Original Research

Cost-effectiveness of Oral Versus Intravenous Ibuprofen Therapy in Preterm Infants With Patent Ductus Arteriosus in the Neonatal Intensive Care Setting: A Cohort-based Study

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ABSTRACT

Purpose: Use of ibuprofen for the patent ductus arteriosus (PDA) has become increasingly common. This study aimed to evaluate the clinical and economic impact of oral ibuprofen versus intravenous ibuprofen for PDA among preterm infants.

Methods: This retrospective, cohort-based pilot study examined the clinical and economic associations of oral versus intravenous ibuprofen for PDA. A decision-analytic model was constructed, from the hospital perspective, to follow the oral versus intravenous administrations of ibuprofen for PDA and their clinical and economic consequences. The course regimen of either formulation was an initial 10 mg/kg followed by 5 mg/kg at 24- and 48-h intervals. Clinical and resource utilization data were extracted from Cerner medical database, from 2014 through 2018, at the tertiary neonatal intensive care unit setting in Qatar. The primary outcome measures were the rate of successful closure based on the ductal diameter measure after the first course of treatment and the overall direct medical cost of PDA management. A population of 118 neonates was required for results with 80% power and 0.05 significance. Sensitivity analyses involving unit costs and a subgroup analysis based on gestational age and birth weight, added to a second-order probabilistic analysis of all model inputs, were performed.

Findings: Forty infants were available for inclusion in the oral ibuprofen study group, not achieving the desired sample size, with successful PDA closure reported in 64% of cases compared with a reduced success of 36% with intravenous ibuprofen (n = 59) (risk ratio = 0.56; 95% CI, 0.32−0.97; $P = 0.04$), which was associated with economic advantage to oral ibuprofen. The probabilistic analysis illustrated that oral ibuprofen costs less than intravenous ibuprofen in 72% of patient cases, with QAR 48,751 (US $13,356) (95% CI, QAR 47,500−50,000, US $13,014−$13,699) in mean savings. Sensitivity analyses confirmed the robustness of study conclusions and found that the rate of closure success versus failure was the most influential on results, followed by the occurrence of adverse drug events with both intravenous and oral ibuprofen. Although both ibuprofen formulations had similar safety profiles ($P = 0.16$), the intravenous formulation was associated with a larger number of adverse drug effects.

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Implications: This is the first cost-effectiveness evaluation of oral versus intravenous formulations of ibuprofen among infants with PDA. The oral ibuprofen might be associated with an enhanced ductal closure at a considerably lower cost. The study results support recent trends in neonatal intensive care unit practices in favor of the oral administration of ibuprofen. (*Clin Ther*. 2021;43:336−348) © 2020 Elsevier Inc.

Key words: cost-effectiveness, ductus arteriosus, ibuprofen, intravenous, oral, preterm infants.

INTRODUCTION

Patent ductus arteriosus (PDA) is important during pregnancy for fetal survival, and it usually closes within 72 h after full-term birth. In preterm infants, the closure of PDA might be delayed or not take place. Spontaneous PDA closure occurs in only approximately 34% of infants with extremely low birth weight (BW; <1000 g) by 4 postnatal days.[1] Approximately 60%−70% of newborns with hemodynamically significant PDA (HSPDA) receive pharmacologic or surgical ligation for the ductus closure.[2,3] There is, however, no unequivocal data to determine the optimal management of PDA in preterm infants, especially among those born at a gestational age (GA) of <28 weeks and with recent literature indicating no significant long-term outcome benefits in preterm infants who received interventions compared with those who did not.[4] Controversy about the management of PDA exists among centers and among neonatologists and pediatric cardiologists worldwide; whereby, in addition to clinicians' clinical experience, the choice of intervention is also influenced by the availability and cost. Management of PDA includes conservative management; pharmacologic interventions with nonselective cyclooxygenase inhibitors, such as indomethacin and ibuprofen or acetaminophen, which affects the peroxidase segment; or surgery or a combination of different approaches.[4] Pharmacologic interventions with cyclooxygenase inhibitors 1 became the main approach and is preferred over surgery because the latter is associated with short- and long-term adverse events and is, therefore, reserved for refractory cases.[5] The conservative approach is another modality used and includes fluid restriction, thiazide diuretics, and respiratory support. However, differential evidence to support the use of this is lacking.[4] The failure of the duct to close can result in life-threatening complications, such as hemodynamically significant left to right shunt, prolonged ventilatory support, congestive cardiac failure, intraventricular hemorrhage, pulmonary edema and hemorrhage, bronchopulmonary dysplasia, acute renal failure, necrotizing enterocolitis (NEC), periventricular leukomalacia, feeding intolerance, and poor overall survival rate.[2,3,6,7]

The use of ibuprofen for the management and closure of PDA has become increasingly common. Ibuprofen is as effective as indomethacin, which is another inhibitor of cyclooxygenase 1 enzyme that has been recommended as standard therapy for many years, but with fewer adverse events.[8,9]

Ibuprofen is available in intravenous and oral formulations. Throughout the neonatal intensive care units (NICUs) of Hamad Medical Corporation (HMC) in Qatar, clinicians use intravenous ibuprofen as the first-line therapy for PDA. The use of oral or intravenous ibuprofen formulations for the management of PDA has become a debatable issue.[8] Intravenous ibuprofen is effective in treating preterm infants with PDA without affecting the cerebral, renal, or gastrointestinal hemodynamics, but it is associated with high acquisition cost, whereas oral ibuprofen given as a nasogastric tube is cheaper. Earlier studies suggest that oral ibuprofen is equally effective to intravenous ibuprofen, but more recent randomized controlled trials (RCTs) suggest that the oral ibuprofen is superior.[1,10,11] In the HMC, therefore, in addition to intravenous ibuprofen, some clinicians have also considered administering oral ibuprofen as a first-line therapy. The intravenous ibuprofen is approved, but the off-label oral use of ibuprofen, and despite fewer data in support of its efficacy, tolerability, and pharmacokinetic profile,[9] is increasingly of comparative advantage for its lower cost, added to the ease of availability and administration.[12−18] There are no economic evaluations of how the two ibuprofen formulations are compared for the treatment of PDA. An analysis of both the effectiveness and the cost considerations of oral versus intravenous ibuprofen is critical in determining care practices in NICUs in high- and low-income settings. For example, oral ibuprofen is used now in up to 29% of NICUs in the European countries.[19] This, however, is without proper evaluations of overall costs. This study sought to

evaluate the cost-effectiveness of oral ibuprofen versus intravenous ibuprofen through assessing their comparative clinical and economic values based on the first course of therapy for PDA treatment in preterm infants.

