QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

THE EFFECTIVENESS, HEALTH CARE RESOURCE UTILIZATION AND COST-EFFECTIVENESS OF INTRAVENOUS PARACETAMOL VERSUS ALTERNATIVE ANALGESICS USED AMONG PATIENTS WITH ACUTE PAIN IN EMERGENCY DEPARTMENTS: SYSTEMATIC REVIEWS AND A META-ANALYSIS

BY

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ABSTRACT

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Title: The Effectiveness, Health Care Resource Utilization and Cost-effectiveness of Intravenous Paracetamol Versus Alternative Analgesics Used Among Patients with Acute Pain in Emergency Departments: Systematic Reviews and A Meta-Analysis.

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Background: Intravenous paracetamol (IVP), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids are widely used to provide analgesia in the emergency department (ED). This study evaluates the level of analgesia provided by IVP alone as compared to NSAIDs, opioids alone, or in combination in adults attending the ED with acute pain. Additionally, the study assesses systematic economic evaluation evidence to determine health care resource utilization and costs associated with drug administration for the management of acute pain.

Methods: To study the effectiveness of IVP, PubMed (MEDLINE), Web of Science, EMBASE OVID, Cochrane Library, SCOPUS, and Google Scholar were searched for randomized trials conducted on adult patients presenting to EDs with acute pain. The risk of bias (ROB 2) tool was used to evaluate the quality of identified trials. Meta-analysis was conducted to synthesize evidence on the clinical effectiveness of IVP versus NSAIDs or opioids or a combination for managing ED acute pain from these trials. A systematic review of economic evaluation studies was further conducted to assess health care resource utilization and costs of drugs used in patients with acute pain. Electronic searches were conducted in EMBASE, PubMed, and the Health Technology Assessment Database (HTA). Drummond et al. and Phillips checklists were used to evaluate the quality of identified studies. No meta-analysis was done for

synthesizing economic evaluation evidence.

Results: To study the effectiveness of IVP, twenty-seven trials (including 5426 patients) were included in the systematic review and twenty-five trials (5002 patients) in the meta-analysis. At 30 minutes IVP provided equivalent levels of analgesia compared to opioids, NSAIDs alone or in combination; pooled mean difference=0.09 [95%CI: -0.85, 1.05]. Patients treated with IVP, and opioids required similar quantities of rescue analgesia, but this was lower in those who received NSAIDs. Adverse events were 50% lower in patients receiving IVP (RR: 0.50; 95%CI: 0.40, 0.62) as compared to opioids and 30% higher in IVP than NSAIDs (RR: 1.30; 95%CI: 0.78, 2.17). Seven studies were included in the systematic review on economic evaluation with varied pain etiologies, suggesting that ED acute pain management treatments vary across healthcare systems which lead to differential costs and healthcare resource use. The IV administration of opioids was associated with significant costs and most of the cost of IV opioid administration occurs in the initial IV-line setting.

Conclusion: Based on the available evidence, IVP is an equally effective analgesic as opioids or NSAIDs or combined at initial 30 minutes in patients with acute pain. However, the use of IV opioids inflicts an economic burden on the healthcare system. A considerable heterogeneity was estimated in the meta-analysis results, and we were unable to assess the cost-effectiveness of IVP due to a lack of published studies.

نبذة مختصرة

الخلفية: يستخدم الباراسيتامول الوريدي(IVP) ، والأدوية غير الستيرويدية المضادة للالتهابات (NSAIDs) ، والمواد الأفيونية على نطاق واسع لتوفير التسكين في قسم الطوارئ (ED). تقييم هذه الدراسة مستوى التسكين الذي يقدمه IVP وحده مقارنة بالأدوية غير الستيرويدية المضادة للالتهابات و المواد الأفيونية وحدها أو مجتمعة في البالغين الذين يعانون من الألم الحاد في قسم الطوارئ. بالإضافة إلى ذلك، تقييم الدراسة أدلة التقييم الاقتصادي لتحديد استخدام موارد الرعاية الصحية والتكاليف المرتبطة بالأدوية المستخدمة لإدارة الألم الحاد.

المنهج: لدراسة فعالية الباراسيتامول الوريدي تم البحث في PubMed (MEDLINE) و Web of Science و EMBASE OVIDو Cochrane Libraryو SCOPUS وGoogle Scholar عن تجارب عشوائية أجريت على مرضى بالغين يعانون من ألم حاد في قسم الطوارئ. تم استخدام أداة خطر التحيز (ROB 2) لتقييم جودة التجارب المحددة. تم إجراء التحليل التلوي لتجميع الأدلة على فعالية الباراسيتامول الوريدي مقابل مضادات الالتهاب غير الستيرويدية أو المواد الأفيونية وحدها أو مجتمعاً لإدارة الألم الحاد في قسم الطوارئ. كذلك، تم إجراء مراجعة منهجية لدراسات التقييم الاقتصادي لتقييم استخدام موارد الرعاية الصحية وتكاليف الأدوية المستخدمة في المرضى الذين يعانون من الألم الحاد. أجريت عمليات البحث الإلكترونية في EMBASE و PubMedو(Health Technology Assessment Database (HTA وتم استخدام Drummondو Phillips checklistsلتقييم جودة الدراسات المحددة. لم يتم إجراء تحليل تلوي لتجميع أدلة التقييم الاقتصادي.

النتائج: لدراسة فعالية الباراسيتامول الوريدي، تم تضمين سبعة وعشرين تجربة (بما في ذلك 5426 مريضًا) في المراجعة المنهجية وخمسة وعشرين تجربة (5002 مريض) في التحليل التلوي. في الدقيقة 30، قدم الباراسيتامول الوريدي مستويات مكافئة من التسكين مقارنة بالمواد الأفيونية ومضادات الالتهاب غير الستيرويدية وحدها أو مجتمعة؛ فرق المتوسط المجمع =[95%CI: -0.85, 1.05] 0.09. المرضى الذين تم علاجهم بالباراسيتامول الوريدي، والمواد الأفيونية تطلبوا كميات مماثلة من المسكنات الإنقاذية، لكن هذا كان أقل لدى أولئك الذين تلقوا مضادات الالتهاب غير الستيرويدية. وكانت الأحداث الضارة أقل بنسبة 50٪ في المرضى الذين تلقوا البارسيتامول الوريدي مقارنة بالمواد الأفيونية (RR:0.50; 95%CI:0.40,0.62) و30% أعلى في مجموعة الباراسيتامول الوريدي مقارنة بمجموعة مضادات الالتهاب غير الستيرويدية(RR:1.30; 95%CI: 0.78, 2.17) وتم تضمين سبع دراسات في المراجعة المنهجية للتقييم الاقتصادي مع مسببات الألم المتنوعة. اشارت الدراسة إلى أن علاجات إدارة الألم الحاد في اقسام الطوارئ تختلف عبر أنظمة الرعاية الصحية مما يؤدي إلى تكاليف تفاضلية. ارتبط

إعطاء المواد الأفيونية عن طريق الوريد بتكاليف كبيرة، ومعظم تكلفة إدارة المواد الأفيونية الوريدية تحدث في الإعداد الأولي للخط الوريدي.

الخلاصة: بناءً على الأدلة المتاحة، فإن الباراسيتامول الوريدي هو مسكن فعال بنفس القدر مثل المواد الأفيونية أو مضادات الالتهاب غير الستيرويدية أو مجتمعة في أول 30 دقيقة في المرضى الذين يعانون من الألم الحاد. ولكن استخدام المواد الأفيونية الوريدية يفرض عبئًا اقتصاديًا على نظام الرعاية الصحية. تم تقدير عدم تجانس كبير في نتائج التحليل التلوي، ولم نتمكن من تقييم فعالية تكلفة الباراسيتامول الوريدي بسبب نقص الدراسات المنشورة.

DEDICATION

This thesis is dedicated to my parents. For their endless love, support, and encouragement.

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ABBREVIATIONS

ED	Emergency department
VAS	Visual analogue scale
NRS	Numerical analogue scale
T	Time
T0	Time point 0
T30	Time points 30 minutes
T60	Time points 60 minutes
T90	Time points 90 minutes
T120	Time points 120 minutes
IV	Intravenous
IM	Intramuscular
IVP	Intravenous paracetamol
PO	Oral paracetamol
PR	Rectally
NSAIDs	Non-steroidal anti-inflammatory drugs
RCT	Randomized control trials
IVhet	Inverse variance heterogeneity
AE	Adverse event
ICER	Incremental cost effectiveness ratio
WTP	Willingness-to-pay
PSA	Probabilistic sensitivity analysis
CEAC	Cost effectiveness acceptability curve
QALY	Quality Adjusted Life Year

CHAPTER 1: INTRODUCTION

Background

Pain is a common reason for attendance in Emergency Departments (EDs) and is reported by around two-thirds of patients [(1)]. Analgesia is prescribed in response to pain severity with mild-moderate pain treated with oral or intravenous non-steroidal medications, paracetamol (acetaminophen) and/or weak opioids, and severe pain commonly treated with titrated intravenous opioids [(2)]. Pain may be assessed using the visual analogue scale (VAS) and/or numeric rating scale (NRS) [(3)].

Paracetamol is widely used in ED and prehospital, and in many countries is widely available for self-administration [(4)]. Paracetamol can be administered orally (PO), parenterally (IV and IM), rectally (PR), and trans buccally. Paracetamol is a centrally acting cyclooxygenases inhibitor with an excellent safety profile at therapeutic doses. Dosages are 10-15 mg/kg in children and most commonly 1 gram in adults, with pharmacokinetic evidence suggesting little need for dosage adjustment in various adult subpopulations.

Studies have reported variable efficacy paracetamol as an analgesic in the ED. Intravenous paracetamol offers a more rapid (around 10 minutes) analgesic effect than oral and rectal preparations, which see peak effects within around 30-60 minutes. Plasma concentration is comparable at 30-60 minutes for analgesic effect of intravenous paracetamol [(5)]. Oral and intravenous paracetamol have similar analgesic effects at 30 minutes post-dosing [(6)]. Intravenous paracetamol is associated with higher costs and complexity but allows administration in patients who are unable to tolerate the oral route. However, it is widely used in EDs [(7-11)]. Paracetamol is reported as having fewer side effects compared to opioids and non-steroidal anti-inflammatory drugs (NSAIDs) in therapeutic doses [(12)].

A 2016 systematic review concluded that there was low-quality and poor evidence for the use of intravenous paracetamol in the ED with no basis for its use as a primary analgesic for ED care [13]. However, many patient groups are attending the EDs who are not able to tolerate oral medications. Previous systematic reviews on the use of intravenous paracetamol in the ED, have focused on specific patient groups, such as renal colic or musculoskeletal injuries [14, 15]. The 2016 systematic review did not include a meta-analysis, and 23 relevant trials were subsequently published after this study.

Previous studies addressed the efficacy and the related adverse events (AE) of different medications such as paracetamol, opioids and NSAIDs, etc. used in ED. However, there is a lack of evidence on health care resources utilization and costs associated with the administration of these drugs for patients presented in EDs.

Research questions

- Is IV paracetamol more effective than NSAIDs and opioids in reducing pain scores at the time 30 minutes?
- Is IV paracetamol more effective than NSAIDs and opioids in reducing pain scores at the time, 60, 90, and 120 minutes?
- Which analgesic medication is associated with lower AEs?
- Which analgesic medication requires a lower proportion of rescue analgesia?
- Which analgesic medication is cost-effective compared to an alternative drug in ED?

Objectives

A. Conduct a systematic review and meta-analysis of trials comparing the efficacy of intravenous paracetamol to alternative analgesics in patients attending EDs:
    i. To evaluate the effectiveness of intravenous paracetamol in reducing pain

at different time points (30, 60, 90, and 120 minutes from presentation) compared to opioids and NSAIDs.

ii. To identify AEs associated with each group of medications.

iii. To estimate the proportion of patients who require rescue analgesia in each group.

A. Systematically review existing economic evaluation evidence to determine health care resource utilization and costs associated with drug administration for the management of acute pain:

i. To identify which drug (paracetamol, NSAIDs, and opioids) is more cost-effective in managing acute pain in the EDs.

ii. To assess the related costs associated with IV administration in paracetamol, NSAIDs, and opioids including complications and AEs management associated with IV administration in these drugs, costs spent to administer and monitor drugs.

THESIS STRUCTURE

This thesis consists of two related studies. The first study is a systematic review and a meta-analysis of the analgesic effect of intravenous paracetamol in patients presenting to the emergency departments (EDs) with acute pain conditions, presented in Chapter 2 as the effectiveness study. The effectiveness of intravenous paracetamol is compared to the most common analgesics (opioids and NSAIDs) used in EDs at different time points.

The second study of this thesis, presented in Chapter 3, is a systematic review of the economic evaluation of the same medications used in the first part. This economic evaluation study research's cost-effectiveness studies considering costs along with the health outcomes.

Chapter 4 includes an overall conclusion and recommendations for the two studies.

CHAPTER 2: EFFECTIVENESS STUDY

Literature review

Acute pain

Acute pain is defined as "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness" [16]. It is caused by injury, illness, surgery, trauma, or painful medical procedures and it serves as a warning of disease or a threat to the body. It generally lasts a few days and goes away after the underlying reason is treated. Acute pain from a new tissue injury may last for six months. Untreated acute pain may lead to chronic pain that increases the burden on the health care system [17].

The neurobiology of pain described by J-M Besson [18], Glifford Woolf, and Richard Mannion [19] When the tissue integrity is threatened by mechanical, chemical, or thermal threats, nociceptive neurons increase their discharge rate. Nociceptors release in accordance with the logarithm of stimulus intensity. high-threshold nociceptors respond when the intensity of pain exceeds the threshold [18, 19]. Nociceptors are activated by tissue damage, which initiates a local inflammatory response that is sustained by numerous mediators and immune cells. These mediators either activate dormant or sensitize functional nociceptors. It thought the constant or recurrent release of mediators differentiates between cancer or chronic illnesses [18, 19].

Several guidelines for managing acute pain were initiated in the 1980s, where various models implemented that share key strategy including [20]: the assessment of the available options for pain control for patients that provides instruction in simple cognitive-behavioral techniques; a routine assessment of pain by monitoring vital signs; early treatment of pain as possible; the use of different intervention together (drug and

non-drug); selection of treatment based on the clinical situation, modification of treatment based on patient response, and maintenance of pain control after discharge.

Acute pain by disease etiology

Kidney stone disease (Urolithiasis)

Urolithiasis is a common urologic condition that affects between 8-19 % in males and 3-5 % in females [(21)]. The most common cause of renal colic is urinary tract obstruction [(22)]. The obstructions usually occur in the vescoureteric junction, mid ureter, and pelvi-ureteric junction between the kidney pelvis and the ureter [(22)]. These junctions are usually obstructed by stones, approximately 80% of the obstructions were caused by stones [(23)].

Stones are divided into four categories. Calcium oxalate is the most common type of kidney stone. It is formed when calcium was combined with oxalate in the urine. Another prevalent type of kidney stone is uric acid; the high intake of purine increases the production of monosodium urate that potentially forms stones in the kidney. Infections in the upper urinary tract are responsible for struvite stones, but these stones are less prevalent compared to previously mentioned stones. Cystine stones are another rare type and are caused by a rare disorder called “cystinuria”; this condition causes natural substances called “cystine” into the urine, the high concentration of these substances forms kidney stones [(23)].

Musculoskeletal disorders (MSD)

Musculoskeletal disorders are injuries or disorders of the muscles, tendons, nerves, cartilage, and spinal discs. Traumas to the musculoskeletal system are among the most common presentations in the emergency department [(24)]. Musculoskeletal

conditions are characterized by pain and limitations in mobility, dexterity, and in the overall level of functioning [24]. In a recent analysis [23], results showed approximately 1.71 billion people globally have a musculoskeletal condition; 441 million are in High-Income countries, 427 million in the Western Pacific Region, and 369 million in South-East Asia Region [25].

Abdomen pain (ABD)

The acute abdomen may be caused by inflammation, infection, vascular occlusion, or obstruction. The major causes of an acute abdomen include acute pancreatitis, appendicitis, cholecystitis, and diverticulitis [26]. For pancreatitis, the annual incidence is between 4.9 and 73.4 cases per 100,000 worldwide [27, 28]. Dysmenorrhea is a common issue among women in reproductive. In a systematic review of fifteen studies, the prevalence of dysmenorrhea varies between 16% and 91%, and 2% - 29% of women studied suffered from severe pain [29].

The pathogenesis of acute pancreatitis is associated with inappropriate activation of "trypsinogen to trypsin and due to the lack of prompt elimination of active trypsin inside the pancreas". Activation of digestive enzymes causes pancreatic injury and therefore causes an inflammatory response that is out of proportion to the response of other organs to a similar insult. Where the acute inflammatory response itself causes substantial tissue damage and might progress beyond the pancreas to a systemic inflammatory response syndrome, multiorgan failure, or death [30].

Low back pain (LBP)

Acute mechanical low back pain (LBP) is a common disorder including the muscles, bones, and nerves of the back where the pain varies from a dull constant ache

to sudden sharp feelings. Acute low back pain is defined as pain lasting for less than six weeks [31]. It is a common cause of attending ED where in the United States, it accounts for more than six million cases. Two-thirds of adults' experience low back pain at some point in their lives [31]. The most common causes of acute low back pain involve lumbar strain or sprain, abdominal aortic aneurysms, and osteoporotic fracture of the vertebraor pelvis [32].

Headache (HA)

Headaches conditions are among the most frequent disorders of the nervous system. Epidemiological studies reported the prevalence of headaches in the general population, where the average prevalence rate for one year was 46% and for a lifetime was 64%. In Western Europe and North America, the rates of migraine ranged between 5% and 9% in men and between 12% and 25% in women [33].

Burden of acute pain

A 2021 analysis of Global Burden of Disease (GBD), Musculoskeletal conditions were considered as the highest contributor to years lived with disability (YLDs) worldwide, it attributes by with approximately 149 million YLDS and accounts for 17% of all YLDs worldwide [15]. The results show that low back pain was the most significant contributor to the overall burden of musculoskeletal conditions [15]. Other contributors to the total burden of musculoskeletal conditions include fractures with 436 million people globally, "osteoarthritis (343 million), other injuries (305 million), neck pain (222 million), amputations (175 million), and rheumatoid arthritis (14 million)" [25]. Headache disorders are associated with personal and societal burdens of pain, damaged quality of life, disability, and financial cost. In 2019, headache disorders

contribute to 46.6 million YLDs globally, and 5.4% of total YLDs, with 88.2% of these being attributable to migraine [34].

A 2015 review reported that dysmenorrhea negatively impacts the quality of life [35]. It affects the relationships with family members, colleagues, and friends. In addition, the performance of the affected women in work and school work [35]. Another review done in 2016 included 50 studies on 41,140 adolescences and young women, a high proportion in school absenteeism was due to lack of class concentration during their period (79.4%). Where dysmenorrhea was associated with abdominal cramps (53.2%), low back pain (34.2%), and fatigue (21.6%). Furthermore, short sleeping hours <6 hours per day were associated with moderate to severe dysmenorrhea (OR: 3.05, 95%CI: 1.06 -8.77) [36].

In 2015, low back pain contributed to 60 million disability-adjusted life years, with an increase of 54% since 1990, where the highest increase was seen in low and middle-income countries [37]. While in several western countries, studies showed a high socioeconomic burden of low back pain [38, 39]. Where the societal costs for low back pain are estimated between 1% to 2% of the gross national product. About 80-90% of these costs were caused by productivity loss and disability [40].

Assessment of pain

To provide safe and effective pain management, a reliable and accurate assessment of pain is required. It assists in the diagnosis of the source of pain, the administration of suitable analgesia, and the monitoring of the therapy's effectiveness [41]. Pain perception is subjective, which complicates assessing the degree of pain a patient is experiencing .Self-reporting of pain severity is mostly used where possible as proxy ratings of pain have been shown to underestimate high pain levels [42]. In

emergency settings, usually, the assessment of pain takes place approximately every 15 minutes, with a more frequent assessment for severe pain [43]. There are several individual patient factors influencing the healthcare provider's choice in selecting the pain measurement tool to be used in assessing pain: developmental, emotional, cognitive, language, and cultural [41].

Numerical rating scale (NRS)

The numerical analogue scale can be delivered verbally or in written format [44]. Patients are asked to rate the intensity of their pain confirming to an 11-point scale of 0 (no pain) to 10 (worst pain). pain scores of 1-3 would be considered as mild pain, a score of 4-7 as moderate pain, and a score of >7 as severe [44].

Visual analogue scale (VAS)

In clinical studies, the visual analogue scale is the most commonly used scale for assessing pain intensity [44]. It takes the form of a 100/10 cm horizontal line with 'no pain' on the left end and 'worst possible pain' on the right. Where the patient marks the point along with the line that they feel corresponds to the level of pain they are experiencing. The pain score is reported as the measurement in millimeters or centimeters from the left end of the scale to the patient's mark [44].

Analgesia delivery in ED

In recent years, many different types of therapeutic agents have been used to relieve pain. However, three general categories of analgesic agents are frequently used for the most common types of pain: paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids [45].

