: ……

Route of administration: …….

Duration of sedative: …….

Date of administration of sedative: …….

Time of administration of sedative: …… am / pm

Duration of mechanical ventilator (hours): …….

Date of mechanical ventilation initiation: …….

Time of mechanical ventilation initiation: …….

Date of mechanical ventilation discontinuation: …….

Time of mechanical ventilation discontinuation: …….

Mechanical ventilation mode: …….

Inspiratory time: …….

Data of NICU admission: …….

Time of NICU admission: …….

Data of NICU discharge: …….

Time of NICU discharge: …….

Length of NICU stay (days): …….

Death: ……. Date: …….. On MV ☐ Off MV ☐

Initial Premature Infant Pain Profile (PIPP) Pain score when sedative was initiated:

…….

Final Premature Infant Pain Profile (PIPP) Pain score when sedative was discontinued:

…….

Vital signs during sedation:

1. Temperature: Maximum: ……. Minimum: …….
2. Heart rate: Maximum: ……. Minimum: …….
3. Respiratory rate: Maximum: ……. Minimum: …….
4. Blood pressure: Maximum: ……. Minimum: …….

Adverse drug reactions, times of events, and sedative associated with event:

Respiratory Secretion ……

Airway obstruction ……

Oxygen desaturation (<90%) ……

Hypotension (depends on GA and age) ……

Tachypnea ……

Bradycardia ……

Respiratory depression ……

Edema ……

Dystonic reactions/movement disorders ……

Seizures ……

Vomiting ……

Aspiration of stomach contents ……

Phlebitis, line irritation ……

Allergic reaction, describe: ……

Urinary retention (need for a urinary catheter) ……

Enterocolitis: ……

Intraventricular hemorrhage: ……

Other: ……..

Medications used to resolve drug reactions: ……

Other medications administered in NICU: ……

Arterial Blood Gas (ABG)

pH …….

pCO2 ……

pO2 ……

HCO3 ……

Base D/E ……

Non- pharmacological interventions while in NICU:

……..

Laboratory tests while in NICU

Number of hematology tests: ……

Number of chemistry tests: ……

Number of blood gases tests: ……

Number of metabolic tests: ……

Number of microbiology tests: ……

Number of general virology tests: ……

Number of metabolic tests: ……

Number of body fluid tests: ……

Diagnostic tests while in NICU:

X-ray scan: …… Number of tests: ……

CT scan: …… Number of tests: ……

US: …… Number of tests: ……

MRI: …… Number of tests: ……

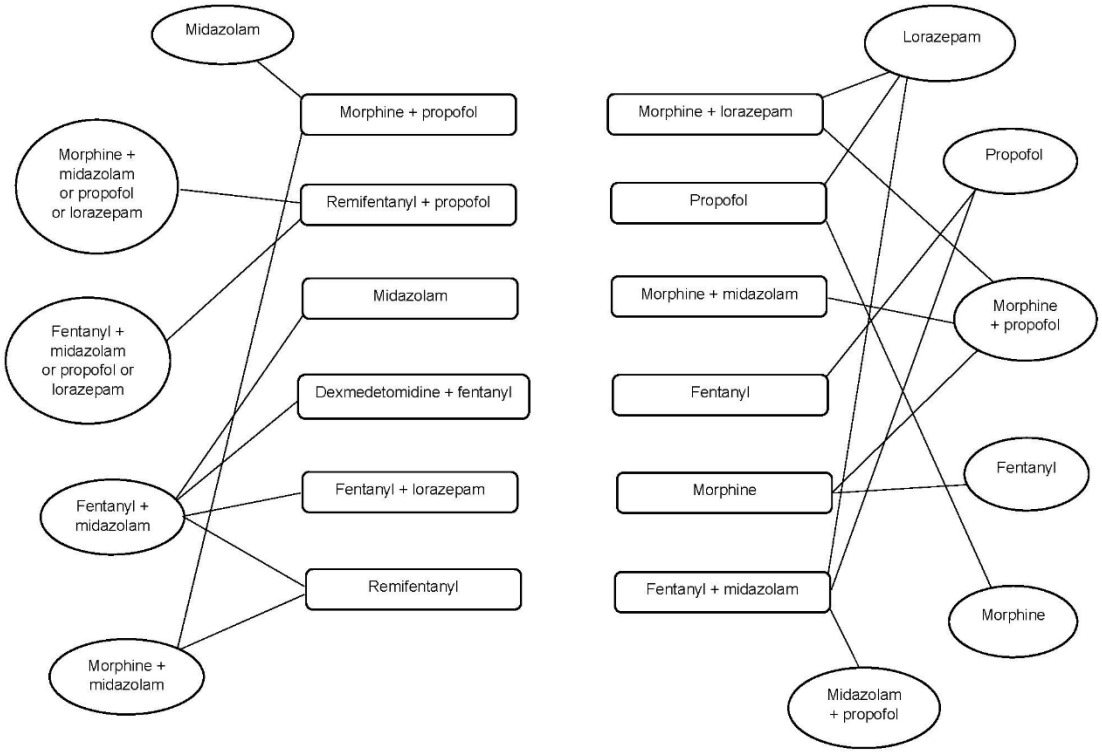
Other tests: ……. Number of tests: ……

Appendix 5: Underlying diseases in the included studies

N	Study	Medical Disorders
1	Carrasco et al	NA
2	Al MJ et al	NA
3	Zhou et al	Sepsis, COPD, CHE, pneumonia, pancreatitis, trauma, and postoperation
4	Barrientos et al	Cardiorespiratory insufficiency, trauma, and postoperation
5	Tobias et al	NA
6	Mehta et al	Respiratory disorders
7	Rozendaal et al	Cardiovascular, respiratory, sepsis, and GI diseases
8	Breen et al	NA
9	Karir et al	Cardiovascular, pulmonary, neurological, surgical, and infectious diseases
10	Watling et al	Respiratory disorders
11	Strøm et al	Sepsis, respiratory disorders, pancreatitis, peritonitis, GI bleeding, trauma, liver, and biliary diseases
12	Jarman et al	NA
13	Tedders et al	NA
14	Riker et al	Severe sepsis, shock, and pneumonia
15	Junior et al	Respiratory failure, ARDS, sepsis, cardiogenic shock, pneumonia, and acute pulmonary edema
16	Shehabi et al	Patients with operative, respiratory failure, cardiovascular admission
17	Aitkenhead et al	Respiratory or ventilator failure
18	Cox et al	NA
19	Anand et al	NA
20	Saarenmaa et al	ARDS, infection, PPHN, NEC, IVH grades 3, 4
21	Wood et al	ARDS, apnea, pneumonia, and asphyxia
22	Quinn et al	HMD
23	Tobias et al	NA
24	Tobias et al	NA
25	Kress et al	ARDS, pulmonary edema, COPD, ventilator failure, asthma, sepsis, cardiogenic shock, delirium, hemorrhagic shock, drug overuse
26	Carson et al	Pneumonia, septic shock, cystic fibrosis, COPD, sickle cell chest syndrome, upper airway obstruction, interstitial lung diseases, and other diagnosis
27	Barrientos et al	Cardiorespiratory failure, trauma, postoperation, and miscellaneous
28	Simons et al	RDS, primary infection, pneumonia, pulmonary edema, and meconium aspiration
29	Grunau et al	NA
30	Orsini et al	RDS
31	Guinsburg et al	RDS
32	Richman et al	Sepsis, pneumonia, COPD, asthma, neuromuscular, and cardiovascular diseases
33	Anand et al	Cardiovascular, and neurological disorders, shock, and trauma

*NA= Not available; COPD = chronic obstructive pulmonary disease; CHE = covert hepatic encephalopathy
†GI= gastrointestinal; ARDS = acute respiratory distress syndrome; PPHN = persistent pulmonary hypertension of neonate
‡NEC = necrotizing enterocolitis; IVH = intraventricular hemorrhage; HMD = hyaline membrane disease; RDS = respiratory distress syndrome

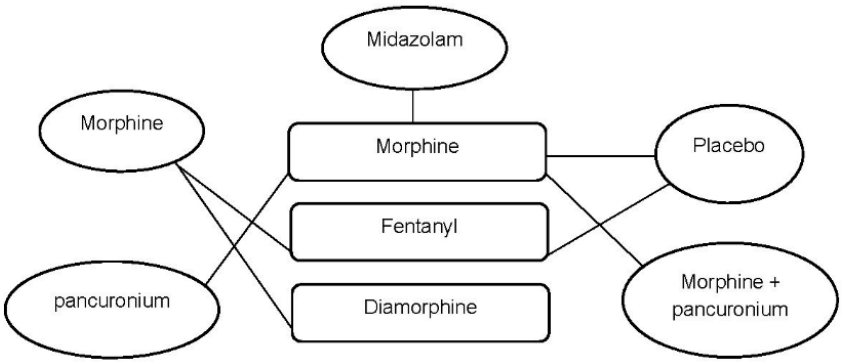
Appendix 6: Sedative comparisons in adult populations



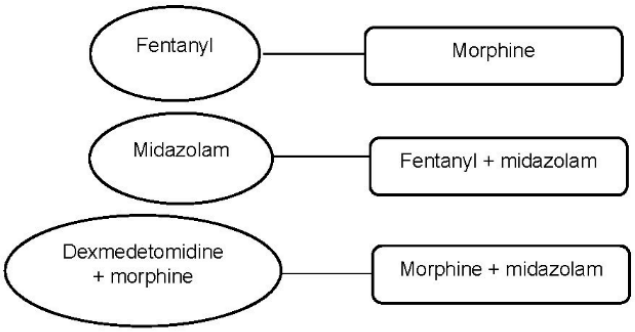
*Rectangles represent study interventions, and circles represent the comparators

Appendix 7: Sedative comparisons in pediatric and neonate populations

Neonate population



Pediatric population



*Rectangles represent study interventions, and circles represent the comparators.