METHODS

Study Design and Setting

This study was a pilot, cohort-based, cost-effectiveness study in neonates admitted to the tertiary NICU setting of HMC, which is the main health care facility in the country, incorporating 13 hospitals. The HMC tertiary NICU setting is specialized and the largest in the region to offer care for critically ill newborns.[18] Required ethics approvals were received via the Medical Research Center at HMC (MRC-01-18-385).

Study Population

Included in the analysis are preterm infants, born alive before 37 weeks of pregnancy, with postnatal age of ≥24 h, ductal diameter of >1.5 mm, and HSPDA.[10,20] HSPDA is defined as infants with hyperdynamic precordium, pulse pressure (>25 mm Hg), prominent precordial pulsation, systolic/continuous murmur at the left second parasternal area, metabolic acidosis (not attributed to sepsis or hypoperfusion), pulmonary edema, hypotension, cardiac failure, or increased ventilatory and supplemental oxygen requirements.[21,22] The presence of HSPDA is proven via color Doppler echocardiography, which confirms the presence of ductal patency, measurement of ductal dimensions, as well as the assessment of the direction and velocity of ductal blood flow. A large ratio of left atrial to aortic root dimensions ≥1.5:1, ductal diameter ≥1.5 mm, left ventricular volume and pressure loading, and reversal of diastolic flow in the descending aorta or in cerebral or renal arteries may be associated with significant ductal shunting.[23]

As a first-line strategy, infants with HSPDA are offered pharmacologic therapy, and if this is not feasible because of contraindications, infants become eligible for surgical ligation. The contraindications include proven or suspected infection, active bleeding, thrombocytopenia (thrombocyte count <60,000/mm^3) and/or coagulation defects, NEC or suspected NEC, urine output <0.6 mL/kg per hour, blood urea level >30 mg/dL, and/or creatinine level >160 μmol/L. If there are no contraindications to ibuprofen as pharmacologic therapy, intravenous ibuprofen is administered using a regimen of an initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24 and 48 h.[24] If the first course of intravenous ibuprofen fails, the alternative is a second course of intravenous ibuprofen, unless venous access is not accessible. In the study setting, if off-label oral ibuprofen is administered as the first-line therapy, this regimen will be an initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24 and 48 h.[24] If the first course of oral ibuprofen fails, the alternative is a second course of oral ibuprofen, unless an enteral administration is contraindicated because of gastrointestinal conditions or complications, such as intestinal perforation and feeding intolerance. If the second course of intravenous or oral ibuprofen fails, intravenous indomethacin course is administered as an alternative using a regimen of an initial dose of 0.2 mg/kg IV and subsequent doses: (1) 0.1 mg/kg IV dose every 12 h for 2 doses (<2 days), (2) 0.2 mg/kg IV dose every 12 h for 2 doses (2−7 days), and (3) 0.25 mg/kg IV dose every 12 h for 2 doses (>7 days).[24] When pharmacologic interventions fail or after the failure of a first-course therapy in infants with advanced postnatal age or with lung diseases, surgery ligation can then be indicated to close the ductus.

In this study, infants were initially classified into those who received the first course of oral ibuprofen given via an orogastric tube (initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24 and 48 h) or received the first course of intravenous ibuprofen (initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24 and 48 h). Exclusion criteria were congenital malformations, renal failure (renal failure definition in the neonates is nonspecific because the infant's serum creatinine after birth reflects the maternal renal function, usually <1 mg/dL, which consequently decreases over time). Clinicians mostly consider infants to have a renal failure when the serum creatinine level is ≥ 1.5 mg/dL when the maternal renal function is normal. Renal failure in neonates can also be defined as urine output of <1 mL/kg per hour or lack of urine output at 48 h of birth.[25] Patients with severe liver failure, defined as elevated levels of the liver enzymes alanine aminotransferase and aspartate aminotransferase >2

times the upper boundary of the reference range, were also excluded.

Outcome Measures

The primary outcomes were the success rate in closing the PDA and the total direct medical cost of managing PDA in preterm infants based on the economic value of resource use during the NICU stay. Success was defined as a transductal diameter of <1.5 mm via cardiac echocardiography by 24 h after receiving one course of therapy of an initial dose of 10 mg/kg of ibuprofen, followed by 2 doses of 5 mg/kg at 24-h intervals of either formulation.[1,3,6,10,20] Success was with and without adverse drug events (ADEs).

Secondary outcome measures included the difference in PDA closure; based on multiple courses of ibuprofen management; rate of premature discontinuation of therapy; need for an alternative route of administration (from oral to intravenous or vice versa); need for alternative therapy (from oral or intravenous ibuprofen to intravenous indomethacin), which is the standard alternative in the Qatari NICU; ADEs (defined as any events that occur after receiving either route of administration, such as intestinal perforation, gastrointestinal bleeding, NEC, bronchopulmonary dysplasia, oliguria, and hyperbilirubinemia)[1,3]; the difference in the need for surgical ligation (when the infant continues to have HSPDA after pharmacologic therapies); and newborn death (defined as all-cause mortality during the first 28 days of the infant's life).[26]

Model and Clinical Inputs

A traditional decision tree form of a decision-analytic model was constructed to follow the two different formulations (oral and intravenous ibuprofen) and their consequences as per the development of different clinical outcomes. Treated patients were first differentiated based on whether the PDA closure was achieved after one course of therapy. Infants, in whom PDA management failed, were further differentiated based on whether the patients had premature discontinuation of therapy because of comorbidities, received a second course of oral or intravenous ibuprofen, received intravenous indomethacin as an alternative, required surgery, or died (Appendix I). The model's clinical inputs of the study cohort, concerning demographic information and clinical data, were retrospectively obtained via HMC's Cerner medical records database from 2014 through 2018.

Sample Size

The literature contains several studies of oral versus intravenous ibuprofen for preterm infants with PDA.[1,10,11,20,27] The sample size calculation was based on the only head-to-head RCT by Gokmen et al.[11] The success rate of PDA was significantly higher in the oral ibuprofen group compared with the intravenous ibuprofen after the first course of treatment (84.6% vs 62%, $P = 0.011$). Accordingly, a total sample size of 118 infants needed to be included in the study at $\alpha = 0.05$ and power of 80% (https://clincalc.com/).

Patient medical records were ordered for inclusion into the study groups based on the descending order of hospital admission numbers in the Cerner database. Patients were screened for inclusion until the sample size was achieved or no more patient records were available. Any excluded patient record was replaced with another record order if additional records were available.