Paracetamol (Acetaminophen)

In many national clinical practice guidelines, paracetamol is the first-line choice as an analgesic drug [46]. This drug has fewer side effects compared to opioids and Non-steroidal anti-inflammatory drugs (NSAIDs) in therapeutic doses [47]. In addition,

studies demonstrated that injected paracetamol could have comparable analgesic effects to injectable NSAIDs in ED, as well as morphine administration in several painful procedures [48, 49]. The other advantage of paracetamol is that it is affordable, and it is cheap in comparison with opiates [50, 51]. Just like most medications, the direct injection of paracetamol in the blood is the current practice in ED because of the pharmaco-kinetic advantages including higher bioavailability, achieving target plasma concentrations faster, and avoiding the hepatic first-pass effect [52]. This is in fact a common method used compared to oral administration in order to relieve patient's pain more effectively, despite the above considerations, a clear disadvantage regarding the use of the IV formulation is the noticeable cost difference when compared to oral administration but allows administration in patients who are unable to tolerate the oral route [53], the onset of analgesia occurs rapidly within 5-10 minutes [5]. The peak analgesic effect is obtained in 1 hour and its duration is approximately 4-6 hours [5]. To sum up, intravenous formulation paracetamol compared to oral involves a faster onset of action and greater analgesic efficacy.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used medications in the world due to their demonstrated efficacy in decreasing pain and inflammation [52]. NSAIDs are a group of therapeutic agents that have diverse structural and pharmacodynamics profiles but are similar in the mode of action [54]. Despite the similarities in the mechanism of action and toxicity, there is a slight difference in the manner of interaction with the cyclooxygenase enzyme [54]. The main mechanism of NSAIDs action involves the inhibition of the cyclooxygenase enzyme. This process results in the inhibition of prostaglandin and other eicosanoid synthesis to mitigate pain, inflammation, and fever [55]. NSAIDs' effectiveness has been proven in inflammatory

conditions such as acute trauma, arthritis, and pain associated with inflammation [54]. However, NSAIDs are also associated with increasing the risk of adverse gastrointestinal side effects, where about 60% of people who use NSAIDs experience some types of adverse effects [56, 57]. NSAIDs can affect the cardiovascular in numerous ways. The interference with the antiplatelet activity of aspirin worsens heart failure, increases blood pressure, and increases the risk of cardiovascular disease [58, 59].

Opioids

Opioids are another common group of medications that works by stimulating opioids receptors and exert their effects by mimicking endogenous opioids peptides called endorphins [60]. These receptors are distributed in the central nervous system with high concentrations in the nuclei of tractus solitarius, cerebral cortex, periaqueductal grey area, thalamus, and in the substantia gelatinosa of the spinal cord [61]. The receptors are coupled with inhibitory G-proteins and the activation process involves several actions including: closing of voltage sensitive calcium channels; simulation of potassium efflux causing hyperpolarization and reducing cyclic adenosine monophosphate production; subsequently causing a reduction in the neuronal cell excitability that in turn results in reducing the transmission of nociceptive impulses [61].

Opioids are mostly used in the treatment of acute pain including surgical procedures, labor, and other acute medical issues such as renal colic. Reasons for the common use of opioids include their relative safety, ease of titration, multiple routes of administration, and reliability as well as their effectiveness in somatic, visceral, and neuropathic pain [60]. Common opioid adverse effects include gastrointestinal side effects, central nervous system effects, and cholinergic as well as weight gain [62].

Pain management guidelines

Currently, there is no single standard of care exists for the management of pain in an emergency situation. The type of analgesic to use is determined by the severity of the pain, the nature of the injury, and local protocols. Generally, paracetamol or nonsteroidal anti-inflammatory medications (NSAIDs) drugs are commonly used for mild pain. While those with moderate pain receive paracetamol, NSAIDs, nitrous oxide or weak opioids. However, IV morphine or ketamine are recommended for patients with severe pain [63, 64].

World health organization (WHO) pain management strategy

The WHO analgesic ladder is a strategy proposed by the World health organization (WHO) in 1986 to provide adequate pain relief for cancer patients [64]. This analgesic path was established following the recommendations of an international group of experts and has undergone several modifications over years. Currently applied to manage several pain conditions including acute and chronic non-cancer such as degenerative disorders, musculoskeletal diseases, neuropathic pain disorders, and other chronic pain conditions. Where the original ladder consists of three main steps as follows:

- First step: "Mild pain: non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants".
- Second step: "Moderate pain: weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics, and with or without adjuvants".
- Third step: "Severe and persistent pain: potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol,

hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants".

The adjuvant indicates for a wide range of medications that belong to different medication classes. These medications can be of particular help in various painful conditions. Example of adjuvant includes tricyclic antidepressants (TCA) and serotonin-norepinephrine reuptake inhibitors (SNRIs)[64].

European guidelines

The French Society of Emergency Medicine (SFMU) published a guideline in 2010 [65], on the safe and effective administration of analgesia. Their most important recommendations were about the use of local and/or regional analgesia in managing pain when indicated and feasible, for slight trauma nitrous oxide is recommended while IV morphine is recommended in severe conditions alone or as part of multimodal analgesia [65]. Additionally, after opioid administration, the analgesia must be given again before pain recurrence. The recommendations emphasized the role of the nurses in pain assessment and treatment as part of a known service protocol, provided that an emergency physician can intervene without delay and at any time [65].

In Italy (2010), recommendations of seven pain and emergency medicine consensus groups were published [66]. The key recommendations state the use of IV paracetamol. Where oral paracetamol and NSAIDs were recommended for mild pain. However, NSAIDs, IV paracetamol and paracetamol in combination with weak oral opioids were recommended for moderate pain; and morphine and fentanyl for severe pain. The use of opioids in patients with acute abdominal pain does not increase the risk of error in the diagnostic and therapeutic pathway in adults, according to the researchers, therefore such concerns should not be used to delay analgesia [66].

The Netherlands Association of Emergency Nurses has developed pain management guidelines for trauma patients in the emergency care chain [67, 68]. The recommendations state that pain scores must be reported (NRS is suggested) and assessed at least three times, according to the guidelines: upon arrival, post-intervention, and at the end of the medical visit. The first treatment option is paracetamol, with additional NSAIDs or opioids as needed. While fentanyl and morphine are the preferred options for severe pain [67, 68].

The Pre-Hospital Emergency Care Council (PHECC) in the Republic of Ireland [69], has created clinical practice recommendations that cover a wide range of clinical scenarios faced by pre-hospital staff, including pain in adults and children, and have recently been updated. The guidelines suggest using an analogue or visual pain scale to quantify pain, as well as considering non-pharmacological pain management techniques such splinting, psychological support, heat or cold therapy, and patient positioning. If pain relief is insufficient, mild pain should be treated with oral paracetamol or ibuprofen, while moderate pain should be treated with inhaled methoxyflurane or nitrous oxide, as well as oral paracetamol and ibuprofen. In patients with severe pain, intranasal (IN) fentanyl should be used as first-line, followed by IV fentanyl or IV morphine; if pain persists, IV paracetamol or IV ketamine should be considered [69].

In the United Kingdom (UK), recommendations provided in 2017 by the Joint Royal Colleges Ambulance Liaison Committee and the Ambulance Service Association [70], recommend that all patients with pain be assessed for pain severity, with a simple 10-point verbal scale being the most appropriate. After each intervention,

the pain assessment should be repeated. A multimodal approach using analgesics with diverse modes of action is recommended for balanced analgesia [70].

United States (US) guidelines

Paracetamol or a nonsteroidal anti-inflammatory medication are the first-line pharmacologic agents for symptomatic pain relief in mild to moderate pain (NSAID)[71]. The best option depends on the type of pain and the patient's risk factors for NSAID-related side effects (e.g., gastrointestinal, renovascular, or cardiovascular effects). The analgesic effects of many NSAIDs are comparable. However, in patients with cardiovascular risk factors, cyclooxygenase-2 selective NSAIDs (e.g., celecoxib) should be used with caution and are more expensive than nonselective NSAIDs. If these first-line drugs aren't enough for mild to moderate pain, medications that target multiple pathways at once, such as a paracetamol/opioid combination, are reasonable options. Potent opioids are recommended to treat severe acute pain. Adjuvant medicines directed at the underlying condition can be administered at each step, for example, Tapentadol is a newer drug having dual effects [71].

Protocol of pain management in Qatar

Hamad medical corporation (HMC) developed an emergency medicine evidence-based clinical algorithm, endorsed by HMC emergency medicine physicians and other consultants for education and assistance with clinical practice in HMCs EDs [72]. The algorithm is not based on a specific international or regional guideline, but on several sources of evidence. It is intended to complement any related multispecialty Clinical Practice Guideline prepared as per HMC policy. It is not presented as the binding standard of care but is rather a reference tool to inform clinical judgment. The algorithm is applied to all adult patients (more than 14 years old) with pain that does

not have a diagnosis-driven approach; the aim is to provide early effective pain relief (figure1).

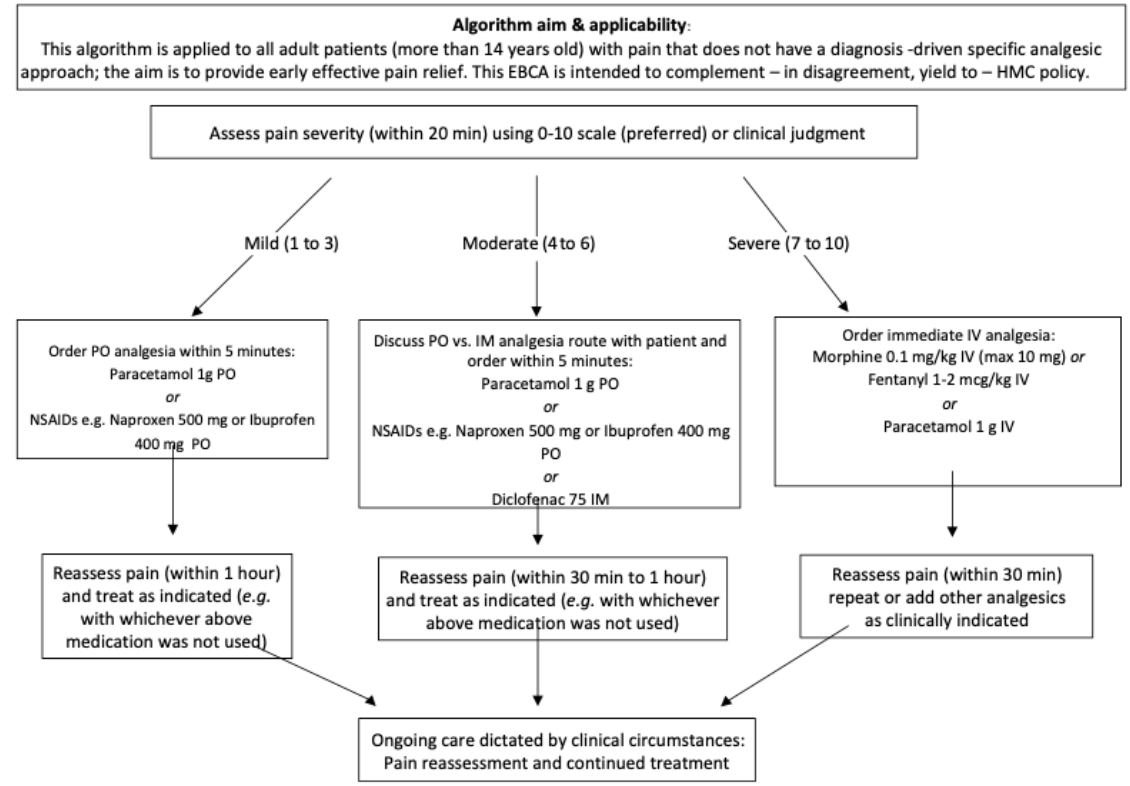

Figure 1.Algorithm of pain management in Qatar.

Methods

Protocol and registration

The review was designed utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [73]. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42021240099.

Inclusion and exclusion criteria

We included only RCTs performed on adults (>18 years) in the ED settings reporting NRS or VAS pain scores at baseline (T0) and 30 minutes (T30) post medication administration. There was no restriction on language (Table 1).

Table 1. PICO Research Question

Item	Description
Population:	Adult (>=18 years) patients visiting an ED with acute pain (no restriction on aetiology, acute pain defined as < 1 week).
Intervention:	Intravenous paracetamol, either fixed dose or as mg/kg.
Comparator:	Non-steroidal anti-inflammatory medications or opioids/opiates delivered (intravenous or intramuscular route).
Primary Outcome:	Reduction in pain score time zero (T= 0) to T= 30 minutes (T= 30) post administration of medication, no restriction on methods used to assess pain or pain scores.

Information sources and databases

The literature search was conducted using the electronic databases of MEDLINE (through PUBMED interface), Web of Science, EMBASE, and Cochrane Library with searches conducted with snowballing of related articles. The grey literature was accessed using Google Scholar and Trip Medical Databases (TRIP). The publication period was defined by each database searched. Previous systematic review

articles reporting on the use of intravenous paracetamol (IVP) as the analgesic drug for acute pain conditions in an ED setting were also reviewed. The Clinical Trials registry (clinicaltrial.gov) was searched for ongoing trials. Non-English language papers were translated to English for review except for one trial which was in Persian language.

Search strategy

The Medical Subject Headings (MeSh) used for the search strategy were as follows: (Paracetamol OR Acetaminophen OR Tylenol OR Panadol) AND (intravenous OR IV ORparenteral OR infusion OR drip OR venous OR injecting OR syringing OR shot) AND ("emergency medicine" OR "emergency department" OR causality OR acute care OR "emergency room" OR "triage room" OR ER OR "emergency clinic" OR "critical care") AND (analgesia OR analgesic OR "pain reduction" OR "pain relief" OR palliative OR pain killer) AND (Opioids OR NSAIDs OR "Non- steroidal anti-inflammatory drugs").

The following medical Journals were additionally hand searched: Journal of Pain Research, The American Journal of Emergency Medicine, Emergency Medicine Australia, European Journal of Emergency Medicine, Academic Emergency Medicine, Emergency Medicine Journal, and Annals Emergency Medicine.

Study selection and data extraction

Two reviewers independently screened titles, abstracts, and full-text articles. Any disagreements were resolved by a third reviewer. Two authors independently extracted data using a priori defined data collection sheets. Data extracted included author, year of publication, country, study design, aetiology of pain, sample size, time, method of pain scores, pain scores at T0, T30, T60, and T120, rescue analgesia at T30, T60, and T120, and all reported AEs. Pain scores were recorded exactly as published with some authors using the VAS and others NRS. After full analysis 12 trials were

excluded (Figure 2)

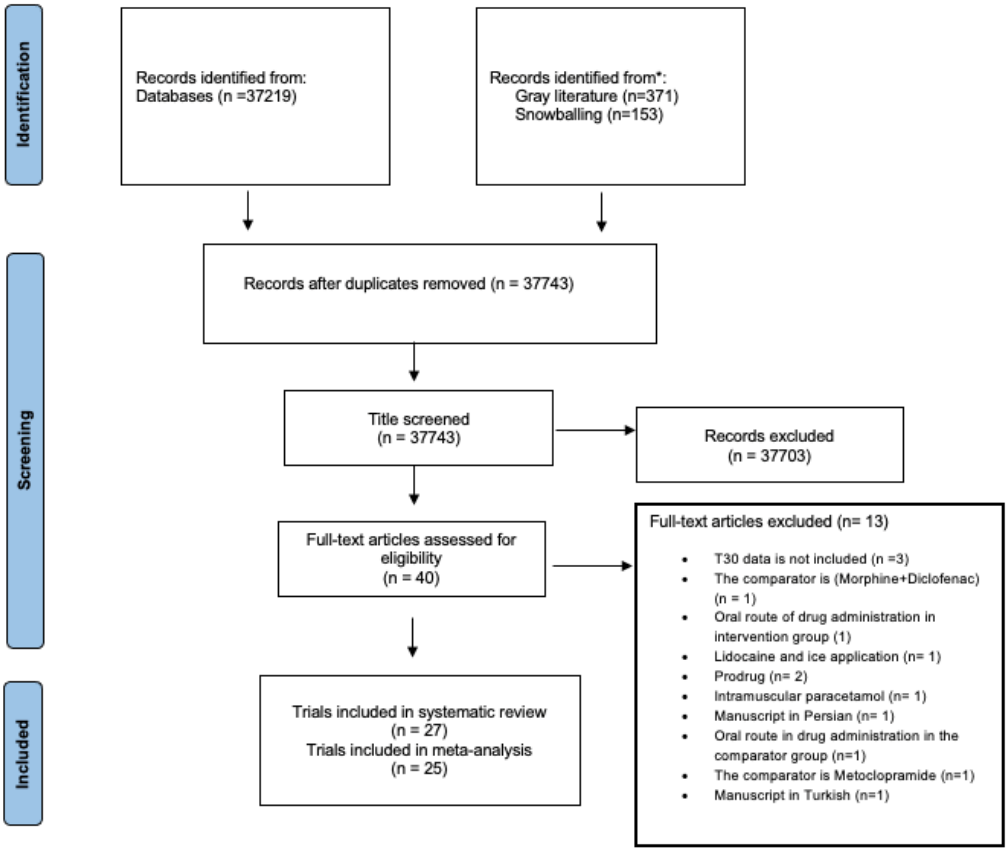

Figure 2. Flowchart representing the process of screening and selection of eligible trials, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methodological quality assessment

The quality assessment was performed independently by two reviewers using Risk of Bias (ROB 2) tool [74] (Table 2). Disagreement among the two reviewers was resolved by a third reviewer. Key data was missing from 25 papers and the lead authors were contacted to request the information [7, 8, 11, 28-33, 34-38, 41-43, 45, 46-53]. The ROB 2 assessment was reported as low risk, high risk, and unclear (Table 2). Twenty trials [7, 11, 31, 75-91] were classified as high risk or unclear due to missing or insufficient

information concerning baseline characteristics, allocation concealment, and analysis of the results. Seven trials [8, 9, 92-96] were assessed as low risk of bias.

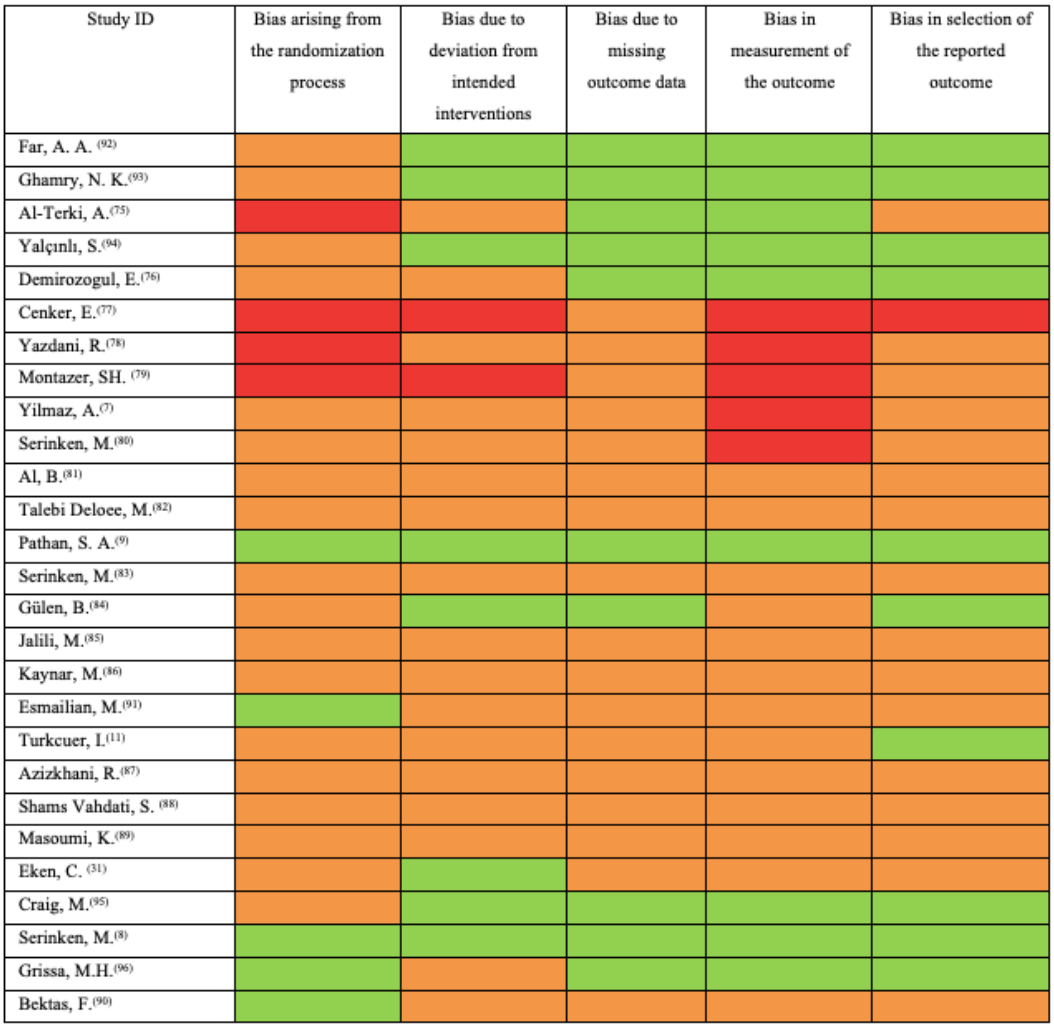

Figure 3. Methodological Quality Assessment of The 27 Studies Included

Statistical analysis

Stata 17 software [97] was used to calculate the overall pooled effect size using the inverse variance heterogeneity (IVhet) model [98]. The IVhet model makes no assumption regarding the distribution of the true effects and is a robust model in the presence of both heterogeneity and publication bias. In each trial, the effect size was calculated using the difference between the mean pain scores in the IVP and comparator groups at the T30, T60, T90, and T120. Forest plots were used to display the results. Statistical heterogeneity was assessed using Cochrane Q statistic (chi-square test) and I-squared(I2) statistics [51]. VAS and NRS scores were scaled 0 to 10, to allow pooling of all data. The lower limit usually indicates 'no pain at all' whereas the upper limit usually represent 'the worst pain ever' [44].

The pooled effect sizes were presented using standardized mean differences (SMD) and 95% confidence intervals (CI). Subgroups analyses were performed by pain aetiology classified in five a priori defined groups: renal colic, headache (migraine, tension headache), back pain, abdominal pain, and musculoskeletal injuries. A second subgroup analysis compared the comparator analgesics (opioids and NSAIDS) each to IVP. The pooled risk ratio (RR) of AE and the proportion of patients requiring rescue analgesia at T30, T60, and T120 were estimated between the IVP and comparator groups. Relative risk was calculated based on the number of participants with at least one AE at any endpoint time during the trial periods. The need for rescue analgesia was identified either by patient request or VAS/ NRS scores. Potential publication bias was examined by funnel plots [99].

To enhance the interpretability of results, the standardized mean difference was transformed back to the natural units of NRS by multiplying it by the pooled baseline standard deviation of the most representative trial [53, 54], and the results

were presented as mean difference (MD) and 95% CI.

Results

Systematic review

Study characteristics

Twenty-seven articles (including 5426 patients) were included in the systematic review, all published in English (2009 to 2020) and all using the VAS or NRS to assess pain severity (Figure 2 and tables 3, 4). The trials included in this review had no restriction on the severity of pain with pain scores at recruitment ranging from 3.0 to 9.2 (mean 7.6) and included patients reporting mild (3-4), moderate (5-7), and severe (8-10) pain. All trials were double-blind RCTs except one, which was not blinded and in which the comparator arm was acupuncture [86]. IVP was administered as a single dose of one gram in 100 ml NS in 24 trials [7-9, 11, 31, 75-80, 84-86, 88-91, 93, 95, 96] , at a dose of 10 mg/kg in two trials [81, 94] and at 15 mg/kg in three trials [82, 87, 92]. The infusion rate for the administration of IVP was as a rapid bolus infusion [7, 11, 76] or slow infusion over five to 20 minutes [8, 9, 80, 82-84, 89].

All included trials measured pain scores at T0 and at T30, nine [20, 22, 27, 30, 40, 44-47] trials measured pain at T60, two at T90 [22, 48], and two [30, 45] at T120. Twelve trials compared IVP with opioids [21, 30, 33, 34, 36, 38-40, 42, 43, 45, 47], eleven to IV morphine and one to IV tramadol [45]. In nine trials the comparator arm was NSAIDs [11, 20, 26-28, 31, 37, 46, 48]; diclofenac in one [37], parecoxib in two [26, 48], ibuprofen in two [28, 46] and dexketoprofen in four [11, 20, 27, 31]. In six trials [22, 29, 32, 35, 41, 44] IVP was compared with opioids (five compared to morphine and one to fentanyl) and NSAIDs. Two of the total included trials also compared IVP to placebo as an extra arm [34, 42]. Nine trials assessed IVP against opioids at time points other than T30: six at T60 [22, 30, 40,44, 45, 47] one at T90 [22] and two at T120 [30, 45], five trials compared IVP to NSAID's at T60 [20, 22, 27,

[44, 46] and two at T90 [22, 48] (Table 3).

The trials included varied pain aetiology. Twelve trials involved patients with renal colic (3544 patients) [8, 9, 75, 77-79, 81, 86, 87, 89, 90, 96], seven musculoskeletal injuries (791 patients) [7, 76, 82, 85, 91, 94, 95], three (365 patients) headaches (migraine, tension headache)[11, 88, 92], three (289 patients) abdominal pain (pancreatitis, dysmenorrhea) [84, 93, 100], and two (437 patients) back pain [31, 83].

Twelve trials concluded that there was no significant difference in pain scores between IVP and the comparator groups (opioids or NSAIDs) at T30 post-delivery [7, 11, 31, 75, 78, 79, 81, 84, 88, 91, 95, 101]. Six trials reported that IVP provided superior analgesia to comparator medications [8, 85, 88-90, 96]; five to IV morphine [8, 85, 88-90], one to IM NSAIDs (piroxicam) [96]. Six trials concluded that IVP provided inferior analgesia; two compared to NSAIDs [9, 76, 77, 80, 81, 94] and three to opioids (two[83, 87] to morphine and one to tramadol [93])

Table 2. Characteristics of Included Trials

Authors and Year of publication	Country	Pain Condition	Pain Analogue Scale	No.of Patients in (Paracetamol/Opioids/NSAIDs/ placebo/other) groups	Intervention Dose and the Route of Administration	Comparator Dose and the Route of Administration	Timing
Far et al., 2020	Iran	Post trauma headache	VAS	35/35/35/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, ketorolac: 30 mg/mL IV, morphine: 5 mg/mL	T= 0, 15, 30 and 60 minutes
Ghamry et al., 2020	Egypt	Dysmenorrhea	VAS	50/50/-/-/-	IV, paracetamol: 1 g (1,000 mg/mL)	IV, 100-mg tramadol in 100-mL normal saline	T= 0, 15, 30, 60 and 120 minutes
Al-Terki et al., 2020	Kuwait	Renal colic	VAS	105/-/103/-/-	IV, paracetamol: 1 g (1,000 mg/mL)	IV, 40 mg of parecoxib infusion	T= 0 and 30 minutes
Yalçinli et al., 2020	Turkey	Soft tissue injury	NRS	86/-/86/-/-	IV, paracetamol: 10 mg/mL 1000 mg	IV, ibuprofen: 400 mg/mL 4 mL	T= 0, 15,30 and 60 minutes
Demirozogul et al., 2019	Turkey	Non traumatic musculoskeletal pain	NRS	100/-/100/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, Dexketoprofen: 50 mg in 150 mL normal saline.	T= 0, 15, 30 and 60 minutes
Cenker et al., 2018	Turkey	Renal colic	VAS	99/-/97/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, ibuprofen: 800 mg in 100 mL normal saline	T= 0, 15 and 30 minutes
Serinken et al., 2018	Turkey	Dysmenorrhea	VAS	50/-/49/-/-	lV, paracetamol: 1 g (1000 mg/mL)	IV, dexketoprofen: 50 mg in 100 mL normal saline	T= 0, 15 and 30 minutes
Yazdani et al., 2018	Turkey	Renal colic	VAS	50/50/50/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 10 mg sulfate in 100 mL normal saline IV, ketorolac: 30 mg in 100 mL normal saline	T= 0 and 30 minutes
Yilmaz et al., 2019	Turkey	Musculoskeletal trauma	VAS	100/-/100/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, dexketoprofen: 50 mg in 150 mL normal saline	T= 0, 15, 30 and 60 minutes
Montazer et al., 2018	Iran	Renal colic	VAS	152/192/-/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 0.1 mg/kg in 100 mL normal saline	T= 0, 15, 30, 60 and 120 minutes
Al et al., 2017	Turkey	Renal colic	VAS	100/100/100	IV, paracetamol: 10 mg	IV, dexketoprofen: 50 mg	T=0, 15 and 30

						IV, fentanyl: 2 µg/kg	minutes
Talebi Deloee et al., 2017	Iran	Isolated long bone fractures	VAS	24/26/-/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine sulfate: 0.1 mg/kg	T= 0, 5 and 30 minutes
Gulen et al., 2016	Turkey	Pancreatitis	VAS	30/30/30/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, dexketoprofen: 50 mg IV, tramadol: 1 mg/kg in 100 mL normal saline	T= 0 and 30 minutes
Jalili et al., 2016	Iran	Limb trauma	NRS	30/30/-/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 0.1 mg/kg in 100 mL normal saline	T= 0, 15 and 30 minutes
Pathan et al., 2016	Qatar	Renal colic	NRS	548/549/548/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 0·1 mg/kg Intramuscular injection of diclofenac: 75 mg/3 mL	T= 0, 30, 60 and 90 minutes
Serinken et al., 2016	Turkey	Sciatica	VAS	100/100/-/100/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, Morphine:0.1 mg/kg in 100 mL of normal saline IV placebo: 100 mL of normal saline	T= 0 and 30 minutes
Esmailian et al., 2015	Iran	Rib fracture	NRS	25/29/-/-/-	IV, paracetamol: 1g (1000 mg/mL)	IV, morphine: 0.1 milligram per kilogram of body weight, single dose	T= 0 and 30 minutes
Kaynar et al., 2015	Turkey	Renal colic	VAS	42/-/40/-/42	IV, paracetamol: 1 g	IM, diclofenac sodium: 75 mg Acupuncture	T= 0, 10, 30, 60 and 120 minutes
Azizkhani et al., 2013	Iran	Renal colic	VAS	62/62/-/-/-	IV, paracetamol: 15 mg/kg	IV, morphine: 0.1 mg/kg	T= 0 and 30 minutes
Eken et al., 2014	Turkey	Low back pain	VAS	46/45/46-/-	IV, paracetamol; 1 g (1000 mg/mL)	IV, morphine:0.1 mg/kg in 100 mL normal saline IV, dexketoprofen: 50 mg in	T= 0,15 and 30 minutes

						100 mL normal saline solution	
Masoumi et al., 2014	Iran	Renal colic	VAS	54/54/-/-/-	IV, paracetamol: (1000 mg/mL)	IV, morphine: 0.1mg/kg in 100 mL normal saline	T= 0, 15, 30 and 60 minutes
Shams Vahdati et al., 2014	Iran	Post trauma headache	VAS	30/30/-/-/-	IV, paracetamol: 1 g/100 mL	IV, morphine: 0.1 mg/kg/100 mL/10 minutes	T= 0, 15, 30 minutes and after 1 week
Turkcuer et al., 2014	Turkey	Acute migraine	NRS	100/-/100/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, dexketoprofen: 50 mg	T= 0, 15 and 30 minutes
Craig et al., 2012	US	Isolated limb injury	VAS	28/27/-/-/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 10 mg	T= 0, 5, 15, 30 and 60 minutes
Serinken et al., 2012	Turkey	Renal colic	VAS	40/40/-/-/-	IV, Paracetamol: 1 g (1000 mg/mL)	IV, morphine: 0.1 mg/kg in 100 mL normal saline bolus infusion in 4 to 5 minutes	T= 0, 15 and 30 minutes
Grissa et al., 2011	Tunisia	Renal colic	VAS	50/-/50/-/-	IV, paracetamol: 1 g (1000 mg/mL)	Intramuscular injection of piroxicam: 20 mg	T= 0, 5, 10, 15, 30, 45 and 90 minutes
Bektas et al., 2009	Turkey	Renal colic	VAS	55/55/-/55/-	IV, paracetamol: 1 g (1000 mg/mL)	IV, morphine: 0.1 mg/kg in 100 mL normal saline	T= 0, 15 and 30 minutes
						IV, placebo: 100 mL normal saline	

Table 3. Demographic Data of Trials.

Study ID	Pain condition	Gender Distribution by Drug Group				Age Distribution by Drug Group Mean ± SD / Median (IQR)			
		Paracetamol	Opioids	NSAIDs	Other	Paracetamol	Opioids	NSAIDs	Other
Far, A. A. [92]	Headache	M (65.7%) F (34.3%)	M (68.6%) F (31.4%)	M (57.1%) F (42.9%)	-	30.6 ± 5.7	32.8 ± 8.3	33.5 ± 9.7	-
Ghamry, N. K.[93]	Dysmenorrhea	-	-	-	-	22.1 ± 4.5	22.9 ± 4.5	-	-
Al-Terki, A.[75]	Renal colic	M (79.4%) F (20.6%)	-	M (82.2%) F (17.8%)	-	41.7 ± 11	-	41.9 ± 10.5	-
Yalçınlı, S.[94]	Soft issue injuries	M (62%) F (38%)	-	M (71%) F (29%)	-	32.8 ± 11.4	-	32.4 ± 10	-
Demirozogul, E.[76]	Non-traumatic musculoskeletal pain	* Overall, (48%) of study subjects were female and (52%) were male. The mean age was 32.6.							
Cenker, E.[77]	Renal colic	* Overall, (64.5%) of study subjects were male and (35.5%) were female. The mean age was 36 ± 9.							
Yazdani, R.[78]	Renal colic	* Overall, (74%) of study subjects were male and (26%) were female. The mean age was 33.51 ± 10.12.							
Montazer, SH. [79]		M (69.08%) F (30.92%)	M (67.71%) F (32.29)	-	-	41.29 ±12.65	41.54±13.93	-	-
Yilmaz, A.[7]	Acute musculoskeletal trauma	* Overall, (63%) of study subjects were male and (37%) were female.				36.75 ± 1.94	-	37.8 ± 15.37	-
Serinken, M.[80]	Dysmenorrhea					21 (19 to 23)		21 (19 to 22)	
Al, B.[81]	Renal colic	* Overall, (72%) of study subjects were male and (28%) were female. The majority of cases were between the ages of 25–39 (49.7%) and the average age was 42.2 years.							
Talebi Deloee, M.[82]	Isolated diaphyseal long bone fracture	* Overall, (78%) of study subjects were male and (22%) were female. The mean age of the patients was 39 ± 14.6.							
Pathan, S. A.[9]	Renal colic	M (81%) F (19%)	M (83%) F (17%)	M (84%) F (16%)	-	34.4 (28.6 to 41.5)	34.7 (28.8 to 41.7)	35.1 (29.2 to 42.6)	-
Serinken, M.[83]	Sciatica	M (43%) F (57%)	M (48%) F (52%)	-	(57%)	43.7 ± 9.8	44.6 ± 10.2		40.3 ± 9.5
Gülen, B.[84]	Pancreatitis	* Overall, (58.9%) of study subjects were male and (41.1%) were female. The mean age of the patient was 53.5±13.3.							
Jalili, M.[85]	Acute limb trauma	* Participants aged 18 years and older.							
Kaynar, M.[86]	Renal colic	M (55%) F (45%)	-	M (65%) F (14%)	-	46.3 (19-81)	-	37.98 (18-72)	-
Esmailian, M.[91]	Rib fracture	M (80%) F (20%)	M (65.5%) F (34.5%)	-	-	41.0 ± 14.3	41.3 ± 14.1	-	-
Turkcuer, I.[11]	Acute migraine attack	* Overall, (81%) of study subjects were female and (19%) were male. The mean age of patients was 30.1±11 years.							
Azizkhani, R.[87]	Renal colic	M (67.7%) F (32.3%)	M (67.7%) F (32.3%)	-	-	38.40 ± 11.60	39.73 ± 11.62	-	-
Shams Vahdati, S. [88]	Headache	M (60%) F (40%)	M (80%) F (20%)	-	-	37.6 ± 12.5	32.9 ± 11.1	-	-
Masoumi, K.[89]	Renal colic	M (79.6%) F (20.4%)	M (72.2%) F (27.8%)	-	-	36.07 ± 9.7	34.96 ± 8.94	-	-
Eken, C. [31]	Back pain	* Overall, (60.6%) of study subjects were male and (39.4%) were female. The mean age of study subjects was 31.5±9.5 years.							
Craig, M.[95]	Acute traumatic limb pain	M (55.6%) F (44.4%)	M (53.57%) F (46.42)	-	-	38 (16 to 64)	35 (16 to 62)	-	-
Serinken, M.[8]	Renal colic	M (73.7%) F (26.3%)	M (65.7%) F (34.3%)	-	-	29.168.2	31.369.0	-	-

Study ID	Pain condition	Gender Distribution by Drug Group				Age Distribution by Drug Group Mean ± SD / Median (IQR)			
		Paracetamol	Opioids	NSAIDs	Other	Paracetamol	Opioids	NSAIDs	Other
Grissa, M.H.[96]	Renal colic	M (40%) F (60%)	-	M (42%) F (58%)	-	39 ± 13	-	40 ± 14	-
Bektas, F.[90]	Renal colic	M (67%) F (33%)	M (55%) F (45%)	-	M (63%) F (37%)	35 ± 10	39 ± 11	-	36 ± 10

Abbreviations: F: Female; M: Male
Data presented as mean ± SD or Median (IQR) as reported in trials
* Studies mentioned the overall (%) of gender and mean± SD of study subject

Headache

Three trials evaluated IVP in patients presenting to the ED with headache. Two trials recruited patients with post traumatic headache. One reported a statistically and clinically significant difference in favour of IVP at T30 when compared to 0.1 mg/kg IV morphine [88]. A second trial, [92] compared IVP to IV morphine 0.1 mg/kg and 30 mg/kg ketorolac, reporting a statistically and clinically significant reduction in pain score in favour of IVP at T30 but not at T60. The third trial compared IVP to dexketoprofen (NSAID) in patients with migraine and showed no statistically significant difference [11]. These trials were all at high risk of bias.

Renal colic

Twelve trials assessed IVP in patients presenting to ED with renal colic, with ten trials included in the meta-analysis. Eleven trials involved IV morphine and one IV fentanyl 2 μg/kg as the opioid as the comparator arm [81]. Four trials [8, 89, 90, 96] reported IVP to provide a statistically significant greater reduction in pain scores than comparators at T30, with two reporting statistically and clinically significant differences, one comparing IVP to morphine [89] and one to NSAIDS [96].

Four trials reported a greater reduction in pain score in favour of comparator medications [9, 77, 81, 87]. One of these four trials reported 85% of patients in NSAID group had pain scores less than five at T30 as compared to 70% in those treated with IVP and 73% with fentanyl [81]. A second trial concluded patients treated with intramuscular diclofenac had more sustained pain relief with clinically and statistically lower pain scores at T30 and T60 as compared to IVP and morphine [9]. The third trial also reported clinically and statistically lower pain scores in patients treated with Ibuprofen as compared to IVP at T30 [77]. The fourth trial reported IVP as superior to morphine [77].

One trial compared IVP, IM diclofenac, and acupuncture, concluding that IM diclofenac provided statistically and clinically significant better analgesia than IVP at T30 [86]. Three trials reported equivalent levels of analgesia for IVP and comparator groups at T30 (one vs. morphine [79] one vs NSAIDs [75] and one to both IV morphine and ketorolac) [78]. Nine trials were assessed as high risk [75, 77-79, 81, 86, 87, 89, 90] and three as low risk of bias [8, 9, 96].

Musculoskeletal injury

Seven trials assessed IVP in patients with musculoskeletal injuries. One trial reported patients treated with IVP to describe clinically and statistically significant lower pain scores at T30 as compared to patients treated with 0.1 mg/kg IV morphine. [85] One trial [94] concluded IV NSAIDs offered statistically and clinically lower pain scores and one [76] trial a statistically but not clinically significant reduction at T30. A fourth trial reported no statistically significant differences in pain scores for patients treated with IVP and NSAIDs [7] and two trials reported similarly for patients treated with IVP or IV morphine 10 mg [91, 95]. Finally, the seventh trial reported a statistically significant lower pain score for those treated with IVP as compared 0.1 mg/kg IV morphine [82]. Six of the seven trials were at high [7, 76, 82, 85, 91, 94] and one at low risk of bias [95].

Abdominal pain

Three trials were conducted among patients presenting with abdominal pain (one pancreatitis [35], two dysmenorrhea [80, 93]). One trial involving patients with dysmenorrhea reported patients treated with IVP to have clinically and statistically significantly higher pain scores than those treated with tramadol at T30. These scores were statistically but not clinically significantly higher at T15, T60, and T120 [93]. The second trial reported that there was no statically significant difference in pain score

between patients with dysmenorrhea treated with IVP or dexketoprofen at T15 and T30 [80]. A trial recruiting patients with non-traumatic pancreatitis concluded IVP, dexketoprofen, and tramadol offered similar levels of analgesia with no statistically significant difference between groups [84]. Two trials were high [80, 84] and one low risk of bias [93].

Back pain

Two trials recruited patients with non-traumatic back pain in an ED setting. One concluded that 0.1 mg/kg IV morphine provided statistically, and clinically significant higher levels of analgesia compared to IVP at T30 [83]. The second trial concluded IVP, dexketoprofen and morphine offered similar pain relief [31]. In both the above-mentioned trials, no other time points were recorded. Both the trials were considered as high risk of bias.