Statistical Analysis

Patient demographic and clinical characteristics were tabulated for descriptive analysis. For continuous variables, findings were presented as mean (SD), whereas for categorical measures, number (percentage) is used. The *t* test or Mann–Whitney test was used for continuous variables, and the χ^2 test or Fisher exact tests was used for categorical variables. All tests were at 95% CI and 80% power. Binary regression analyses were performed to account for the impact of differences in baseline characteristics on the success rate outcome. Targeted characteristics were sex, GA, BW, nationality, type of delivery, multiple pregnancies, postnatal age, 1- and 5-min Apgar score, surfactant treatment, number of doses of surfactant, antenatal steroid, postnatal steroid, premature rupture of membrane, duration of premature rupture of membrane, maternal preeclampsia, caffeine treatment, doses of caffeine, degree of PDA opening, and respiratory support. All statistical analyses were conducted using SPSS Statistics for Windows, version 24.0 (IBM Corporation, Armonk, New York).

Model Cost Inputs and Calculations

Resources consumed in patient management, including for ADEs, and the patterns of use were derived from the patients' medical records. After a list of all used recourses was developed, the list was directly submitted to the Finance and Accounting Department at HMC for the unit costs of resources to be provided. The values of unit costs are based on hospital charges.

The decision model adopted a public hospital perspective; therefore, only the costs of direct medical resources were included in the analysis. Included resources are (1) intravenous and oral ibuprofen, (2) management of ADEs, (3) diagnostics, laboratory, and monitoring tests received during the NICU stay, and (4) NICU stay (bed cost, not including other resources). A microcosting approach was used for cost calculations, relying on unit costs of individual resources not categories of resources.

All calculated costs were in Qatari Riyal, adjusted for the financial year 2019−2020, using the Qatari Health Consumer Price Index as appropriate. The cost-effectiveness analysis was as per case of success, with and without ADEs. No discounting was applied because outcomes were not projected beyond a 1-year time horizon.

Sensitivity Analysis

Sensitivity analyses were performed to test the model's robustness against input uncertainty, identify key determinants of cost-effectiveness outcomes, and increase the generalizability of results. Sensitivity analyses were performed via the Monte Carlo simulation approach using @Risk-7.5 (Palisade Corporation, Ithaca, New York). The Monte Carlo simulation approach is a cornerstone in sensitivity analyses of economic evaluations, which is used to predict the possible deviation of outcomes from their base-case values because of anticipated uncertainties in the values of model inputs, such as with the limited sample size. Random input values, chosen across a range of an uncertainty input distribution of a model input, are simulated, and the model is run for each simulated input set. The sensitivity analysis typically requires $\geq$1000 model runs, whereas in one-way sensitivity analysis, this occurs for an input at a run, with all first-order probability inputs varied in each run as part of the probabilistic analysis. The latter enables a probability of cost-saving analysis and a tornado analysis of multivariate correlation or regression models.[28] One-way sensitivity analyses were performed by varying each of the resource unit costs with ±10% uncertainty. A uniform type of uncertain Monte Carlo value distribution was used, with 10,000 iterations. A second-order probabilistic sensitivity analysis was used based on 95% CI for the uncertainty range, a trigen type of distribution, and 10,000 iterations. A scenario analysis was also performed to investigate the robustness of the study conclusion against the broad inclusion GA and BW criteria. The model was rerun under several alternative scenarios in which, in each, the analyzed study population constituted only one of the several distribution categories of baseline neonatal GA and BW. PDA closure success and the associated cost with oral ibuprofen relative to intravenous ibuprofen were recalculated based on each subgroup.

RESULTS

Although the targeted 59 neonates receiving intravenous ibuprofen met all the inclusion criteria, only 40 neonates receiving oral ibuprofen met the inclusion criteria and were analyzed, making the clinical cohort analysis in the present study a pilot one. Baseline characteristics were similar in both groups. Both oral and intravenous preterm ibuprofen groups received surfactant, antenatal steroids during pregnancy, and caffeine and were less likely to have received postnatal steroids. The groups' baseline characteristics are given in Table I and Appendix II.

Base-case Analysis

During the neonatal stay in the NICU, compared with a 64% closure success with oral ibuprofen, intravenous ibuprofen achieved a closure success of 36% (risk ratio = 0.56; 95% CI, 0.32−0.97; $P = 0.04$), associated with a cost saving of QAR 31,537.62 (US $8640) per case of closure success in favor of the oral formulation.

Clinical Outcomes

The overall closure rate after multiple courses of management (first, second, and/or third) was similar between the study groups (odds ratio [OR] = 1.1; 95% CI, 0.97−1.19; $P = 0.49$). In each of the oral and intravenous groups, 5 infants received a second course of oral therapy (OR = 1.09; 95% CI,

Table I. Main baseline patient characteristics.

Characteristic	Oral ibuprofen (n = 40)	Intravenous ibuprofen (n = 59)	*P*
Sex, No. (%)			
Male	16 (40)	34 (57.6)	0.14
Female	24 (60)	25 (42.4)	
Gestational age group, No. (%)			
Extremely preterm (<28 weeks)	24 (60)	33 (55.93)	0.4
Very preterm (28 $\leq$ 32 weeks)	13 (32.5)	22 (37.29)	
Moderate or late preterm (32 $\leq$ 37 weeks)	3 (7.5)	4 (6.78)	
Gestational age, mean (SD), wk	28.36 (2.91)	27.1 (2.8)	0.38
Birth weight group, No. (%)			
$\geq$2500 g	0 (0)	0 (0)	0.2
<2500 and $\geq$ 1500 g	10 (25)	3 (5.1)	
<1500 and $\geq$ 1000 g	14 (35)	24 (40.68)	
<1000 g	16 (40)	32 (54.24)	
Birth weight, mean (SD), g	1213.6 (430.74)	1025 (354.8)	0.2
Postnatal age at time of diagnosis, mean (SD), d	4.96 (2.65)	2.80 (1.39)	0.69
Surfactant use, No. (%)			
Yes	26 (65)	50 (84.7)	0.05
No	14 (35)	9 (15.3)	
Antenatal steroid use, No. (%)			
Yes	35 (87.5)	45 (76.3)	0.2
No	5 (12.5)	14 (23.7)	
Postnatal steroid use, No. (%)			
Yes	3 (7.5)	2 (3.4)	0.36
No	37 (92.5)	57 (96.6)	
Maternal preeclampsia, No. (%)			
Yes	8 (20)	10 (16.9)	0.74
No	32 (80)	49 (83.1)	
Perinatal asphyxia, No. (%)			
Yes	0 (0)	0 (0)	1
No	40 (100)	59 (100)	
Received caffeine treatment (maintenance dose), No. (%)			
Yes	24 (60)	46 (78)	0.1
No	16 (40)	13 (22)	
Ductal size at baseline, mean (SD), mm	2.4 (0.58)	2.46 (0.77)	0.36
Degree of patent ductus arteriosus opening, No. (%)			
Large	26 (65)	49 (83.1)	0.12
Moderate	14 (35)	8 (13.6)	
Small	0 (0)	2 (3.4)	
Respiratory support, No. (%)			
None	0 (0)	1 (1.7)	0.34
Nasal cannula	2 (5)	3 (5.1)	
Continuous positive airway pressure	15 (37.5)	15 (25.4)	