Meta-analysis

Overall, 25 trials were included in the quantitative synthesis [7-9, 11, 31, 75-80, 82-85, 87-96]. We excluded two trials from our primary analysis; one trial reported the outcome as four different categories of the VAS [81] and one did not report the result as mean (SD) or median (IQR)[86]. Five papers [9, 31, 78, 84, 92] compared IVP with two comparator arms, opioids and NSAIDs. In the analysis of these five trials, two medication groups were combined as one comparator and used for the analyses as recommended by Higgins et al. [99].

Subgroups analyses were performed by pain aetiology and medication group (opioids and NSAIDS) each to IVP (Table 5).

Table 4. Results of Pain Reduction at Different Time Points

Pain reduction outcome and time point			Number of trials	Changes on analogue scores [3] (MD) (95% CI)	SMD (95% CI)	Heterogeneity (I^2, *P)*
Paracetamol compared to comparator group (opioids, NSAIDs or combined group) [1]		T= 30	25	0.09 [95%CI: -0.85, 1.05]	0.04 [95%CI: -0.38, 0.47]	I^2 =93.4%, *P<0.001*
		T= 60	9	0.29 [95%CI: -1.56, 2.16]	0.13 [95%CI: -0.70, 0.95]	I^2 =96.6%, *P<0.001*
		T= 90	2	0.29 [95%CI: 0.07, 0.51]	0.13 [95%CI: 0.03, 0.23]	I^2 =0%, *P= 0.40*
		T= 120	2	1.54 [95%CI: -6.73, 9.80]	0.69 [95%CI: -3.02, 4.40]	I^2 =99.2%, *P<0.001*
Paracetamol compared to opioids[2]		T= 30	17	-0.13 [95%CI: -1.49, 1.22]	-0.06 [95%CI: -0.67, 0.55]	I^2 =93.7%, *P<0.001*
		T= 60	6	-0.09 [95%CI: -2.69, 2.52]	-0.04 [95%CI: -1.21, 1.13]	I^2 =97.1%, *P<0.001*
		T= 120	2	1.25[95%CI: -7.33, 9.82]	0.56 [95%CI: -3.29, 4.41]	I^2 =98.9%, *P<0.001*
Paracetamol compared to NSAIDs[2]		T= 30	14	0.27 [95%CI: -1.0, 1.54]	0.12 [95%CI: -0.45, 0.69]	I^2 =94.2%, *P<0.001*
		T= 60	6	0.51 [95%CI: 0.11, 0.91]	0.23 [95%CI: 0.05, 0.41]	I^2 =46.4%, *P<0.001*
Paracetamol compared to the placebo[2]		T= 30	2	-2.18 [95%CI: -4.08, -0.29]	-0.98 [95%CI: -1.83, -0.13	I^2 =91.5%, *P=0.02*
Paracetamol comparator group (opioids, NSAIDs or combined group) in subgroup analysis	Headache	T= 30	3	-0.42[95%CI: -2.16, 1,31]	-0.19 [95%CI: -0.97, 0.59]	I^2 =89.3%, *P=<0.001*
	Renal colic	T= 30	10	-0.09 [95%CI: -0.91, 0.73]	-0.04 [95%CI: -0.41, 0.33]	I^2 =*86*.3%, *P=<0.001*
	Abdominal pain	T= 30	3	2.41 [95%CI: -3.30, 8.13]	1.08 [95%CI: -1.48, 3.65]	I^2 =98.7%, *P=<0.001*
	Musculoskeletal injuries	T= 30	7	0.20 [95%CI: -0.85, 1.22]	0.09 [95%CI: -0.38, 0.55]	I^2 =86.7%, *P=<0.001*
	Back pain	T= 30	2	0.53 [95%CI: -0.94, 2.0]	0.24[95%CI: -0.42, 0.90]	I^2 =87.8%, *P=<0.001*
	Renal colic	T= 60	3	0.02 [95%CI: -0.85, 0.90]	0.01 [95%CI: -0.38, 0.40]	I^2 =84.4%, *P=0.05*
	Musculoskeletal injuries	T= 60	4	0.56 [95%CI: 0.04, 1.07]	0.25 [95%CI: 0.02, 0.48]	I^2 =46.8%, *P=0.11*
Paracetamol compared to opioids in subgroup analysis	Renal colic	T= 30	7	-0.31 [95%CI: -0.82, 0.20]	-0.14 [95%CI: -0.37, 0.09]	I^2 =62.4%, *P=<0.001*
	Musculoskeletal injuries	T= 30	4	0.09 [95%CI: -2.07, 2.25]	0.04 [95%CI: -0.93, 1.01]	I^2 =91.7%, *P=<0.001*
	Back pain	T= 30	2	0.85 [95%CI: 0.13, 1.60]	0.38 [95%CI:0.06,0.71]	*42.6%, P=<0.001*
	Abdominal pain	T= 30	2	3.25 [95%CI: -7.97, 14.48]	1.46 [95%CI: -3.58, 6.50]	I^2 =99.0%, *P=<0.001*
	Renal colic	T= 60	3	-0.28 [95%CI: -1.29, 0.71]	-0.13 [95%CI: -0.58, 0.32]	I^2 *=88.2*%, *P=0.14*
Paracetamol compared to NSAIDs in subgroup analysis	Headaches	T= 30	2	0.04 [95%CI: -1.63, 1.73]	0.02 [95%CI: -0.73, 0.78]	I^2 *=84.5*% *P=<0.001*
	Renal colic	T=30	4	0.18 [95%CI: -1.05, 1.43]	0.08 [95%CI: -0.47, 0.64]	I^2*=90.6%, P=<0.001*
	Abdominal pain	T= 30	3	2.16 [95%CI: 3.50, 7.79]	0.97 [95%CI: -1.57, 3.50]	I^2 =98.2%, *P=<0.001*
	Musculoskeletal injuries	T= 30	3	0.22 [95%CI: -0.53, 1.0]	0.10 [95%CI: -0.24, 0.45]	I^2 =76.9%, *P=0.02*
	Musculoskeletal injuries	T= 60	3	0.53 [95%CI: -0.07, 1.14]	0.24 [95%CI: -0.03, 0.51]	I^2 =63.4%, *P=0.06*
Paracetamol compared to NSAIDs drugs	Ketorolac	T=30	2	- 0.70[95%CI: 1.40, 0.00]	-0.31[95%CI: -0.63, 0.00]	I^2 *=7.5%, P=0.32*
	Ibuprofen	T=30	2	1.52[95%CI:0.31, 2.70]	0.68[95%CI: 0.14,1.21]	I^2 *=84%, p=0.02*

	Dexketoprofen	T=30	6	0.13[95%CI: -0.42, 0.67]	0.06[95%CI: -0.19, 0.30]	I^2 =65.6%, p=0.02
	Dexketoprofen	T=60	2	0.27[95%CI:-0.16, 0.71]	0.12[95%CI:-0.07, 0.32]	I^2 =0.0%, p=0.33
Paracetamol compared to dexketoprofen in subgroup analysis	Musculoskeletal injuries	T=30	2	-0.04[95%CI: -0.84, 0.76]	-0.02[95%CI: -0.38, 0.34]	I^2 =70.5%, p=0.08
	Musculoskeletal injuries	T=60	2	0.27[95%CI: -0.16, 0.71]	0.12[95%CI: -0.07, 0.32]	I^2 =0.0%, p=0.33

Abbreviations: T: Time; SMD: Standardized Mean Difference; CI: Confidence Interval; MD: Mean difference.

[1] The main outcome at T=30, included all eligible trials (25 trials). Where the comparator group was any (opioids or NSAIDs or the combined group).

[2] Paracetamol compared to each drug group separately.

[3]Indicating for the changes on the analogue scale, the interpretation depends on the direction of the sign (Negative sign: in favour of paracetamol; positive sign: in favour of the comparator group).

There was no statistically significant difference in baseline pain scores between groups in any analyzed trial. The mean pain scores at T30, T60, T90, and T120 were pooled for IVP and comparator groups. A change of 1.39 ± 1.05 (95% CI: 1.27-1.51) on the NRS was considered as a clinically significant difference in pain scores [102].

Pain reduction T0-T30

IVP and the comparator medication (NSAIDs, opioids, alone or in combination) reduced pain scores by 4.14 ± 1.33 and 4.21± 1.25 on NRS.

IVP and the comparator medication both provided similarly adequate analgesia at T30, with the simple pooled mean pain scores falling from 7.58 ± 1.31 and 7.57+1.06 on arrival to 3.41 ± 1.30 and 3.38 ± 1.55, respectively. Pain scores reduced further to 2.89 ± 1.40 and 2.37 ± 1.10 at T60 (0.33 difference in NRS score, 11 studies), and to 2.35± 2.33 and 1.27± 1.04 at T90 (0.31 difference, 2 studies) (Figure 3)

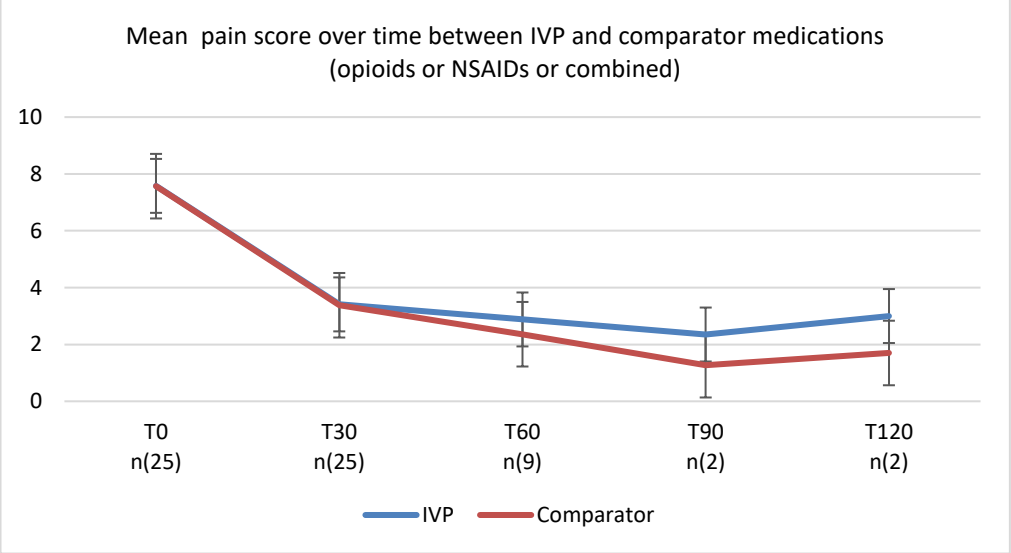

Figure 4 The mean pain scores as reported in trials over time between IVP and comparator medications (opioids or NSAIDs or combined), where the x-axis shows the

time points, and the y-axis shows the pain scores. n indicates the number of studies included in each time point.

Pain reduction at T30, T60, T90 and 120

Overall, at T30 there was no statistically significant difference in pain scores on the NRS between IVP and comparator (opioids or NSAIDs or combined) (Figure 4), (Table 5). Pain scores were almost identical, with scores MD: 0.09 (95%CI: [-1.03,1.10], 25 trials) lower in the comparator group (opioids or NSAIDs or combined) than in those receiving IVP at T30. All figures of standardized mean difference (SMD) are presented in Appendix.

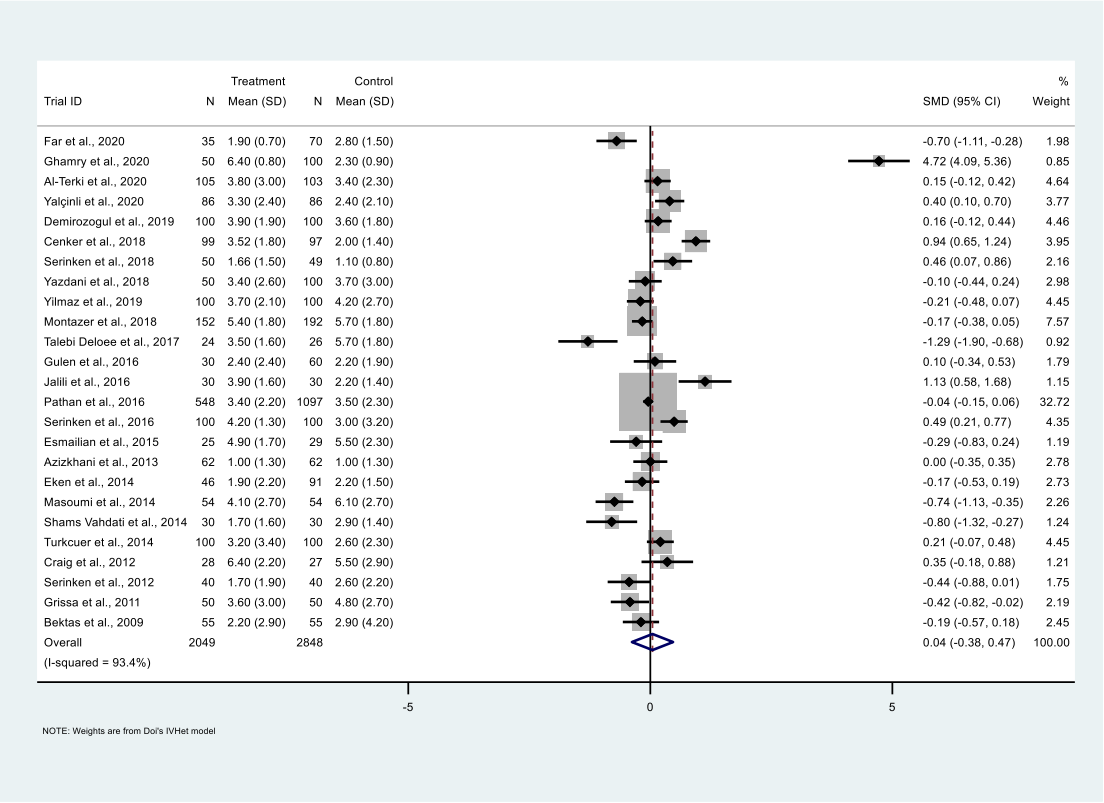

Figure 5. Forest plot of standardized mean difference of pain reduction at time 30 minutes (IVP compared to opioids or NSAIDs or combined group).

The pain scores were not significantly different at T60 (MD:0.33, 95%CI: [-1.47,2.14]**,** 11 trials), were statistically but not clinically significantly lower in the

comparator groups at T90 (MD:0.31, 95%CI: [0.31,0.51], 2 trials) and non-significantly lower in the comparator group at T120 (1.96, 95%CI [-5.69, 9.63], 2 trials) (Table 5).

IVP versus opioids

Paracetamol provided lower pain scores at T30 and T60 as compared to opioids, but pain scores were not statistically and clinically significant (MD:-0.13 [95%CI: -1.49, 1.22]) and (MD:-0.09 [95%CI: -2.69, 2.52]), figures 5 and 6 retrospectively. While at T120, the comparator medication reported lower pain scores (MD:1.25[95%CI: -7.33, 9.82]), figure 7.

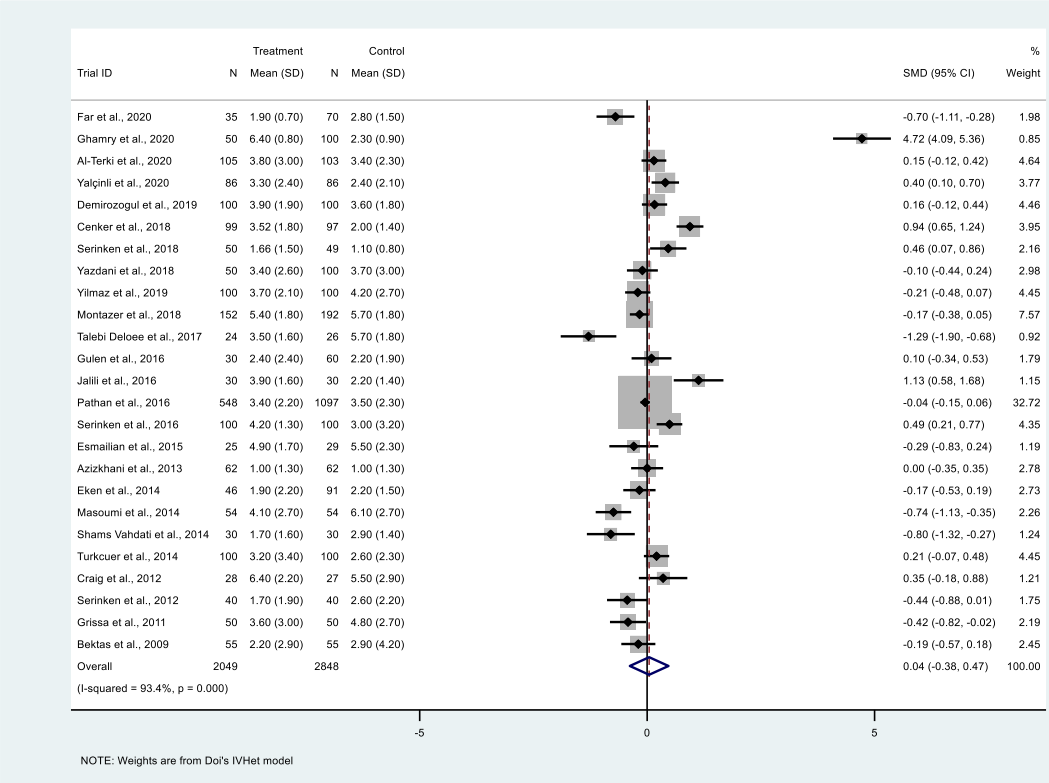

Figure 6.Forest plot of standardized mean difference of pain reduction at time 30 minutes (IVP compared to opioids).

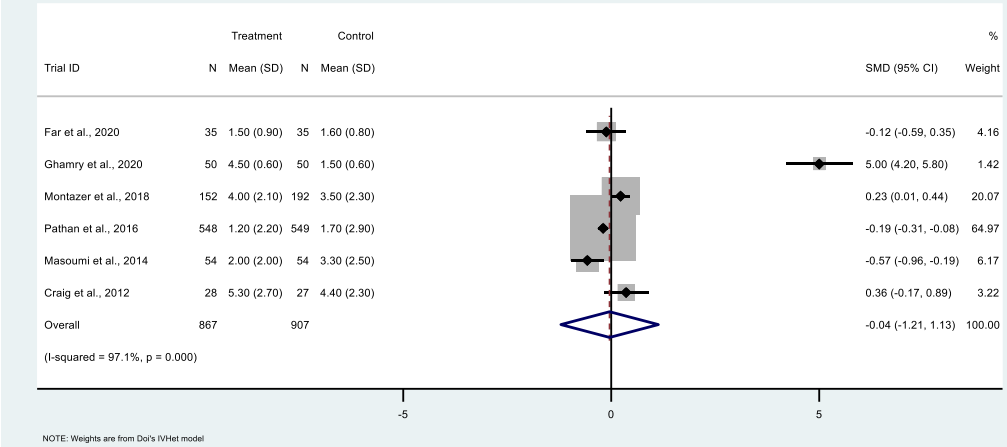

Figure 7.Forest plot of standardized mean difference of pain reduction at time 60 minutes (IVP compared to opioids)

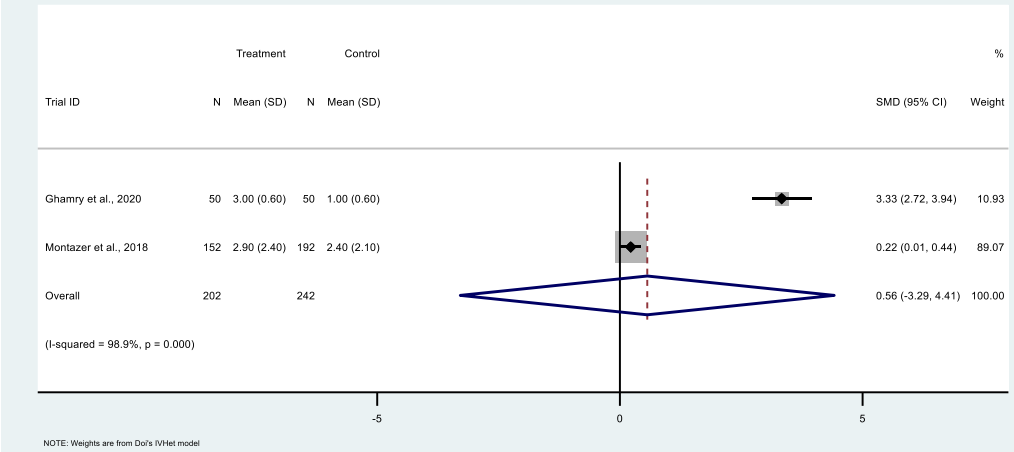

Figure 8. Forest plot of standardized mean difference of pain reduction at time 120 minutes (IVP compared to opioids)

IVP versus NSAIDs

NSAIDs medications provided lower pain scores at T30 and T60 as compared to IVP, but pain scores were not statistically and clinically significant at T30 (MD: 0.27 [95%CI: -1.0, 1.54]) and not clinically significant at T60 (MD: 0.51 [95%CI: 0.11, 0.91]) figures 8 and 9, retrospectively.

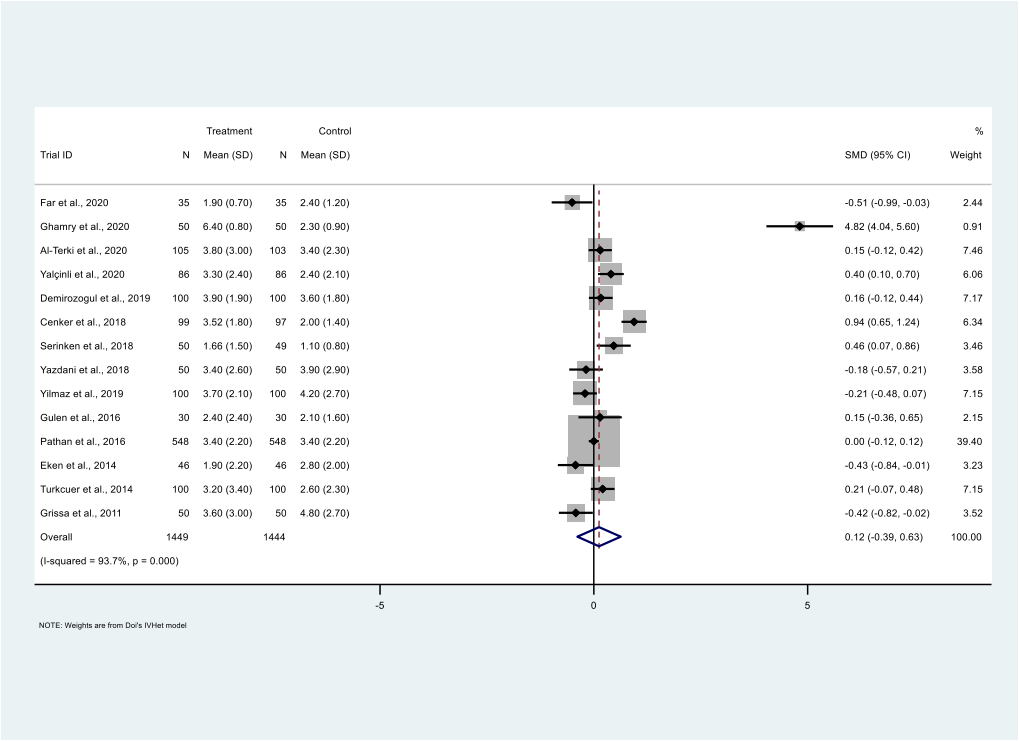

Figure 9. Forest plot of standardized mean difference of pain reduction at time 30 minutes (Paracetamol compared to NSAID

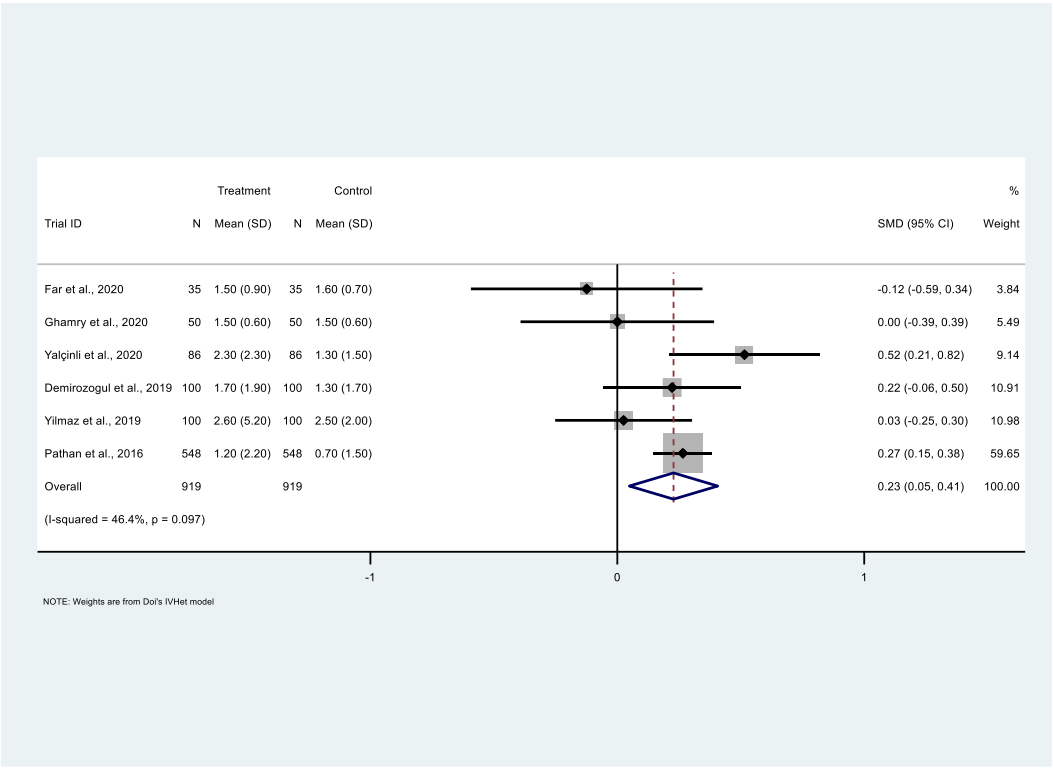

Figure 10. Forest plot of standardized mean difference of pain reduction at time 60 minutes (Paracetamol compared to NSAIDs).

Rescue analgesia

The pooled proportion of rescue analgesia in each drug group at T30 and T60 is reported in Table 6.

Table 5. Pooled Proportion of Rescue Analgesia in Each Drug Group

Drug		Number of studies	Proportion	95% CI	Heterogeneity
Paracetamol	T=30	15	0.20	[0.16, 0.25]	I^2= *75.4%, P< 0.001*
	T= 60	2	0.20	[0.15, 0.26]	I^2= *0%, P< 0.001*
	T= 30	8	0.13	[0.07, 0.19]	$I^{2=}$ *89.9%, P<0.001*

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	T= 60	2	0.09	[0.05, 0.13]	*I^2= 0%, P=0.027*
Opioids	T= 30	10	0.23	[0.14, 0.32]	*I^2 = 92.8%, P<0.001*

Abbreviations: CI: Confidence Interval; *I^2*: Heterogeneity; *P*: p-value for heterogeneity; T: Time.

Adverse events

Patients who suffered from at least one AE were considered as events in calculating the RR (Table 7) and (Table 8). There was no standardized definition of AEs between trials and only eight trials reported AEs atT30 [22, 30, 34, 36, 40-42, 47]. All trials included in the analysis used the same doses of IVP except one, we conducted separate analyses for each comparator medication. Three trials [29, 38, 39] were excluded from the analysis as the number of patients experiencing AEs was not clear. The results are presented in (Table 7) and in (Figure 10).

Table 6. Pooled Risk Ratio of Adverse Events by Each Drug Group

Drug	Number of trials	RR	95% CI	Heterogeneity
Paracetamol compared to opioids	13	0.50	[0.40, 0.62]	I^2= *0%* *P= 0.59*
Paracetamol compared to non-steroidal anti-inflammatory drugs (NSAIDs)	9	1.30	[0.78, 2.17]	$I^{2=}$ *0%* *P: 0.83*
Paracetamol compared to placebo	2	0.97	[0.21, 4.46]	I^2 = *30%* *P= 0.23*

Abbreviations: RR: Risk Ratio; CI: Confidence Interval; I^2: Heterogeneity; *P*: p-value for heterogeneity.

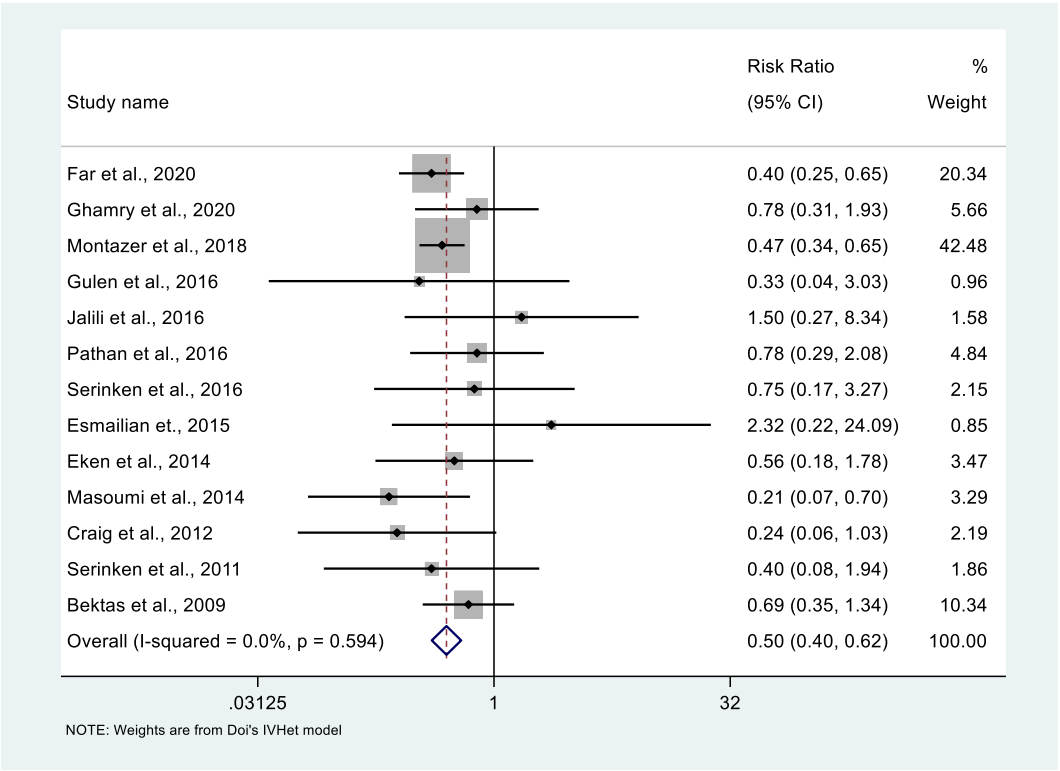

Figure 11. Forest plot of risk ratio (RR) of adverse events of paracetamol compared to opioids.

Table 7. Number of Adverse Events of Each Group Compared to Paracetamol

Study ID	Paracetamol		Opioids	
	Sample size	Number of adverse events	Sample size	Number of adverse events
Far et al., 2020	35	12	35	30
Ghamry et al., 2020	50	7	50	9
Montazer et al., 2018	152	34	192	92
Gulen et al., 2016	30	1	30	3
Jalili et al., 2016	30	3	30	2
Pathan et al., 2016	548	7	549	9
Serinken et al., 2016	100	3	100	4
Esmailian et., 2015	25	2	29	1
Eken et al., 2014	46	4	45	7
Masoumi et al., 2014	54	3	54	14
Craig et al., 2012	28	2	27	8
Serinken et al., 2011	40	2	40	5
Bektas et al., 2009	55	11	55	16
	Paracetamol		NSAIDs	
Far et al., 2020	35	12	35	4
Al-Terki et al., 2020	105	2	103	3
Yalçinli et al., 2020	86	0	86	0
Cenker et al., 2018	99	6	97	4
Serinken et al., 2018	50	1	49	1
Gulen et al., 2016	30	1	30	2
Pathan et al., 2016	548	7	548	7
Eken et al., 2014	46	4	46	4
Grissa et al., 2010	50	1	50	1
	Paracetamol		Placebo	
Serinken et al., 2016	100	3	78	0
Bektas et al., 2009	55	11	34	8

Publication bias

Publication bias was suggested by the funnel plot (Figure 11). The figure is showing that there is a publication bias by which an asymmetric shape is observed. More trials scattering the right side because some trials were small, they are scattering widely.

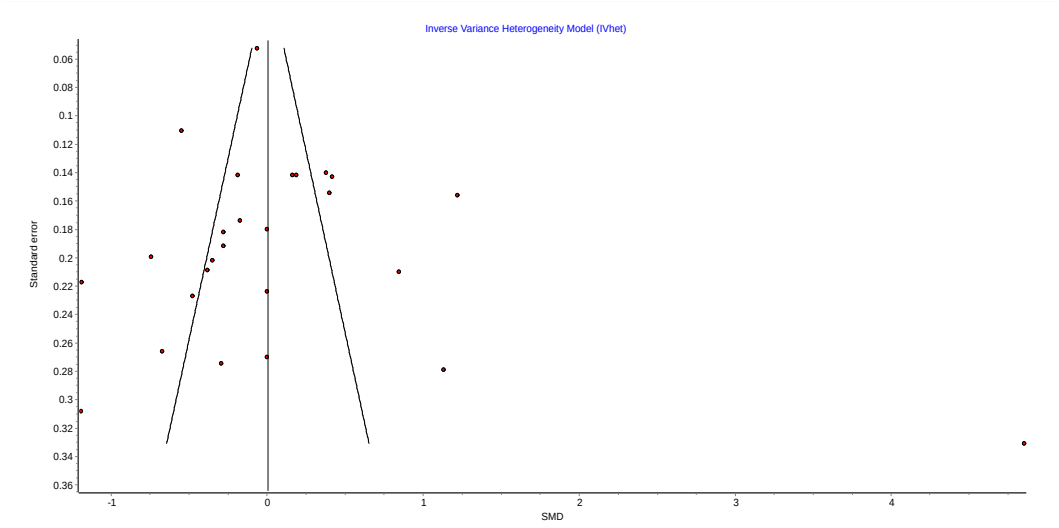

Figure 12. Funnel plot of trials included in the meta-analysis. Each dot represents a study, the y-axis represents standard error (SE) of effect size, and the x-axis shows the effect size.

Missing data

In pooling the data, the median and the Interquartile Range (IQR) values were used to estimate missing mean and SD as described by Wan et al. [(103)] and Luo et al. [(104)]. Missing SDs were calculated from summary measures. Two trials were excluded

from the meta-analysis; one reported only proportions, and the other reported only mean pain scores without any summary measures.

Discussion

This systematic review is concise evidence on the effectiveness of IVP over the other comparators in conditions with acute pain. IVP and the comparator medications, all provided similarly adequate analgesia at T30 minutes. The adverse events reported in patients receiving IVP were 50% fewer as compared to those receiving opioids. The proportion of patients requiring rescue analgesia was similar in patients treated with IVP and opioids but lower in those who received NSAIDs.

The robustness of the current review in that each acute pain condition has been evaluated according to its etiologies and the effects of different pharmacological therapies. This review can guide the clinicians by enlightening them regarding the strengths of the superiority of pharmacological therapies benefiting for managing different types of acute pain.

Renal colic

Overall, both intervention and comparator medications provided adequate analgesic effect by T30, the mean pain scores falling from 7.40± 1.67 and 7.74± 1.08 (retrospectively for IVP and comparator) to 3.24± 1.23 and 3.60± 1.63, and to 2.47± 1.36 and 2.73± 1.42) at T60. At T90, a greater reduction in the mean of pain scores was provided by the comparator medication, 1.25± 1.06 and 2.35± 2.33. In this meta-analysis, ten trials identified no statistically or clinically significant differences between pain scores in patients treated with IVP and comparator medication at T30 (difference 0.09 on NRS). There was no statistically or clinically significant difference in pain scores between IVP and opioids (T30: 0.31 NRS, T60: 0.28 NRS). Four trials compared IVP to NSAIDs with a non-significant lower score (0.18 NRS) in patients treated with

NSAIDs. Rescue analgesia use at T30 was also similar in both groups. Patients in the IVP group reported 50% fewer AEs than those treated with opioids (Figure 4.) and (Table 7).

IVP was slightly better than opioids in reducing pain at T 30 and T60 minutes for renal colic. Rescue analgesia use at T30 was also similar in both groups (IVP and opioids). Patients in the IVP group reported 50% fewer AEs than those treated with opioids and 30% higher in IVP than NSAIDs with less proportion of rescue analgesia for the last (Figure 10) and (Table 7).

These findings are consistent with a 2018 systematic review [(14)] of 36 trials (4887 patients) comparing IV paracetamol, IV / IM NSAIDs, and IV / SC opioids in ED patients with renal colic. The authors concluded each medication offered similar levels of analgesia, but rescue analgesia was required significantly less often in patients treated with NSAIDs. A 2017 systematic review and meta-analysis including 20 trials (3852 patients) compared IVP to PO/IM/IV NSAIDs and IV opioids, concluding IVP provided statistically significant but not clinically significant at T30 when compared to morphine [(105)].

Musculoskeletal injuries

IVP offered similar levels of analgesia as compared to NSAIDs or opioids or both combined. (NRS difference 0.20 at T30 and by 0.56 at T60). At T30 IVP provided no statistically or clinically significant different pain relief as compared to opioids (MD: 0.09). There was no statistically or clinically significant difference in the levels of analgesia provided by IVP and NSAIDs (MD: 0.22). A 2019 systematic review of seven trials including 2100 patients compared levels of pain relief in the initial 24 hours post-injury between patients treated with PO paracetamol, opioids, and NSAIDs in multiple doses [(15)] reported a consistent conclusion. Where the authors concluded that

paracetamol was as effective as NSAIDs alone or in combination with opioids in treating pain in adult patients with minor musculoskeletal injuries at 24 hours. However, the authors reported pain within 24 hours without specific time points. There was significant heterogeneity among included trials, such as the absence of a standardized dosing regimen of both intervention and comparison groups and the lack of standardized outcome measurements. Most trials did not specify standardized measurement for AEs and the requirement for additional analgesia [106].

Headache

The combined trials' data showed no clinically or statistically significant difference in pain scores at T30. A (pain score 0.42 lower for IVP) for patients treated with IVP as compared to NSAIDs, opioids, or in combination. IVP is therefore a suitable first line analgesic in acute headaches where oral medications are contraindicated. A recent narrative review (2018), included data from published reviews, meta-analysis, randomized controlled trials and clinical trials for acute migraine treatments [107] suggested a similar conclusion for the use of paracetamol and oral NSAIDs as first line treatment for mild to moderate migraine. While a 2015 review [108] assessing the available evidence of migraine pharmacotherapies published between 1993 and 2013 reported triptans as an effective analgesia for moderate to severe migraine. A 2015 systematic review [109] evaluated 44 RCTs involving the use of a wide range of therapies in adults with migraine. The authors recommended against the use of IVP, reporting no difference between IVP and placebo, with minor side effects reported among the paracetamol group. A 2016 systematic review including 8079 participants with recurrent tension headache concluded that oral paracetamol 1000 mg (compared to placebo) was associated with a higher proportion of patients pain free at two hours (number needed to treat of 10 patients to be pain free at two hours) [110].

Abdomen pain

Overall, the comparator medication provided more analgesic effect in improving pain by T30 as compared to IVP, the mean pain scores falling from 7.33 ± 1.53 and 7.67± 1.15 to 1.67± 0.58 and 3.33± 2.30 at T30, retrospectively for the comparator and IVP.

In the current meta-analysis, the reduction in pain scores was greater in the opioids group than those treated with NSAIDs (3.25 vs. 2.16 on NRS at T30 as compared to IVP), but the differences were not statistically significant as the pooled estimate included only three small trials. A 2002 meta-analysis comparing trials of oral paracetamol with oral NSAIDs concluded naproxen 400 mg provided greater pain relief than 1000 mg of paracetamol and placebo at T30 and was statistically significant [111]. The systematic review included trials administering naproxen and naproxen sodium with ibuprofen, acetaminophen, and placebo, reporting higher doses of naproxen to be efficacious. Cochrane review of 80 RCTs including 5820 female subjects [112] assessed the effectiveness of PO NSAIDs to placebo or other PO NSAIDs and PO paracetamol. This review provided strong evidence to support PO NSAIDs as first line treatment for primary dysmenorrhea and concluded that NSAIDs were statistically and clinically significant analgesic when compared to placebo and paracetamol. Published evidence suggests that in the setting of abdominal pain IV NSAIDS and/or IV morphine offer superior analgesia to IV or oral paracetamol.

Back pain

Two trials reported significant reductions in pains scores by T30, with the mean pain scores falling from 8.0 to 3.0±1.41 and 2.75±0.35, for IVP and comparators retrospectively.

The comparators (NSAIDs or opioids or these combined) provided equivalent analgesia to IVP. The former reduced pain scores at T30 by 0.53 more than IVP, not statistically or clinically significant. A 2018 clinical practice guideline concluded the use of weak opioids for short periods in acute low back pain if NSAIDS were contraindicated or not effective [113]. A 2008 systematic review of seven trials failed to find evidence to support the widely held view that oral paracetamol is effective in treatment of non-specific low back pain. The authors called for further trials to evaluate paracetamol in this setting. The small sample sizes of most published data contributes to imprecise estimates [114].