(*continued on next page*)

Table I. (*Continued*)

Characteristic	Oral ibuprofen (n = 40)	Intravenous ibuprofen (n = 59)	*P*
Conventional mechanical ventilatory support	21 (52.5)	40 (67.8)	
High-frequency ventilatory support	0 (0)	0 (0)	
Others	2 (5)	0 (0)	
Fraction of inspired oxygen, mean (SD)	37.58 (19.87)	36.78 (16.02)	0.8

0.08−5.21; $P = 0.11$) and 3 versus 24 infants received a second course of intravenous therapy after initial courses of oral and intravenous ibuprofen, respectively (OR = 1.07; 95% CI, 0.12−1.19; $P = 0.15$). Five infants in each group required surgery after the initial courses of ibuprofen (OR = 1.21; 95% CI, 0.97−1.13; $P > 0.99$), and none of the infants received indomethacin in the oral group compared with 2 infants in the intravenous group (OR = 1.07; 95% CI, 0.98−1.17; $P = 0.60$). No statistical difference was found between the groups with regard to the mortality and the ADEs (OR = 1.03; 95% CI, 0.97−1.1; $P > 0.99$) and (OR = 2.21; 95% CI, 0.11−12; $P = 0.16$), respectively. The ADEs and management of ADEs in the study groups are listed in Table II.

The urine outputs were normal and similar between the groups. In the oral versus intravenous group, mean (SD) hourly urine outputs were 4.25 (1.53) mL/kg vs 6.69 (12.02) mL/kg (95% CI, −1.36 to 6.23; $P = 0.21$) after first course. None of the infants in both study groups developed renal impairment throughout the study. The serum creatinine level, nonetheless, was similar between oral versus intravenous groups after the first course of treatment (47.75 [21.09] mmol/L vs 55.15 [24.12] mmol/L;

Table II. Adverse drug events and their management.

Adverse event	No. (%) of oral ibuprofen adverse events (n = 40)			No. (%) of intravenous ibuprofen adverse events (n = 59)		
	First course	Second course	Third course	First course	Second course	Third course
Spontaneous intestinal perforation	0 (0)	0 (0)	0 (0)	1 (1.69)*	1 (1.69)†	0 (0)
Self-resolved						
Gastrointestinal bleeding	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Necrotizing enterocolitis	0 (0)	1 (2.5)	0 (0)	1 (1.69)*	0 (0)	0 (0)
No surgical intervention and supportive care only (bowel rest with discontinuation of enteral feedings, fluid replacement, supplemental oxygen respiratory support, and antibiotic treatment course of 14 days)						
Thrombocytopenia	0 (0)	0 (0)	0 (0)	1 (1.69)*	0 (0)	0 (0)
Platelet transfusion						
Oliguria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Edema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fluid retention	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary retention	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood in urine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mortality	0 (0)	0 (0)	0 (0)	1 (1.69)	0 (0)	2 (3.39)

* Events developed after initial dose of intravenous ibuprofen.
† Patient received second oral ibuprofen course.

95% CI, –1.93 to 16.73; $P = 0.12$). The urea level differed significantly between oral and intravenous groups after the first course of therapy (3.35 [2.36] vs 6.61 [5.04] mmol/L; 95% CI, 1.56–4.96; $P = 0.002$). None of the patients in both groups developed fluid retention, and sodium levels remained normal after the first course of therapy between the oral and intravenous groups (138.15 [47.65] mmol/L vs 137.77 [38.94] mmol/L, 95% CI, –17.72 to 16.96 mmol/L; $P = 0.97$).

The mean durations of mechanical ventilatory support and NICU stay were higher in infants treated with initial intravenous ibuprofen compared with those treated with initial oral ibuprofen, at 59 (51.81) versus 53 (46.26) days (95% CI, –26.18–14.18; $P = 0.57$) and 81 (51.19) versus 61 (33.54) days (95% CI, –38.27 to –1.730; $P = 0.03$), respectively.

The binary logistic regression analysis, performed to investigate the effect of differences in baseline characteristics, despite being insignificant, on the reported significant improvement of success with oral ibuprofen found that none of the reported baseline differences in characteristics between the study groups has a significant influence on the reported therapeutic advantage of oral ibuprofen (OR = 1.67; 95% CI, 0.29–9.71; $P = 0.57$).

Cost Outcomes

In both study groups, the overall cost of therapy was predominantly driven by the total cost of closure success, with or without ADEs, followed by the total cost of patients who received alternatives, whereas the premature discontinuation of therapy contributed the least to the total management of patients receiving ibuprofen. Outcomes, their probabilities

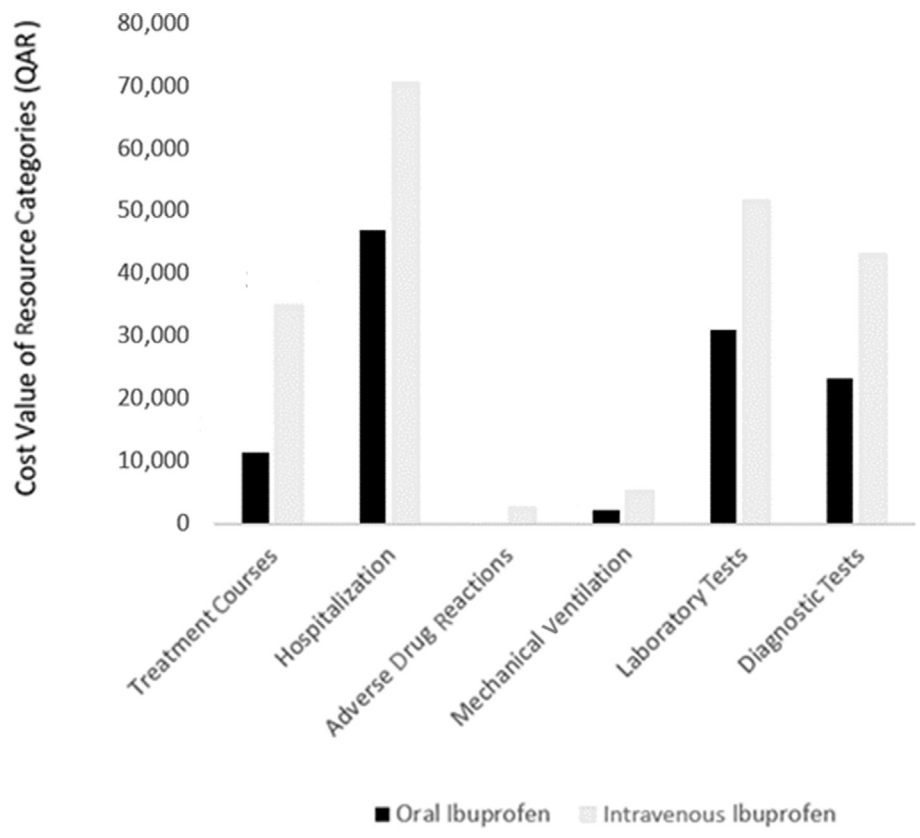

Figure 1. The relative values of cost components for each of the study drugs. QAR 1 = US $3.65.

and weighted costs, and the overall costs of oral ibuprofen and intravenous ibuprofen are presented in Appendix III. The relative values of cost components for each of the study drugs are summarized in Figure 1.

One-way Sensitivity Analysis

Unit costs of resources and their uncertainty distributions are given in Appendix IV. The model was insensitive to changes in all unit cost variables.

Probabilistic Sensitivity Analysis

Base-case outcome probabilities and their uncertainty ranges are given in Appendix IV. The Monto Carlo simulation illustrated that, with lower cost and higher success, oral ibuprofen maintains dominance over IV ibuprofen in 72.3% of simulated patient cases. Oral ibuprofen was 24.44% more successful than IV ibuprofen (95% CI, 0.242−0.247), with a mean cost saving of QAR 48,751 (US$ 13,356) (95% CI, QAR 47,500−50,000, US $13,014−$13,699). A tornado diagram of Spearman rank of main model outcomes per the correlation coefficient of the consistency of their impact on the overall cost saving is given in Figure 2. Based on the results of a multivariate regression model to rank the size (strength) of the relationship between the outcome and the input variability, including input costs, the result was consistent with that by the correlation tornado, where the rate of closure success versus failure was the most influential on results, followed by the occurrence of ADEs with both intravenous and oral ibuprofen. The rate of receiving indomethacin as an alternative had the least impact on the results.

Scenario Analysis

Although a relative measure of significance cannot be reported because of the small sample size in each of the analyzed subgroups of the GA and BW distributions, oral ibuprofen was associated with higher closure success and cost saving relative to intravenous ibuprofen in each of the subgroups (Appendix V).

DISCUSSION

Because the intravenous formulation of ibuprofen may not be available at all medical centers, particularly in low-income countries, the oral formulation of ibuprofen has become of interest as an off-label formulation with a lower acquisition cost. Even in settings where intravenous ibuprofen has been available for many years, oral ibuprofen has been increasingly considered as an alternative but without

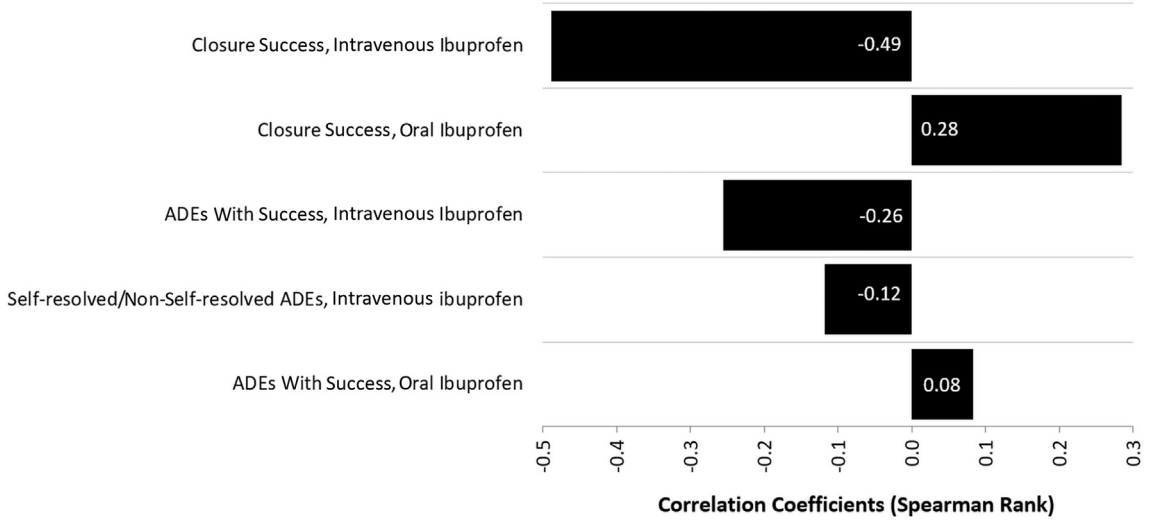

Figure 2. Tornado diagram of oral versus intravenous ibuprofen based on Spearman rank of the correlation coefficient. ADEs = mean adverse drug events.

any evidence of advantages in many settings, such as in the NICU of Qatar.

The current clinicoeconomic study is the first to report the economic consequences of ibuprofen in PDA management, relying on local data that reflect realistic costs borne by neonates (between extreme to late preterm and with a BW of <1000 to <2500 g). Oral ibuprofen was associated with a 27% higher success rate and reduced the lower overall cost by 15%, dominating IV ibuprofen in >72% of simulated patient cases in the study model. This is in addition to a shortened NICU stay and duration of mechanical ventilatory support.