This study restricted the route of drug administration to intravenous route for IVP. However, in comparators group three studies used NSAIDS (Diclofenac and Piroxicam) as intramuscular injections. All the three studies had acute pain from renal colic. Diclofenac by the intramuscular route provide better and more sustained pain relief than IVP, while piroxicam did not prove to be as efficient as IVP. It is important to note that the medication dose varied among the comparator groups in this review. Thus, the evidence of this review doesn't mean that the clinicians should be choose the medication as the first line treatment, due to the variation in NSAIDs drugs a sensitivity analysis was performed (Table 5).

In this systematic review, different etiologies of acute pain were included. However, etiologies like headache, musculoskeletal injuries, and abdominal pain further had different etiology of pain. In the headache group, three trials were included out of which two were post-traumatic headaches and one was acute migraine. However, acute migraine should be further reviewed with different medications as being one of the common causes of visiting ED. Three trials included in the abdominal pain group had two trials including dysmenorrhea and one pancreatitis. All three trials were

compared to NSAIDs that were more efficacious in pain relief. Nevertheless, it is important to provide evidence about the effectiveness of opioids. The musculoskeletal group also had a diverse range of populations included like soft tissue injuries, isolated long bone fractures, rib trauma, and non-traumatic musculoskeletal injury. The heterogenicity found was significant. The number of studies included in headache and abdominal pain was also less in number due to the difference in the medications included or end-results.

Although the method of completing this systematic review was robust and followed PRISMA guidelines. However, this review has some limitations to note. As mentioned earlier, there was considerable heterogeneity in the trials included and was encountered in the primary analysis (Table 5). There were variations in pain etiology, participant characteristics, and the methods of reporting pain scores. Most of the trials were small, single center, at high risk of bias, and reporting outcomes were inadequate. Intention to treat analyses were not performed in a high proportion of trials (Table 4). Secondly, there was variation in the methods of reporting pain with two different pain scales used. Six trials used NRS and 22 trials VAS, complicating meta-analysis. Nonetheless, we conclude that is clinically not significant.

Strengths and limitations

This systematic review was comprehensive in the scope and search strategy. Cochrane methodology and guide for conducting the review adhered. PRISMA guideline was used for reporting of the review findings.

The review is the most comprehensive, up to date and reliable synthesis of information on the effectiveness of IVP for treating painful conditions. Previous reviews [13-15], were more limited in scope and often restricted to single conditions or to the Cochrane reviews. This review can guide the clinicians by enlightening them regarding the strengths of the superiority of pharmacological therapies benefiting for

managing different types of acute pain. Additionally, a wide subgroup analysis was performed to address heterogeneity.

This review has some limitations. Firstly, there was considerable heterogeneity in the trials included. Most of the trials were small, single center, at high risk of bias, and reporting outcomes were inadequate. Intention to treat analyses were not performed in a high proportion of trials (Table 2). Secondly, there was variation in the methods of reporting pain with two different pain scales used. Six trials used NRS and 22 trials VAS, complicating meta-analysis. There was a high degree of missing information, 12 trials [7, 31, 75, 77, 82, 83, 85, 88-91, 101] did not provide information regarding the intention to treat analysis, five trials [7, 11, 31, 76, 84] had missing data regarding baseline characteristics, and five trials [78, 86, 87, 94, 95] did not provide information regarding allocation concealment.

Only two of the contacted authors replied but they did not provide adequate data for further analysis. There were insufficient trial numbers for the meta-analysis in all pain aetiology subgroups. Finally, there was no standardized reporting of AE, with only 21 trials [8, 9, 11, 31, 75, 77-80, 83-85, 87, 89-96] reporting these (Table 8).

Finally, we were unable to perform a multivariate meta-analysis that incorporates correlation with outcomes. Where nine studies reported pain scores at T60, two with a low level of evidence measured pain scores at T90 and T120. Meta-regression is not recommended as fewer than 10 studies considered pain scores at T60, T90, and T120 [99].

CHAPTER 3: ECONOMIC EVALUATION STUDY

Literature review

Health care costs and economic evaluation

A study proved the high resource intensity of caring for patients with abdominal pain in the ED, nearly 20 million ED visits each year. Where over 50% of patients received diagnostic imaging, about 70% received blood laboratory testing and 60% received urine laboratory testing. The average number of drugs given to each patient was greater than three. Finally, the average length of stay for admitted patients was over 6 hours, and for discharged patients was over 4 hours. Opioid analgesic use appeared to have leveled off and declined slightly which may reflect successful public health campaigns to reduce the use of these resources in the ED [115]. A study done in the US on patients with headaches, evaluated the healthcare resource utilization, direct healthcare costs, and the indirect costs associated with workdays lost due to short-term disability and absenteeism. The estimated direct cost was $3,132 per patient per year. Where the cluster headache-related inpatient hospitalizations, the cost was $1,604 and for pharmacy was $809 contributed about 75% of the cluster headache-related direct health care cost. The indirect costs per patient per year were $4,928 for absenteeism, $803 for short-term disability [116]. In the US, the annual direct cost of migraine, including all medical care and possible economic repercussions for the patient in both private and public care is about $1 billion; some studies estimated the indirect costs as high as $ 9.6 [117, 118].

A health care utilization study in Canada showed that the person visit rates for musculoskeletal conditions were higher in emergency departments (3,202 per 100,000 population) than inpatient hospitalization (391.0 per 100,000 population). Where person visit rates for trauma and related conditions were 1,214 per 100,000 population

[119]. In the United States alone, there are approximately 66 million visits per year due to musculoskeletal injuries, most of these musculoskeletal injuries are composed of extremity trauma [24, 120]. In addition, about 17 million emergency department visits include sprains strains, and extremity contusions [120]. These health care services utilization leads to substantial costs for health care systems across the globe.

Economic evaluation (EE)

Economic evaluations provide evidence on the health effects and cost implications of different treatment alternatives, which can guide health care policymakers make reimbursement decisions. Economic evaluation can be done using a variety of methodologies such as cost-effectiveness, cost-benefit, cost-utility, or cost-minimization analysis. In these analyses, the net or incremental costs, as well as the outcomes/effects of two or more strategies, are estimated and compared [121]. When the outcomes of the alternatives under consideration are assumed to be equivalent, a cost-minimization analysis is undertaken. It only considers costs, and the least costly option is chosen as cost-effective [121]. In cost-benefit analysis, both costs and benefits of an intervention are expressed in monetary units. The previous method directly calculates the amount of money saved or spent. It accounts for a wide range of effects across a wide range of treatments and programs. Cost-effectiveness analysis is another evaluation method that is usually used when the outcomes of the programs under the study vary, but the outcome is stated in common health related natural units. However, it has some limitations. First, the inability to combine the associated morbidity and mortality into a single index limits the comparison. Second, it is limited in its ability to assist choices between strategies when their outcomes differ. Therefore, cost-utility analysis is an extension of cost-effectiveness analysis is often used. It is based on quality adjusted life years (QALYs) and calculated as the multiplicative product of

utility of a health state and the years lived in that health state [122].

Perspective of economic evaluations

The perspective of an economic evaluation refers to the viewpoint from which costs and outcomes are realized. Economic analysis conclusions may differ based on the viewpoint considered. Health economic evaluations can be conducted from a different perspective including a patient, hospital, third-party payer, or societal perspective. The costs associated with each perspective are briefly described in the next paragraph. Out-of-pocket expenses for treatment and hospitalization costs are typically included in the patient's perspective. While the third payer's perspective involves costs paid by insurance companies, including both inpatient and outpatient costs. The previous perspective does not account for costs, such as patients' out-of-pocket expenses. Costs paid by insurance companies are thought to be good proxies for measuring the value of health care products [123]. While the hospital's perspective includes the costs that hospitals have to bear due to the increase in the length of stay. The societal perspective is the most comprehensive, accounting for all direct and indirect costs related to a condition, such as productivity losses.

Cost-effectiveness decisions

There are several ways of expressing results from the analyses of economic evaluation [121]. In EE, generally, an incremental approach is considered, since the policy makers are interested in the incremental benefit/cost of new technology compared to an existing or current practice. In case a new technology appears to be more effective and more costly compared to a control, an incremental cost-effectiveness ratio (ICER) is calculated as the ratio of the difference in cost (ΔC) and difference in effects (ΔE) between two alternative treatment options, and describes as the additional cost per additional health outcome [121].

ICERs are then compared with a range of willingness-to-pay (WTP) threshold values to make the cost-effectiveness decisions, and many countries apply different decision rules For example, if a new intervention incurs an additional cost, which is less than £20,000 to generate an extra QALY, compared to a control, then the new intervention is considered to be cost-effective according to the National Institute for Health and Care Excellence (NICE) in the UK. In the US, this WTP threshold value is generally $50000/QALY gain. Many countries also apply 1 to 3 GDP per capita values as a WTP threshold.

Uncertainty or sensitivity analysis

The base case analysis generates the ICER from the preferred outcome and cost data. Given the uncertainty in clinical studies which are used as vehicles for conducting economic evaluations, cost-effectiveness results are subject to uncertainty. Sensitivity analysis is used to address the uncertainty in cost-effectiveness results. There are two most common types of sensitivity analysis. First, one-way sensitivity analysis. In which one parameter is changed at a time to explore whether it affects cost-effectiveness results. The second is multiple-way sensitivity analysis. Where changes multiple parameters at a time. Although one-way sensitivity analysis is straightforward, it has the potential to underestimate total uncertainty in ICERs [(124)].

The values of input cost and result variables are assumed to have a probability distribution in the probabilistic sensitivity analysis (PSA). Non-parametric bootstrapping is commonly used in probabilistic sensitivity analysis to generate 95 % confidence intervals that provide a quantitative measure of uncertainty around ICER point estimates (expected value). Cost-effectiveness planes are used to display the distribution of bootstrapped ICERs [(124)].

The cost effectiveness acceptability curve (CEAC) is another type of graphical presentation used in economic evaluation. The CEAC is a method for describing uncertainty information in probabilistic terms. A CEAC demonstrates the probability that an intervention is cost-effective compared with the substitute, given the observed data, for a range of maximum monetary thresholds that policy makers are willing to pay for a specific unit change in effect [121, 124].

Rationale of the economic evaluation

Considering costs along with the health outcomes can lead to a more comprehensive, useful, and practical decision guide. Although acute pain is one of the most common reasons for ED visits, little research has been conducted to assess the economic burden of its management in this setting. Only one systematic review was conducted in five European countries (France, Germany, Italy, Spain, and United Kingdom) [125]. The literature review aimed to identify clinical guidelines for managing moderate to severe acute pain in EDs and provide a comprehensive list of interventional and observational studies on acute pain. The authors identified all the data required for a micro-costing analysis and concluded a high cost of IV morphine administration. Of these costs, the highest cost estimated is the time nurses spent to administer the drug and monitor patients during and after morphine administration. After including the costs associated with the management of adverse events of IV complications, it was estimated that 73% of total costs attributed to IV administration included phlebitis, injection site pain, and infections related to IV administration. However, the highest cost associated with IV morphine adverse events was severe respiratory depression while costs of vomiting and nausea were significantly lower compared to respiratory depression and primarily derived from the time nurses spent to manage these patients. Respiratory depression is a well-known opioid adverse event and is linked to the

number of opioids ingested, the speed of absorption, and the rote of administration [116]. Opioids are characterized to have higher adverse events compared to other common drugs used in ED as estimated in the current systematic review and meta-analysis.

IV complications cost was the main driver of the total cost in ED, at the same time IV administration is a raid-onset and effective analgesic. In the first section of this thesis (Chapter 3), reported IV administration of drugs was an effective method in pain reduction for patients with acute pain, therefore, assessing other related costs (adverse events management costs associated with paracetamol, NSAIDs, and opioids including costs spent to administer and monitor drugs) in these analgesics could potentially assist in deciding for an effective and less costly option.

The previous analysis [125] was restricted to morphine for the management of moderate-to-severe acute pain in ED with several limitations. We, therefore, undertook a systematic review of economic evaluation studies to determine health care resource utilization and costs associated with drug administration for the management of acute pain.

Methods

Protocol and registration

The study design is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Cochrane Handbook for Systematic Reviews was used as a guideline for this study [126]. The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42022303216.

PICO research question

- *Population:* Adult (>=18 years) patients visiting an ED with acute pain (no restriction on etiology, acute pain defined as < 1 week). No restriction on methods used to assess pain or pain scores.
- *Intervention:* Intravenous paracetamol, either fixed dose or as mg/kg.
- *Comparator:* Non-steroidal anti-inflammatory medications or opioids/opiates or any other drugs delivered by any route.
- *Outcome:* Pain score, Quality Adjusted Life Year (QALY), Healthcare resource utilization and costs.

Inclusion and exclusion criteria

Adult (>=18 years) patients visiting an ED with acute pain (no restriction on etiology, acute pain defined as < 1 week. Patients who are presenting with headaches and reported to have comorbid conditions or a history of chronic headaches excluded.

Full economic evaluations (i.e., cost-effectiveness, cost-minimization, cost-benefit, cost-utility, and cost-consequences analysis), undertaken from any perspective (e.g., Ministry of Public Health, Societal, Insurance provider) and conducted alongside RCTs, observational studies or based on decision analytic models, published during the years 2000 to 2021 included.

Search methods for study identification

Electronic searches were conducted in EMBASE, PubMed. Goggle scholar. The Health Technology Assessment Database (HTA) in the Centre for Reviews and Dissemination (CRD) searched. The NHS Economic Evaluation Database (NHS EED) searched. Reference lists were checked to identify relevant publications.

Search strategy

The Mesh (Medical Subject Headings) used for the search strategy was as

follows: “Paracetamol OR Acetaminophen OR Tylenol OR Panadol” OR “intravenous OR IV OR parenteral OR infusion OR drip OR venous OR injecting OR syringing OR shot” AND “emergency medicine OR emergency department OR causality OR acute care OR emergency room OR triage room OR ER OR emergency clinic OR critical care” AND “analgesia OR analgesic OR pain reduction OR pain relief OR palliative OR pain killer” AND “Opioids OR NSAIDs OR Non-steroidal anti-inflammatory drugs” AND “cost-effectiveness OR cost-minimisation OR cost-benefit OR cost- utility OR cost-consequences analysis OR health care utilization OR health care costs OR health care resource use OR Economic evaluation OR Costs.

Study Selection and data extraction

Economic evaluation studies, along with studies reporting only heath care services costs for managing acute pain in emergency departments are screened, and data are extracted from all included studies. One independent reviewer screened titles, abstracts, and full-text articles. Any disagreements were resolved by the thesis supervisor. The reviewer independently extracted data using a priori defined data collection sheets. Data extracted included the type (method) and perspective of the economic evaluation, EE study design (e.g., RCT-based or model-based), economic evaluation methods, year of valuation, country, and currency used in the study, patient characteristics, treatment comparators, sources of cost data/information, health outcomes/effects, whether discounting was applied, the results of the economic evaluation and the results of sensitivity analyses.

Methodological quality assessment

The methodological quality and reporting of economic evaluation studies were evaluated using a number of validated tools, Drummond et al.[127], CHEERS checklists [128], and Phillips checklist [129] for decision analytical model based cost-effectiveness

studies. The economic analyses carried out in the included studies in this review were not high. This was due to the nature of the underlying clinical evidence, which did not all come from rigorous randomized controlled trials (RCTs), and how it was included into the economic evaluations. Not all of the research offered useful information on which components of healthcare and other resource utilization were identified, quantified, and valued (Table 10 and 11).

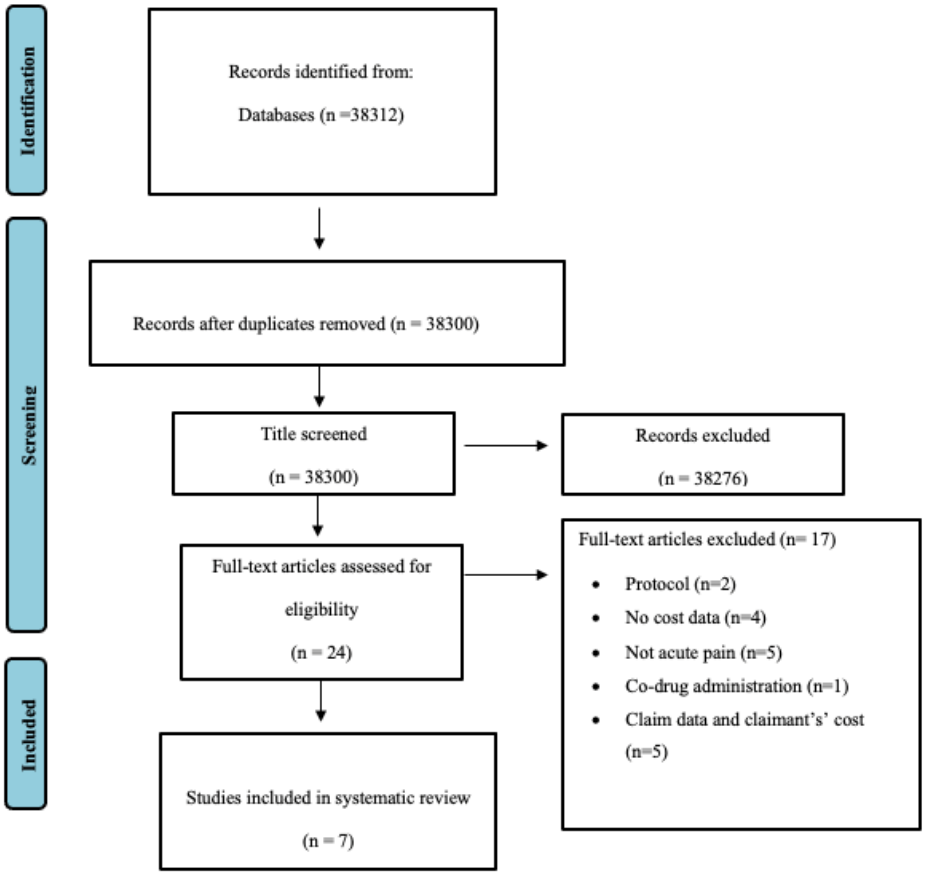

Figure 13. Flowchart representing the process of screening and selection of eligible studies, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Table 8. Table of Characteristics of The Included Studies

Reference and Year	Country	Pain Condition	Study design	Perspective of the economic evaluation	Economic Evaluation's Method	Type of the Drugs	Outcome	Evaluation follow up period
Basri et al., 2020 (130)	Malaysia	Dysmenorrhea	RCT	Health service	Cost-utility analysis	Celecoxib versus mefenamic acid	Pain scores, quality of life and costs	2 months
Palmer et al., 2017 (131)	United States	Acute pain	Cohort	Health service	Cost-analysis	IV, opioids	Costs	2 years
Pritchard et al., 2016 (132)	United States	Traumatic injury or non-traumatic abdominal pain.	RCT	National health service (NHS)	Cost-effectiveness analysis	patient-controlled analgesia versus standard care	Pain scores and costs	12 hours
Fitzsimmons et al., 2014 (133)	UK	Sciatica	Decision trees	National health service (NHS)	Cost-utility analysis	Opioids versus non-opioids	QALY and costs	1 year
Dunlop et al., 2012 (134)	UK	Non-malignant pain	Decision tree	National health service (NHS)	Cost-utility analysis	Oxycodone/Naloxone Versus Oxycodone	QALY and costs	12-weeks RCT period
Lloyd et al., 2004 (135)	UK	Low back pain	Decision tree	National health service (NHS)	Cost-effectiveness	Paracetamol versus ibuprofen	Percentage of patients successfully treated and costs	4 days
Rainer et al., 2000 (136)	China	Limb injuries	RCT	National health service (NHS)	Cost consequence analysis	ketorolac versus morphine	Pain scores and costs	6 hours

Study characteristics

Seven studies were included in the current systematic review; three studies were conducted in the United Kingdom [133-135], two studies were conducted in the United States [131, 132], one in China [136], and one in Malaysia [130]. These studies were published between 2000 and 2021 and all were published in English. The characteristics of the included studies are summarized in (Table 9). Studies included were varied in pain aetiology. One study with all acute pain conditions [131], two with acute low back pain [131, 135], one with musculoskeletal conditions [136], one with primary dysmenorrhea (PD) among females aged 18-25 and sexually inactive [130], one study included patients with traumatic injury or non-traumatic abdominal pain [132], one with sciatica [133] and one conducted among patients with non-malignant pain [134]. Among the included studies; two compared only opioids drugs [131, 132], one only NSAIDs drugs [130], one article compared paracetamol versus NSAIDs (ibuprofen)[135] one compared NSAIDs (ketorolac) versus opioids (morphine) [136], one compare opioid (oxycodone) versus the combination of (oxycodone/naloxone)[134] and one compared different interventions including opioids and non-opioids drugs [133].