The pilot RCT by Cherif et al[1] was the first to find a higher rate of PDA closure with oral versus intravenous ibuprofen, which was later confirmed by three RCTs with a similar conclusion.[10,11,27] These, however, are not comparable to the present study because they only included infants with very low BW (<1500 g) and extremely preterm infants (≤28 weeks of gestation)[1,11] or those with respiratory distress syndrome[27] and excluded moderate to late preterm infants (32 to <37 gestational weeks) or those with low to normal BW (≥1500 g).[10] There is only one pilot retrospective cohort study that evaluated the different ibuprofen formulations against PDA, which found that the oral dose achieved 100% success versus 97.6% seen with the intravenous dose among preterm infants with GA <32 weeks and BW <1500 g. This study, however, was based in Turkey and did not assess the economic impact of therapies. In addition, in infants with a GA of <32 weeks and a BW of <1500 g, those treated with intravenous ibuprofen developed statistically significant hypernatremia compared with those treated with oral ibuprofen.[2]

Although some studies have investigated the success rate of intravenous ibuprofen based on multiple courses of therapy,[29–31] this study followed the recommendations of the head-to-head RCT and observational studies[2,10,11,20,27] and the National Health Service Greater Glasgow and Clyde Paediatric Guidelines, where a second course of ibuprofen was only recommended if the patent remained open after the first course.[32]

Studies suggest that the effectiveness of the oral ibuprofen form compared with the IV form is attributed to a slower absorption and, hence, a longer half-life that prolongs the time of contact with the ductus.[33,34] However, this finding has not been confirmed, particularly because studies investigating the pharmacokinetic properties of ibuprofen are rare and none have compared the oral and intravenous routes head to head.

This economic evaluation study provides evidence that is based on real-life practices and settings and is based on how therapies have performed thus far. Patients were followed up until NICU discharge, and microcosting of realistic resource use in patient management was applied. The analytic decision model adopted in this evaluation followed the comparative head-to-head outcomes reported in the literature,[1,2,10,11,27] but it also extended this further with the inclusion of premature discontinuation of therapy, alternative routes of administration, alternative therapies, and the total NICU stay.

Within the context of performing a cohort study, we attempted to limit the allocation bias in this study via systematic patient selection based on successive hospital admission numbers. This factor was added to the inclusion and exclusion criteria of patients based on a preordered, deidentified patient list and not based on direct access to patient histories on the Cerner database. Moreover, because of the sensitive nature of the population, no clinical data were missing in the records that could jeopardize the quality of results. The sensitivity analyses revealed the robustness of the cost-effectiveness outcome against uncertainty in main model inputs, and a threshold analysis of input values was not required.

The main limitation of this study is that the oral ibuprofen group in the study did not achieve the required calculated sample size. Not achieving the targeted sample size introduces potential model input uncertainty because the measured clinical effect values from the study population may differ from the real population values in the study setting, which may also overestimate the advantage of one formulation over the other. However, this limitation does not necessarily undermine the conclusion of our study for three main reasons. First, the measured clinical advantage of oral ibuprofen in this pilot study is consistent with previous studies.[1,2,10,11,27] Second, even if we assume no confirmed differential PDA closure between oral and intravenous ibuprofen, the standalone cost analysis found that

oral ibuprofen was associated with considerable overall cost savings compared with intravenous ibuprofen, including the cost of therapy and the consequences. This outcome is important because, unlike clinical research, the economic evaluation is not concerned with hypothesis testing but is primarily about cost estimations. As a result, even if an economic evaluation is underpowered, it still provides important information that will guide decision making.[35] Third, a multivariate probabilistic sensitivity analysis accounted for potential variability in model input values, which indicates the persistence of the study conclusion in 72% of varying cases. Within the context of the sample size, this value was calculated based on clinical outcomes only. Although this is acknowledged as a limitation, a cost-based sample size calculation is difficult given that it is based on the willingness to pay for a treatment unit and that this is the first economic evaluation of the use of ibuprofen and no prior data are available on the incremental net monetary benefit to be used.[36] The interpretation of the incremental economic benefit is not generalizable from the general literature, especially when the unit cost and the use of resources are locally specific; thus, enabling generalization will require considerably larger sample sizes.[35–37]

An additional limitation is the broad inclusion criteria concerning the GA and BW of infants. Although the distribution of infants in the different categories of GA and BW in this study represents the current state and nature of the local population on which the study conclusions are most valid and relevant, it is acknowledged that for the purpose of outside settings, this broad distribution may not be generalizable and may represent a potential bias toward infants who are extremely preterm and/or have a BW <1500 g. Nevertheless, the sensitivity analysis of different subgroup categories of infants' GA and BW indicates the robustness of the base-case conclusion, where, in each of the categories, oral ibuprofen was still associated with an increased closure rate and cost savings relative to intravenous ibuprofen.

Overall, the study outcomes are consistent with the recent trends in HMC that use more of the oral ibuprofen strategy for PDA management relative to the more traditional approach of relying on intravenous ibuprofen. Taking similar recent trends in international practices and the lack of cost-effectiveness studies of ibuprofen for PDA, the relevance of the present study extends beyond the local context to be of benefit also to international settings. This relevance is especially notable because of the international standard regimens of ibuprofen used, clear timing of therapy initiation, specific and clearly defined PDA indication and outcome measure, and the uncertainty analyses performed.

CONCLUSION

On the basis of the methods and perspective in this pilot, first-time, cost-effectiveness evaluation of oral versus intravenous ibuprofen for PDA closure in preterm infants in the NICU, the oral formulation of ibuprofen seems to be dominant intravenous IV ibuprofen. Although the effectiveness advantage cannot be concluded with utmost robustness because of the sample size limitation, oral ibuprofen has been associated with considerable overall cost savings.

AUTHOR CONTRIBUTION

D. Al-Badriyeh and D. Abushanab conceived and designed the study, participated in data collection, performed data analysis, interpreted results, and revised manuscript. D. Abushanab wrote the first manuscript draft. All authors discussed study methods and reviewed the manuscript drafts critically, and read and approved the final manuscript.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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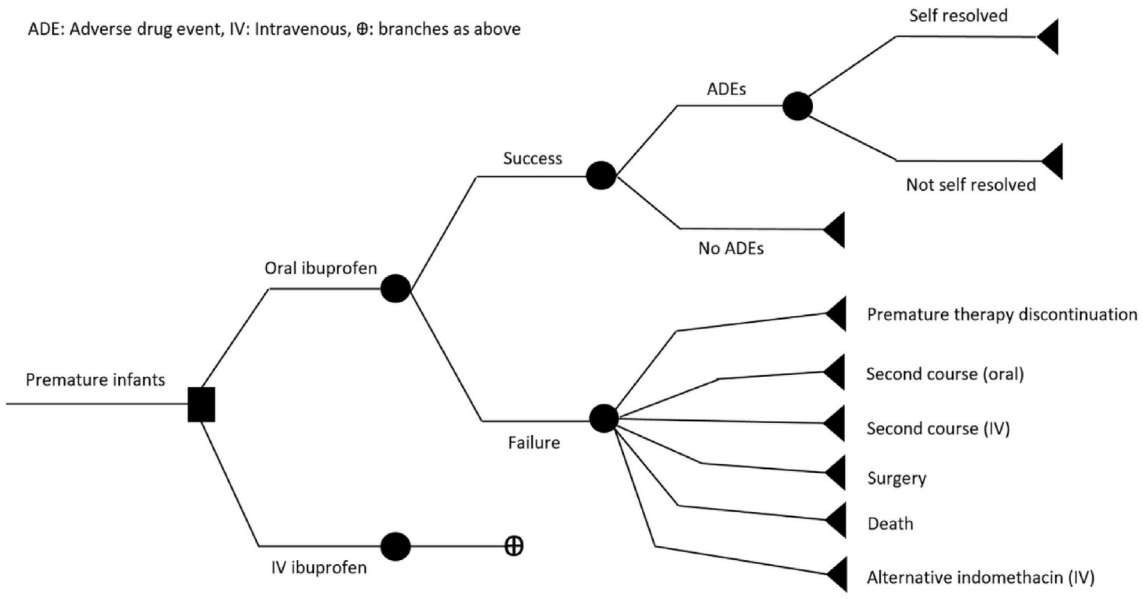
APPENDIX I. DECISION-ANALYTIC MODEL OF IBUPROFEN FORMULATIONS