A wide range of outcome measures was reported in the studies included in this review. In a trial among women with PD [130], the outcome was self-rating of pain scores using VAS (0 to 10 cm) and a validated quality of life questionnaire (EQ-5D-3L)[137], the effectiveness of celecoxib compared with mefenamic acid in pain reduction. Quality of life scores were compared before and after drugs administration. In another cost-effectiveness study, patients presenting ED with either traumatic injuries or non-traumatic abdominal pains [132]. Where the health outcome was measured as reduction in pain using VAS (0 to 10 cm), the cost-effectiveness calculated as an additional cost per hour in moderate to severe pain avoided by using patient-controlled analgesia than

standard care. Another study among patients with limb injury [136], reported the following outcomes: pain relief at rest and with limb movement, patient's satisfaction, adverse events, and time spent in ED. Where VAS (0 to 10 cm) used to measure the pain scores for baseline measurements and at subsequent time intervals after first injection, adverse events evaluated for number, duration and severity. Furthermore, the previous study reported perception outcomes as participant's satisfaction with pain relief in the ED and at the time of discharge from the department. While the costs were calculated according to activates including: the preparation and administration of analgesics and drugs, care associated with adverse events, and admission to hospital. A cost-effectiveness study conducted to evaluate different strategies for acute low back pains [135], the study used data from a phase III trial. The authors conducted a simple evaluation model using National Health Service (NHS) perspective, where the data used from the pivotal study compared heat wrap with paracetamol and ibuprofen. The primary effectiveness measure was the successful in treatment defined as both clinically meaningful pain relief and clinically meaningful reduction in disability. A retrospective cohort study of the Premier database was conducted in US [131] among patients with all acute pains over a 24 month period with total 7.3 million ED encounters, assessed the actual resource utilization and costs associated with IV administration of opioids. A wide range of outcomes were reported such as analgesia costs, AEs and IV complication etc., In another cost-effectiveness study of different strategies for managing pain in patients with sciatica [133], conducting a decision analytic model. The results reported as incremental cost per patient with symptoms successfully resolved. A cohort model [134], evaluated the cost-effectiveness of opioids in patients with moderate-to-severe non-malignant pain experiencing constipation. The study calculated the incremental cost-effectiveness ratio where the effectiveness was defined

in term of quality adjusted life-years gained.

Methodological design and quality assessment

Three of the included studies were conducted alongside RCTs [130, 132, 136], one retrospective cohort [131] and three were model based economic evaluation [133-135]. The quality assessment was performed independently by two reviewers using Drummond et al.[127] , Phillips checklist [129], and STROBE chick list [138] for RCT-based, model-based, and observational study, respectively. Quality assessment of the included studies is presented in (Table 10) and (Table 11).

Table 9. Phillips's Checklist (Model-Based EE Studies)

		Fitzsimmons et al. 2014 [133]	Dunlop et al.2012 [134]	Lloyd et al. 2004 [135]
Structure	Criteria			
1	Is there a clear statement of the decision problem?	Yes	Yes	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes
3	Is the primary decision maker specified?	No	No	No
4	Is the perspective of the model stated clearly?	Yes	Yes	Yes
5	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes
6	Has the scope of the model been stated and justified?	Yes	Yes	Yes
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	yes	yes
9	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes
11	Are the structural assumptions transparent and justified?	Yes	Yes	Yes
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes	Yes	Yes
13	Is there a clear definition of the options under evaluation?	Yes	No	No
14	Have all feasible and practical options been evaluated?	Yes	Yes	Yes
15	Is there justification for the exclusion of feasible options?	NA	No	No
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes	Yes	Yes
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes	Yes	Yes
18	Are the time horizon of the model and the duration of treatment described and justified?	Yes	Yes	Yes
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	Yes	Yes
20	Is the cycle length defined and justified in terms of the natural history of disease?	No	Yes	Yes
Data	Criteria			
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Yes
22	Where choices have been made between data sources are these justified appropriately?	Yes	Yes	Yes
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes	Yes	Yes
24	Has the quality of the data been assessed appropriately?	No	No	No
25	Where expert opinion has been used are the methods described and justified?	Yes	Yes	Yes
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	No	Yes	Yes
27	Is the choice of baseline data described and justified?	Yes	Yes	Yes
28	Are transition probabilities calculated appropriately?	NA	NA	NA
29	Has a half-cycle correction been applied to both costs and outcomes?	NA	NA	NA
30	If not, has the omission been justified?	NA	NA	NA
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes	Yes	Yes

32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	Yes	Yes
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Yes	Yes	Yes
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	No	Yes	Yes
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	No	Yes	Yes
36	Are the costs incorporated into the model justified?	Yes	Yes	Yes
37	Has the source for all costs been described?	Yes	Yes	Yes
38	Have discount rates been described and justified given the target decision maker?	No	No	No
39	Are the utilities incorporated into the model appropriate?	Yes	Yes	Yes
40	Is the source of utility weights referenced?	Yes	Yes	Yes
41	Are the methods of derivation for the utility weights justified?	Yes	Yes	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes	Yes	Yes
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Yes	Yes	Yes
44	Is the process of data incorporation transparent?	Yes	Yes	Yes
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	NA	NA	NA
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	NA	NA
47	Have the four principal types of uncertainty been addressed?	No	Yes	Yes
48	If not, has the omission of particular forms of uncertainty been justified?	Yes	NA	NA
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes	Yes	Yes
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes	Yes	Yes
51	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	Yes	Yes
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Yes	Yes
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No	No
55	Are any counterintuitive results from the model explained and justified?	Yes	Yes	Yes
56	If the model has been calibrated against independent data, have any differences been explained and justified?	No	Yes	Yes
57	Have the results been compared with those of previous models and any differences in results explained?	No	Yes	Yes

Table 10. Drummond Checklist

Item		Pritchard et al. 2016[132]	Rainer et al. 2000 [136]	Basri et al. 2020 [130]
Study design				
1	The research question is stated.	yes	yes	yes
2	The economic importance of the research question is stated.	yes	yes	No
3	The viewpoint(s) of the analysis are clearly stated and justified.	yes	yes	yes
4	The rationale for choosing alternative programmes or interventions compared is stated.	yes	yes	yes
5	The alternatives being compared are clearly described.	yes	yes	yes
6	The form of economic evaluation used is stated.	yes	yes	Not clear
7	The choice of form of economic evaluation is justified in relation to the questions addressed.	yes	yes	Not clear
Data collection				
8	The source(s) of effectiveness estimates used are stated.	yes	yes	yes
9	Details of the design and results of effectiveness study are given (if based on a single study).	yes	yes	yes
10	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Not appropriate	Not appropriate	Not appropriate
11	The primary outcome measure(s) for the economic evaluation are clearly stated.	yes	yes	No
12	Methods to value benefits are stated.	yes	Not clear	Not appropriate
13	Details of the subjects from whom valuations were obtained were given.	Not clear	yes	Not appropriate
14	Productivity changes (if included) are reported separately.	yes	No	Not appropriate
15	The relevance of productivity changes to the study question is discussed.	yes	No	Not appropriate
16	Quantities of resource use are reported separately from their unit costs.	No	yes	Not clear
17	Methods for the estimation of quantities and unit costs are described.	yes	yes	Not clear
18	Currency and price data are recorded.	yes	yes	No
19	Details of currency of price adjustments for inflation or currency conversion are given.	No	No	No
20	Details of any model used are given.	Not appropriate	Not appropriate	Not appropriate
21	The choice of model used and the key parameters on which it is based are justified.	Not appropriate	Not appropriate	Not appropriate
Analysis and interpretation of results				
22	Time horizon of costs and benefits is stated.	yes	yes	Not clear
23	The discount rate(s) is stated.	No	No	No
24	The choice of discount rate(s) is justified.	No	No	No
25	An explanation is given if costs and benefits are not discounted.	No	No	No

26	Details of statistical tests and confidence intervals are given for stochastic data.	No	yes	No
27	The approach to sensitivity analysis is given.	No	No	Not clear
28	The choice of variables for sensitivity analysis is justified.	No	No	Not clear
29	The ranges over which the variables are varied are justified.	Not clear	yes	Not clear
30	Relevant alternatives are compared.	yes	yes	yes
31	Incremental analysis is reported.	yes	yes	No
32	Major outcomes are presented in a disaggregated as well as aggregated form.	yes	yes	yes
33	The answer to the study question is given.	yes	yes	yes
34	Conclusions follow from the data reported.	yes	yes	yes
35	Conclusions are accompanied by the appropriate caveats.	yes	yes	yes

Healthcare resource use and cost

In this review, all studies were based on the national healthcare system perspective. In this perspective, authors might include treatment costs (medications costs, administration, monitoring, condition management (for example GP visits and hospital admission), and cost of managing adverse events associated with treatment. The Healthcare system perspective does not include patients borne costs of obtaining care, and QALYs are based on the general population's valuation of health outcomes [(139)].

In one trial based economic evaluation [(136)], the unit cost of resource was reported in ($HK), the following resources were measured including drugs (the nature and quantity of drugs were reported by a nurse), pharmacy (the estimated time (measured per minute) required by the pharmacist to process a unit of the prescribed drugs), nursing officer in the emergency department (the estimated time (measured per minute) by nurses to check and prepare the blinded formulation of study's drugs), registered nurse in the emergency department (time estimated by nurse manager for the nurse to deliver the drugs in everyday setting), emergency room physician (measured time (measured per minute) by research nurse for nurses to manage adverse drug effects), inpatient ward costs (estimated as the number of bed days in the observation or hospital ward) and the reattendance costs (estimated as emergency department attendance costs).

In a another model-based economic evaluation study [(134)], the unit cost of resources was reported in GBP (£). The following resources were measured: average dose/per day and average cost/week as well additional costs were estimated as the proportion of patients requiring resource as follows: Enema administered by the patient,

enema administered by a practice nurse, enema administered by a district nurse, primary care physician consultation, home visit by primary care physician, a home visit by a district nurse, a home visit by a practice nurse, outpatient appointment, endoscopy/colonoscopy, accident and emergency attendance, manual evacuation, hemorrhoid stapling, average cost/patient per course of therapy and average weekly cost/per patient of additional therapies.

In another modeling study [133], the unit cost of resources was reported in GBP (£). They have reported the cost of drugs (paracetamol, mild opioids, NSAIDs, and strong opioids), GP consultation for all patients (within 6 weeks), GP contact following discharge from intermediate care/ surgery, and Other primary HP contact (surgery patients only) (Typically one intervention to remove suture by practice nurse). Moreover, the study's authors estimated the cost of different interventions including (Magnetic resonance imaging (MRI) and surgery procedures).

In Palmer et al study [131], cost of IV opioids administration, management of adverse events (nausea, vomiting, hypotension, and respiratory depression), and IV complications (phlebitis, extravasation, and IV prescription errors) were reported $. While in another modeling study [135], including the cost of each prescription calculated as the base NHS price for treatment, plus the dispensing charge corrected for the patient's contribution. NHS prices for ibuprofen and paracetamol were obtained from the published sources.

In the economic evaluation of traumatic pain and non-traumatic abdomen pain [132]. The marginal costs of staff, drugs, devices, and total costs time in moderate or severe pain per hour were assessed in patients-controlled analgesia and standard care groups separately for each pain condition and reported in GBP. Whereas in a

randomized controlled trial study [130], only the cost of drugs was reported in Malaysian ringgit.

Dealing with uncertainty

In this review, all modeling studies performed a one-way sensitivity analysis. An ICER value was calculated in three studies but considering a differential health effect measure of denominator in the ICER formula [133-135]. In one study [135], The ICER was calculated by taking the difference in mean NHS prescription costs per patient between therapies by the difference in the proportion of patients successfully treated. Sensitivity tests were performed including varying the definition of treatment success and varying the proportion of patients exempt from prescription charges. Nonparametric bootstrapping was used to calculate confidence intervals around the proportion of effectively treated patients. In another study [134], ICER was defined as the difference in cost/difference in effectiveness (quality-adjusted life years (QALY)) gained. The authors of the previous model compared the utility values from previous studies' published utility values as a sensitivity analysis to assess any uncertainty around the quality-of-life gain. In a retrospective study, the impact of parameter uncertainty was investigated in sensitivity analysis, and sampling variation was evaluated using bootstrap methods [132].

Cost-effectiveness results –Narrative synthesis

Opioids drugs

In the trial of the patient-controlled analgesia versus standard care among patients with traumatic injury or non-traumatic abdominal pain in ED [132]. The pain scores were reported hourly for 12 hours by using the visual analogue scale. The cost-effectiveness was reported as the additional cost per hour in moderate to severe pain avoided by using patient-controlled analgesia rather than standard care. The trial's

results showed the cost per hour in moderate or severe pain averted was estimated to be £24.77 (€29.05, US$30.80) (bootstrap estimated 95%CI £8.72 to £89.17) for patients with traumatic injuries and £15.17 (€17.79, US$18.86) (bootstrap estimate 95%CI £9.03 to £46.00) for patients with non-traumatic abdominal pain. Moreover, a higher cost estimated in patient-controlled analgesia in comparison to the standard care in both groups (pain from traumatic injuries) incurred an additional cost £18.58 (€21.79 US$23.10) (95%CI £15.81 to £21.35) per 12 hours; and in (non-traumatic abdominal pain group) an additional £20.18 (€23.67 US$25.09) (95%CI £19.45 to £20.84) per 12 hours. While in the retrospective cohort study of the Premier database [131] among patients with all acute pains over a 24 month period with total of 7.3 million ED encounters. The study concluded that the mean cost per encounter of IV administration of an initial dose of the most frequent opioids drugs were as follows: morphine $145, hydromorphone $146, and fentanyl $147. Moreover, adding a second dose of opioid brings the average cost between $151 and $154 (Table 12).

In a cost effectiveness study, data from a cohort model used [134] among patients with non-malignant pain and opioids induced constipation, where the difference in costs between treatment calculated by combining the cost of pain therapy with the cost of laxatives in addition to other resources used to manage constipated patients. The results showed that the incremental cost of oxycodone/naloxone (OXN) versus oxycodone (OXY) was £ 159.68 for the average treatment duration. OXN gave an incremental QALY gain of 0.0273. where the probabilistic sensitivity analysis showed that OXN had about 96.6% probability of cost effectiveness at the £20,000 threshold (Table 12).

NSAIDs drugs

A randomized crossover clinical done among sexually inactive females aged 18-25 years with primary dysmenorrhea. Concluded mefenamic acid was found to have a similar effect in relieving symptoms as compared to celecoxib. Both medications were well tolerated and had similar effects on quality of life [(130)]. A full course of mefenamic acid and magnesium trisilicate for one day costs RM 2.55, while a full course of celecoxib for one day was RM 8.00 (Table 12).

Paracetamol versus NSAIDs drugs

In the cost-effectiveness study conducted to evaluate different strategies for acute low back pains [(135)]. The cost per patient was estimated to be £0.26 for paracetamol and £0.28 for ibuprofen and NHS prescription cost per successfully treated patient ICER was £1.00 in the paracetamol group and £1.56 in the ibuprofen group (Table 12).

Opioids versus non-opioids

In a cost-effectiveness analysis of different approaches for treating sciatica patients, [(133)]. Where the results were expressed as incremental cost per patient with symptoms successfully resolved. The study concluded for the initial treatment non-opioids (NSAIDs, musculerelaxants, antidepressants, and antiepileptic medication) were the most successful interventions in the first and second pathways with probabilities of success of 0.613 and 0.996 retrospectively (Table 12).

NSAIDs versus opioids drugs

A clinical trial was conducted to investigate the cost-effectiveness of IV ketorolac versus IV morphine among 148 adult patients with severe pain after limb

injury [136]. They used the marginal cost to measure the difference of cost between the interventions. Results showed that the mean cost per patient (excluding admissions) was estimated to be $HK43.60 (£4; $5.6) for those in the ketorolac group and $HK228.80 for those in the morphine group (P < 0.0001). When including admissions unrelated to analgesia used the cost was $HK11 361.20 for the ketorolac group and $HK7279.62 for the morphine group (P = 0.451). However, in the case of excluding admission costs, much of the differences between the cost in the two interventions was result of the management of adverse events. They concluded IV morphine costs less than IV ketorolac in Hong Kong. However, ketorolac was a cheaper option once all additional costs incurred by the accident and ED and pharmacy are considered. A significant reduction in pain with activity was found in the ketorolac group with significantly less adverse events (Table 12).

Table 11. Economic Evaluation Results.

Study ID	Intervention/Comparator	Health effect measure	Costs measure
Basri et al., 2020 [130]	Celecoxib versus mefenamic acid	Pain scores, quality of life	• A full course of mefenamic acid and magnesium trisilicate for one day costs is RM 2.55 • A full course of celecoxib for one day is RM 8.00.
Palmer et al., 2017 [131]	IV, opioids	Pain scores	The mean cost per encounter of IV administration of an initial dose of the three most frequently prescribed opioids were: • morphine $145 • hydromorphone $146 • fentanyl $147

Pritchard et al., 2016 [132]	patient-controlled analgesia versus standard care	Pain scores	The total cost per hour in moderate or severe pain • Patient controlled analgesia 30.6 £ (12.14) • Standard care 12 £ (7.10)
Fitzsimmons et al., 2014 [133]	Opioids versus non-opioids	QALY	Mean cost of prescriptions: • Paracetamol £3.57 (based on 16 tabs = £0.17) • Ibuprofen £3.74 (based on 84 400 mg tabs = £1.87) • Mild opioids (codeine phosphate) 60 mg tabs = £1.98) • Strong opioids (morphine) £9.61 (MST 30 mg day) for 2 weeks
Dunlop et al., 2012 [134]	Oxycodone/Naloxone versus oxycodone	QALY	• ICER of oxycodone/naloxone (OXN) versus oxycodone (OXY) was £ 159.68 for the average treatment duration.
Lloyd et al., 2004 [135]	Paracetamol versus ibuprofen	Percentage of patients successfully treated	NHS prescription cost per successfully treated patient ICER: • £1.00 in the paracetamol group • £1.56 in the ibuprofen group
Rainer et al., 2000 [136]	ketorolac versus morphine	Pain scores	Mean cost per patient (excluding admissions) • $HK43.60 (£4; $5.6) for those in the ketorolac group • $HK228.80 in the morphine group Including admissions unrelated to analgesia used the cost • $HK11 361.20 in the ketorolac • $HK7279.62in the morphine group

Abbreviations: ICER: Incremental cost-effectiveness ratio, NHS: National Health Service, IV: Intravenous.

Discussion

To our knowledge, this is the first systematic review that summarizes the current evidence about the cost-effectiveness of analgesics used among patients with varied acute pain conditions. Our results showed that there are few studies of the cost-effectiveness of the most common analgesic drugs (paracetamol, NSAIDs, and opioids) used in ED for patients with acute pain.

This systematic review does not allow conclusive statements about cost effectiveness drugs to be made for several reasons including the diversity of the treatments in the included studies in terms of study arms, route of drug administration and reported time after drug administration. However, it suggests that different types of acute pain management strategies could lead to differential costs and health resources use. In a trial-based cost-effectiveness study compared patient-controlled analgesia versus standard care among patients with traumatic injury or non-traumatic abdominal pain in ED [(132)]. The costs were higher in patient-controlled analgesia compared to the standard care for patients with traumatic injuries and acute non-traumatic abdomen pain. In Palmer et al., study [(131)], they have concluded that IV administration in ED setting for moderate to severe pain is associated with significant costs. Where most of the cost of IV opioids administration occurs in the initial IV-line setting. Thus, the study authors suggested the use of newer noninvasive analgesic (sufentanil sublingual) that could prove to be substantial cost-saving among patients with acute pain and not require an IV administration [(140)]. Where a cost-effectiveness study concluded that the previous drug is a cost effective drug option for the management of acute moderate to severe post-operative pain [(141)]. A study conducted in five European countries (France, Germany, Italy, Spain, and United Kingdom) [(125)], evaluated the costs of treating

moderate to severe pain in the ED. These studies provided important estimations of costs related to IV-management (morphine). Where a micro-costing approach was taken to estimate costs, this study showed that the total costs in these EU countries were €121-€132 ($138-$150) per patient for managing an episode of acute pain. Moreover, the main driver of the total cost in these countries was the cost of managing IV-related complications including phlebitis, extravasation and IV prescription error) that accounted for 73% of the total costs. This conclusion supported by a study conducted by Medical Developments International limited [142], aimed to compare the costs of using penthrox (methoxyflurane was given through an inhaler) to those who received IV morphine for patients with acute pain in EDs. The costs were calculated based on published literature and primary interview with emergency department staff. Analgesia costs, material costs, workforce time, and management of adverse events (nausea and vomiting were estimated. These costs were similar to the previous study when excluded costs of respiratory depression and IV prescription errors.

Rainer study [136] in this review recommended the use of IV NSAIDs (ketorolac) for patients with limb injuries as more cost-effective when administered intravenously in titrated doses according to the patient's need was effective as IV opioid (morphine) with fewer adverse effects than opioid (morphine), which made fewer demands on physicians' and nurses' management time resulting in earlier discharge or admonition to a ward. Where NSAIDs drug (ketorolac) was a cheaper option once all additional costs incurred by the accident and ED and pharmacy are considered. A model-based study [133], found a consistent result in favor of nonopioids drugs (NSAIDs, musculerelaxants, antidepressants, and antiepileptic medication) in patients with sciatica as more cost-effective as an initial treatment when compared to opioids in the same treatment stage.