APPENDIX II. OTHER BASELINE PATIENT CHARACTERISTICS

Characteristic	Oral ibuprofen (n = 40)	Intravenous ibuprofen (n = 59)	p-Value
	No (%)	No (%)	
Ethnicity			
Arab	26 (65)	41 (69.5)	0.81
Asian	13 (32.5)	15 (25.4)	
African	1 (2.5)	2 (3.4)	
Others	0 (0)	1 (1.7)	
Type of delivery			
Vaginal	13 (32)	28 (47.5)	0.23
Caesarean	27 (68)	31 (52.5)	
Multiple pregnancy			
Single	26 (65)	35 (59.3)	0.90
Multiple	14 (35)	24 (40.7)	
One- minute APGAR score			
Critically low (0–3)	6 (15)	9 (15.3)	0.1
Fairly low (4–6)	5 (12.5)	25 (42.4)	
Generally normal (7–10)	29 (72.5)	25 (42.4)	
Five- minute APGAR score			
Critically low (0–3)	2 (5)	1 (1.7)	0.32

(*continued on next page*)

. (*Continued*)

Characteristic	Oral ibuprofen (n = 40)	Intravenous ibuprofen (n = 59)	p-Value
	No (%)	No (%)	
Fairly low (4–6)	0 (0)	4 (6.8)	
Generally normal (7–10)	38 (95)	54 (91.5)	
Number of doses of surfactant			
0	0 (0)	9 (15.3)	0.14
1	25 (62.5)	24 (40.7)	
2	15 (37.5)	25 (42.4)	
3	0 (0)	1 (1.7)	
4	0 (0)	0 (0)	
Premature rupture of membrane			
Yes	19 (47.5)	17 (28.8)	0.09
No	21 (52.5)	42 (71.2)	
Duration of rupture of membrane			
<24 h	3 (15.8)	0 (0)	0.06
≥24 h	16 (84.2)	17 (100)	
Caffeine dose (maintenance dose)			
≤10 mg/kg	35 (87.5)	52 (88.1)	0.25
>10 mg/kg	5 (12.5)	7 (11.9)	

APPENDIX III. THE END OF FOLLOW-UP OUTCOME PROBABILITIES AND WEIGHTED COSTS OF ORAL IBUPROFEN AND IV IBUPROFEN

Therapy outcome	Oral ibuprofen			IV ibuprofen		
	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)
Closure success with ADEs (self-resolved)	0	0	0	0.05085	609,396.85 (166,958)	30,987.83 (8490)
Closure success with ADEs (needed further management)	0	0	0	0.01695	611,974.63 (167,664)	10,372.97 (2842)
Closure success without ADEs	0.65	297,558.85 (81,523)	193,413.25 (52,990)	0.28814	609,396.85 (166,958)	175,591.61 (48,107)
Closure failure						
Premature discontinuation of therapy (2 doses)	0.025	18,171.6 (4979)	454.29 (124)	0.01695	11,151.03 (3055)	189.01 (52)

. (*Continued*)

Therapy outcome	Oral ibuprofen			IV ibuprofen		
	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)
Received second course oral ibuprofen	0.1	18,974.6 (5199)	1897.46 (520)	0.08475	30,830.21 (8447)	2612.86 (716)
Received second course oral ibuprofen followed by IV indomethacin	0.025	19,924.4 (5459)	498.11 (137)	NA	NA	NA
Received second course IV ibuprofen	0.05	25,077.2 (6870)	1253.86 (344)	0.32203	25,975.34 (7117)	8364.84 (2292)
Received second course IV ibuprofen followed by third course IV ibuprofen	NA	NA	NA	0.03390	13,307.97 (3646)	451.14 (124)
Received second course IV ibuprofen followed by third course oral ibuprofen	NA	NA	NA	0.01695	13,286.73 (3640)	225.21 (62)
Received second course IV ibuprofen followed by surgery	NA	NA	NA	NA	NA	NA
Received second course IV ibuprofen followed by death	NA	NA	NA	0.03390	16,647.79 (4561)	564.36 (155)
Received second course IV ibuprofen followed by third course IV indomethacin	NA	NA	NA	NA	NA	NA
Received second course IV followed	0.025	25,608.00 (7016)	640.20 (175)	NA	NA	NA

(*continued on next page*)

. (*Continued*)

Therapy outcome	Oral ibuprofen			IV ibuprofen		
	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)	Probability	Cost per patient, QAR (USD)	Proportional cost, QAR (USD)
by IV indomethacin followed by surgery						
Required surgery after first course	0.125	20,872.16 (5718)	2609.02 (715)	0.08475	22,943.60 (6286)	1944.47 (533)
Death	NA	NA	NA	0.01695	18,342.77 (5025)	310.91 (85)
Switched to IV indomethacin (alternative)	NA	NA	NA	0.03390	20,313.27 (5565)	688.62 (189)
Total cost per patient	**QAR 200,766.19 (US$ 55,004)**			**QAR 232,303.81 (US$ 63,645)**		

*IV: intravenous, ADE: adverse drug event, N/A: Not applicable, USD 1: QAR 3.65.

APPENDIX IV. (A) UNIT COSTS OF NEONATAL INTENSIVE CARE RESOURCES, AND THEIR VARIABILITY FOR THE ONE-WAY SENSITIVITY ANALYSIS. (B) OUTCOME PROBABILITIES AND THEIR UNCERTAINTY RANGES

A:

Item/Name of test	Unit	Unit cost (QAR)*	Variation range**	
			Low	High
Ibuprofen	100mg/5 mL bottle	1.48	1.33	1.62
Ibuprofen	10mg/2 mL ampoule	543.7	489.33	598.06
Indomethacin	1 mg vial	2183.26	1964.94	2401.59
Amikacin	100mg/2 mL vial	1.71	1.53	1.88
Vancomycin	500 mg vial	7.315	6.58	8.047
Metronidazole	500mg/100 mL vial	3.261	2.93	3.59
Packed platelet	1 unit	2555	2299.5	2810.5
Complete blood count	1 test during NICU	43	38.7	47.3
Calcium	1 test during NICU	8	7.2	8.8

. (*Continued*)

Item/Name of test	Unit	Unit cost (QAR)*	Variation range**	
			Low	High
Bilirubin	1 test during NICU	8	7.2	8.8
Protein	1 test during NICU	8	7.2	8.8
Albumin	1 test during NICU	8	7.2	8.8
Alkaline phosphatase	1 test during NICU	261	234.9	287.1
Alanine aminotransferase	1 test during NICU	8	7.2	8.8
Aspartate aminotransferase	1 test during NICU	8	7.2	8.8
Glucose	1 test during NICU	8	7.2	8.8
C-reactive protein	1 test during NICU	14	12.6	15.4
PH	1 test during NICU	30	27	33
PO_2	1 test during NICU	8	7.2	8.8
Partial pressure of carbon dioxide (PCO_2)	1 test during NICU	8	7.2	8.8
Bicarbonate (HCO_3)	1 test during NICU	8	7.2	8.8
Base excess	1 test during NICU	8	7.2	8.8
Urea	1 test during NICU	8	7.2	8.8
Creatinine	1 test during NICU	8	7.2	8.8
Sodium	1 test during NICU	8	7.2	8.8
Potassium	1 test during NICU	8	7.2	8.8
Chloride	1 test during NICU	8	7.2	8.8
International normalised ratio	1 test during NICU	57	51.3	62.7
Prothrombin time	1 test during NICU	27	24.3	29.7
Partial thromboplastin time	1 test during NICU	31	27.9	34.1
X-radiation	1 test during NICU	60	54	66
Ultrasound scan	1 test during NICU	210	189	231
Echocardiogram	1 test during NICU	380	342	418
NICU bed stay	Stay per day	5862.37	5276.13	6448.61
Mechanical ventilator	1 machine	429.59	386.63	472.55

*USD 1 = QAR 3.65.

**The values of a unit cost of a resource is highly certain as this was directly and individually collected for the resource based on updated records of the finance department at the study setting. The cost variability in the sensitivity analysis is not to compensate for anticipated uncertainty in values, but to account for potential future variations in the unit price because of cost inflation or discounts, and to increased generalizability. For this purpose, the value of variability (±10%) was arbitrarily chosen based on expert opinion.

The type of variability distribution in the Monte Carlo simulation is uniform, which is to maintain a constant probability of distribution for the randomly selected values from the range. As discussed above, based on the purpose of this one-way sensitivity analysis, a probability distribution where the probability of a random value is highest near the most likely value is not of interest.

B:

	Probability and uncertainty distribution			
	Oral ibuprofen		IV ibuprofen	
Outcome	Base-case estimate*	Distribution range (95%CI)**	Base-case estimate*	Distribution range (95%CI)**
Success	0.6500	0.4832, 0.7937	0.3559	0.2355, 0.4913
Self-resolved ADEs with success	0.0000	0.0000, 0.0881	0.7500	0.1941, 0.9937
ADEs needing management with success	0.0000	0.0000, 0.0881	0.047	0.0004, 0.0909
No ADEs with success	1	0.8677, 1	0.8095	0.5809, 0.9455
Premature discontinuation of therapy (2 doses)	0.0714	0.0018, 0.3387	0.0263	0.0007, 0.1381
Second course oral ibuprofen	0.8000	0.2836, 0.9949	0.1316	0.0441, 0.2809
Second course oral ibuprofen followed by IV indomethacin	0.2000	0.0051, 0.7164	0.0000	0.0000, 0.5218
Second course IV ibuprofen	0.6667	0.0943, 0.9916	0.7917	0.5785, 0.9287
Second course IV ibuprofen followed by IV ibuprofen	0.0000	0.0000, 0.2316	0.0833	0.0103, 0.27
Second course IV ibuprofen followed oral ibuprofen	0.0000	0.0000, 0.2316	0.0417	0.0011, 0.2112
Second course IV ibuprofen followed by IV indomethacin	0.0000	0.0000, 0.2316	0.0000	0.0000, 0.1425
Second course IV ibuprofen followed by death	0.0000	0.0000, 0.2316	0.0833	0.0103, 0.27
Second course IV ibuprofen followed by IV indomethacin and then surgery	0.3333	0.0084, 0.9057	0.0000	0.0000, 0.1425
	0.3571	0.1276, 0.6486	0.1316	0.0441, 0.2809

. (*Continued*)

	Probability and uncertainty distribution			
	Oral ibuprofen		IV ibuprofen	
Surgery after first course				
Death	0.0000	0.0000, 0.2316	0.0263	0.0007, 0.1381
Alternative IV indomethacin	0.0000	0.0000, 0.2316	0.0526	0.0064, 0.1775

Abbreviations: IV: intravenous, ADE: adverse drug event, 95% CI: 95% confidence interval.
*Point estimates were outcome parameters that were directly based on the study cohort analysis.
**The uncertainty range for analysis in the Monte Carlo analysis was based on the 95% CI of the base-case value of model parameters. The trigen type of distribution was used for the point estimate to be the most frequent value (with no historical data available is support), and because the confidence interval is used for the uncertainty range; whereby, this allows the upper and lower boundaries to be skewed and also exceeded within the predefined confidence interval percentage.

APPENDIX V. THE SCENARIO SENSITIVITY ANALYSIS AND ITS CLINICAL AND COST-SAVING OUTCOMES

Categorical subgroups of preterm infant gestational age and birth weight distributions	PDA closure success rate with oral ibuprofen	PDA closure success rate with IV ibuprofen	Cost saving in favor of oral ibuprofen (QAR)*
Extremely preterm (<28 weeks gestational age)	79%	40%	13,415
Very preterm (28 $\leq$ 32 weeks gestational age)	85%	41%	5588
Moderate or late preterm (32 $\leq$ 37 weeks gestational age)	66%	25%	6309
<2500 and $\geq$ 1500 birth weight (gram)	80%	33%	8980
<1500 and $\geq$ 1000 birth weight (gram)	50%	38%	8765
<1000 birth weight (gram)	75%	41%	7116

Abbreviations: PDA: patent ductus arteriosus.
*USD 1 = QAR 3.65.