There was variation in included studies in the cost estimation of adverse events. In a trial among patients with PD [130]. The cost of adverse events was not estimated. However, in another retrospective study[131], The authors assumed that all patients will reach pain relief with an overall fixed dose of opioid equivalent to 10 mg (IV morphine). While patients often receive supportive treatment with oral analgesia and a considerable percentage of patients require a higher dose for pain relief. Which this assumption may lead to underestimation of the total costs and an overestimation of cost per dose. Moreover, there was lack of formal assessment of AEs management cost, therefore, AEs cost, and IV complication estimates drawn from a literature review. Where the approach was conservative, the costs for a reduced number of typical opioids AEs were included. While in Rainer study [136], they considered a wide range of adverse events including nausea, phlebitis, and vomiting also, the economic impact of treating drowsiness, dizziness, and sleeping, however, they failed to include the contribution of respiratory depression. Opioids drugs are known to have respiratory depression. Despite its low incidence, the cost associated with its management including nursing costs, monitoring of vital signs, and oxygen saturation were the highest among all modeled adverse events [125].

limitations

There was high heterogeneity in the included studies. Therefore, a descriptive approach was adopted to present the results. A substantial variation was found in the population considered and samples informing data in the included studies. The trial-based, and observational studies focused on a sample of population meeting specific criteria while economic models also concentrated on a specific patients but identified data from several existing sources and different samples of patients. Therefore, data samples are driven with different characteristics. These characteristics mostly had an

impact on the input including the baseline risk and potentially the outcome. In one trial [130], the study participants were restricted to young women aged 18-25 with only primary dysmenorrhea were included; thus this affects the generalizability of the results. In a retrospective study [131], the data were from a premier database in the US. Where an assumption was made that any encounter in the ED, led to an IV opioid administration for a pain complaint. However, this could not be true in some cases; there will be a small percentage of patients who presented to ED with non-painful conditions such as pulmonary edema due to congestive heart failure, which in this case IV morphine will be used. In a modeling study [133], there was a significant variation across the studies that used to identify data in the management of patients with sciatica, limiting the lessons that can be derived to understand the relative cost-effectiveness of the management strategies.

Lastly, we were unable to estimate the cost-effectiveness of IVP due to a lack of published studies (only one study [135]).

CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

In this meta-analysis patients presenting to the ED with moderately severe, acute pain reported similar levels of analgesia whether treated with IVP or comparator medications (opioids or NSAIDs or these in combination) at T30, T60, and T90. The adverse events reported in patients receiving IVP were 50% fewer as compared to those receiving opioids. The proportion of patients requiring rescue analgesia was similar in patients treated with IVP and opioids but lower in those who received NSAIDs. A high proportion of trials were at risk of bias and recruited small numbers of patients from a single center. While the economic evaluation study highlighted the economic burden of analgesia used in EDs. The use of IV morphine inflicts an economic burden.

Our economic evaluation study highlighted the economic burden of analgesia used in EDs,thus suggesting that the use of IV morphine inflicts an economic burden. Our review concluded that different management strategies contribute to a differential in cost and health service use where the IV administration of morphine was associated with significant costs, as most of the cost of IV opioid administration occurs in the initial IV-line setting. The drivers of these costs included managing IV-related complications including phlebitis, extravasation, and IV prescription error. An important limitation of our review is that we could not make a conclusive statement about the cost-effectiveness results due to the variation in alternative treatment strategies of the trials included in our review.

This study recommends more well-designed trials that measure the effectiveness of these drugs at different time points as well more well-designed economic evaluation studies on other analgesic such as IVP and IV NSAIDs to provide a comprehensive comparison of all related health care resource use and associated costs of the drugs.

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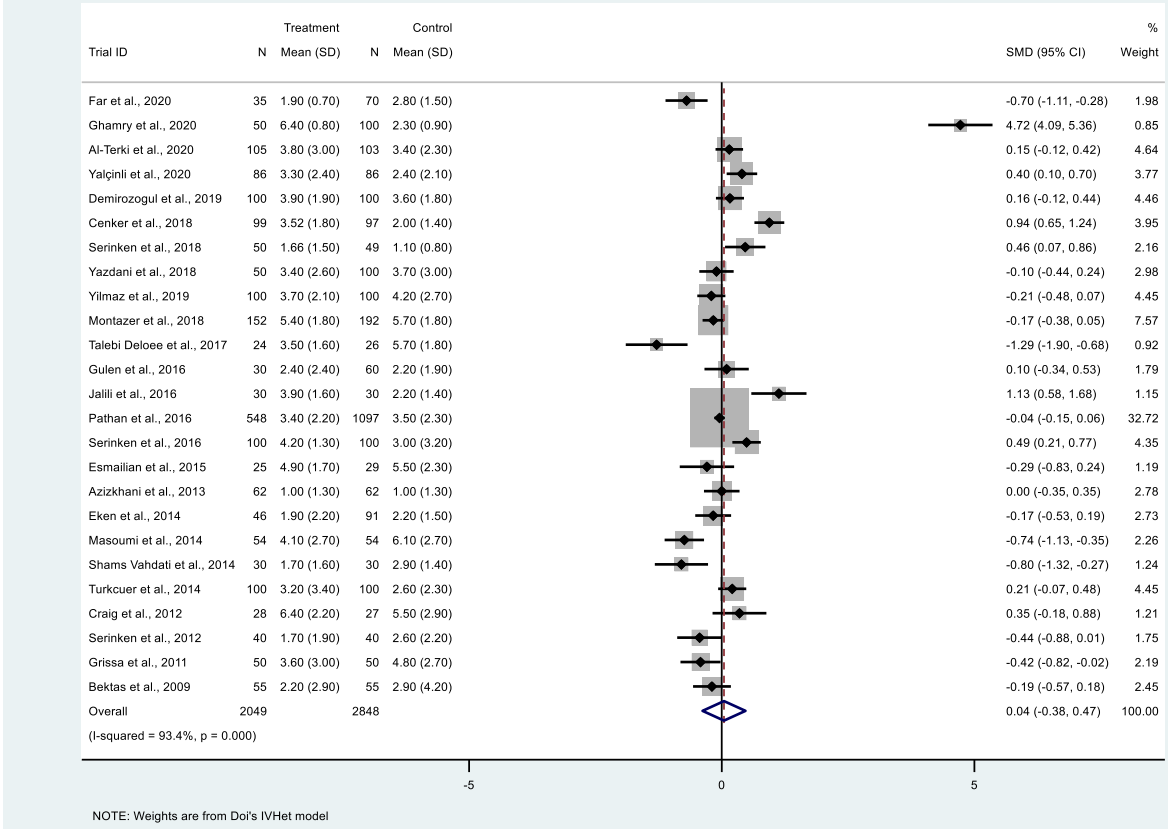
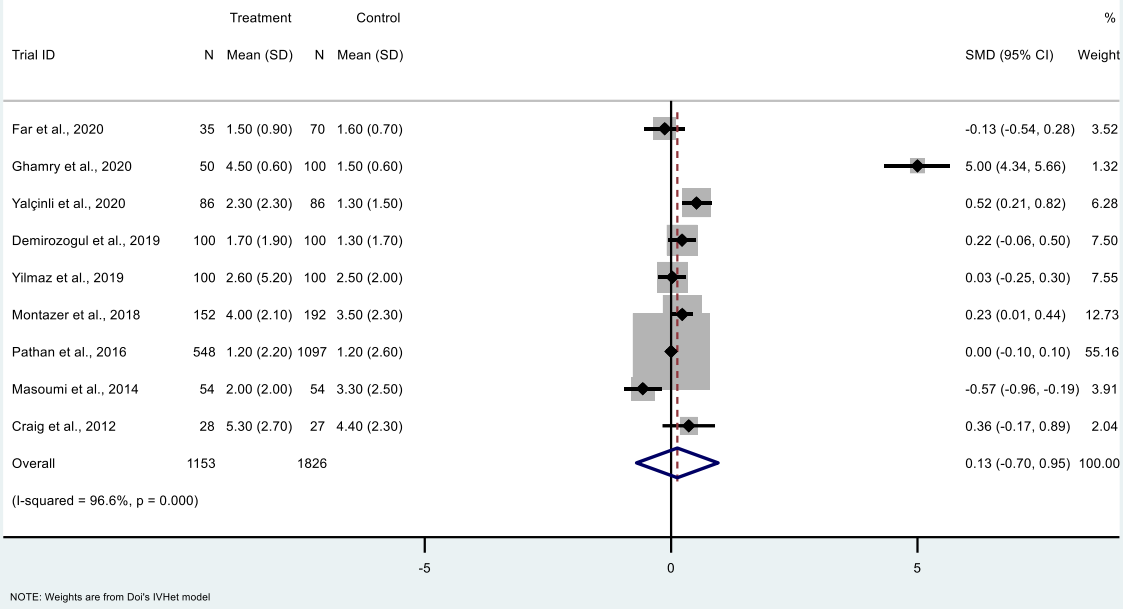
Appendix

List of figures



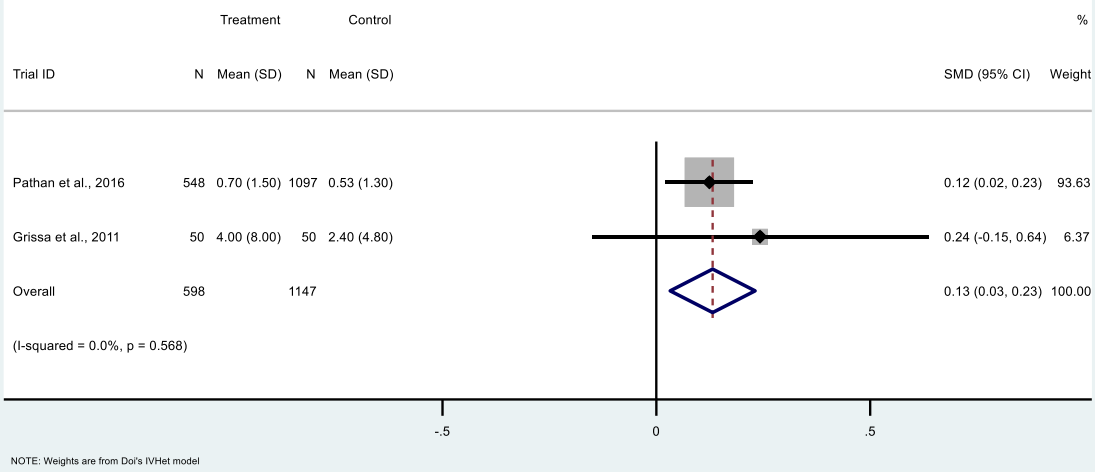
Forest plot of standardized mean difference of pain reduction at time 30 minutes

(Paracetamol compared to opioids or NSAIDs or combined group)



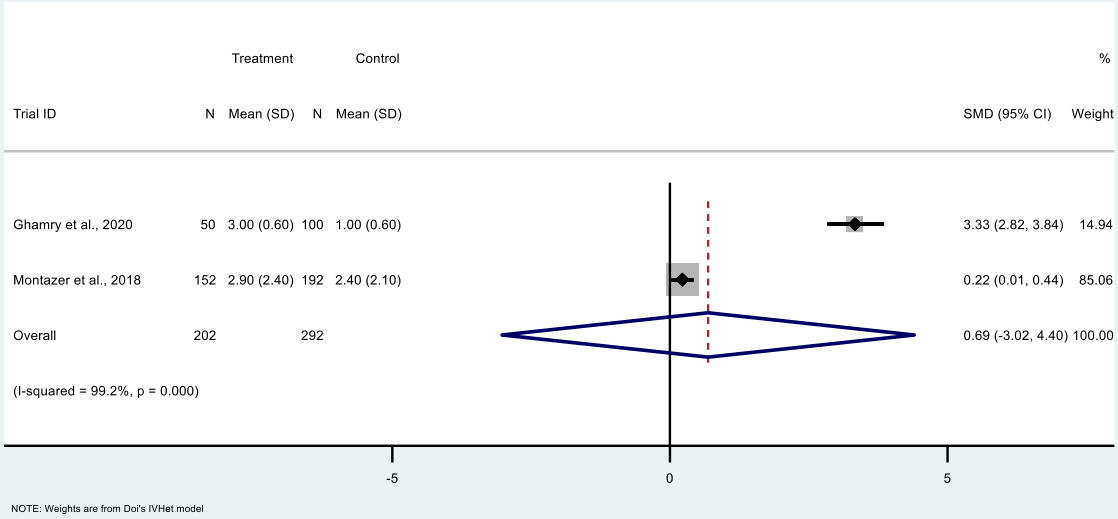
Forest plot of standardized mean difference of pain reduction at time 60 minutes

(Paracetamol compared to opioids or NSAIDs or combined group)



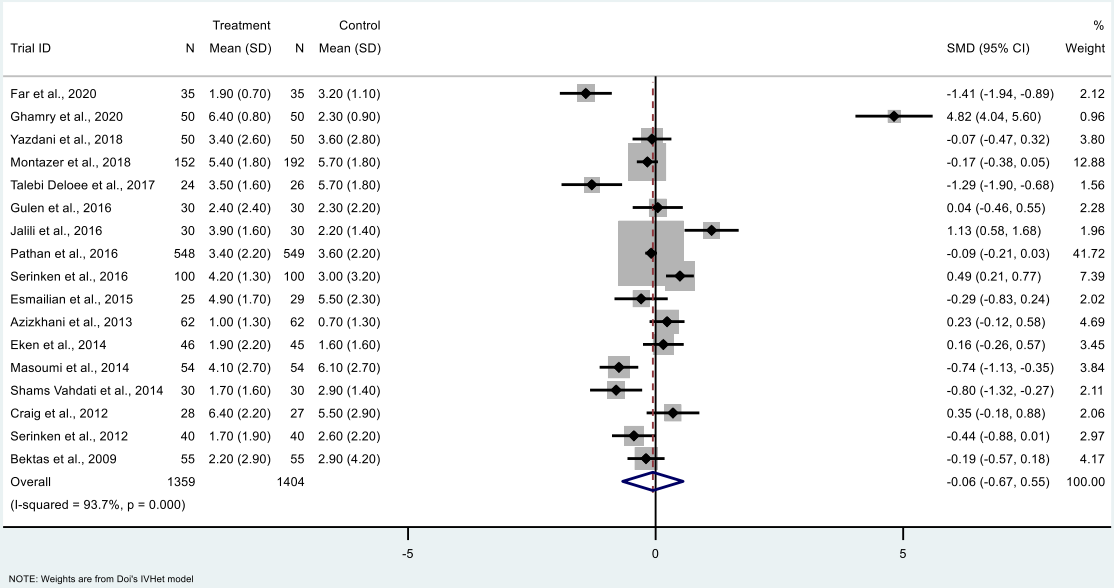
Forest plot of standardized mean difference of pain reduction at time 90 minutes

(Paracetamol compared to opioids or NSAIDs or combined group)



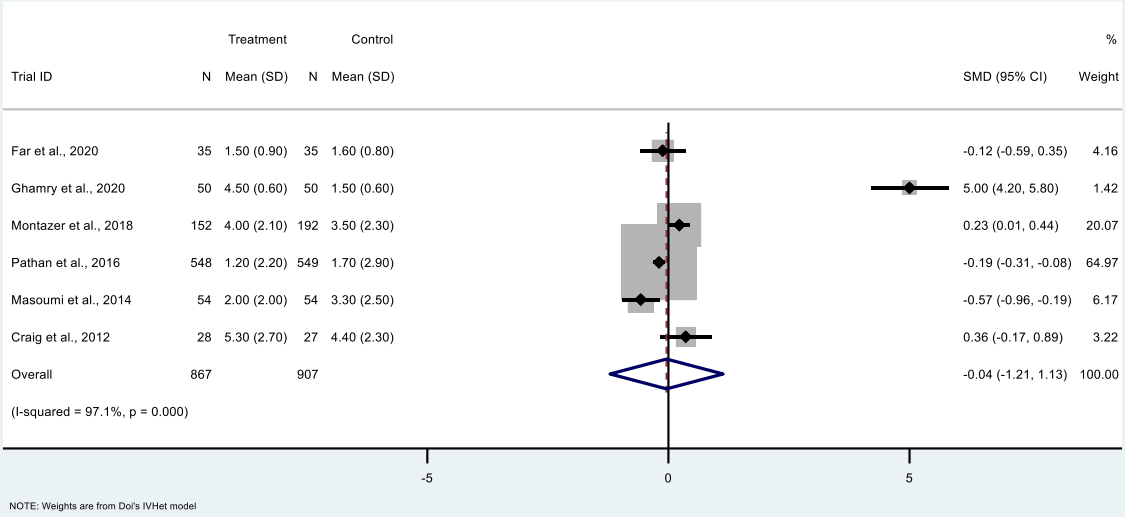
Forest plot of standardized mean difference of pain reduction at time 120 minutes

(Paracetamol compared to opioids or NSAIDs or combined group)



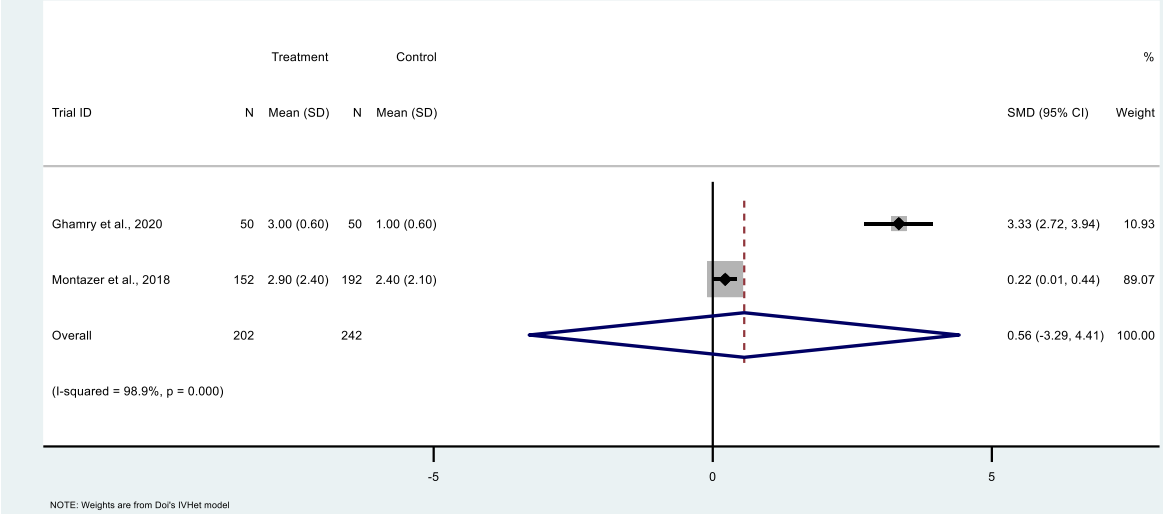
Forest plot of standardized mean difference of pain reduction at time 30 minutes

(Paracetamol compared to opioids)



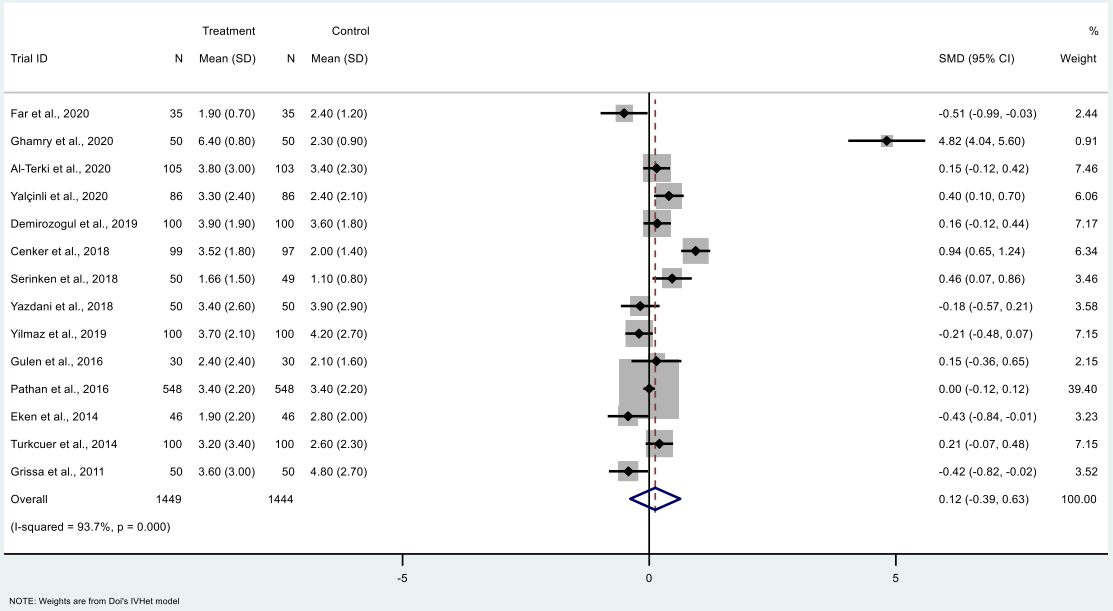
Forest plot of standardized mean difference of pain reduction at time 60 minutes

(Paracetamol compared to opioids)



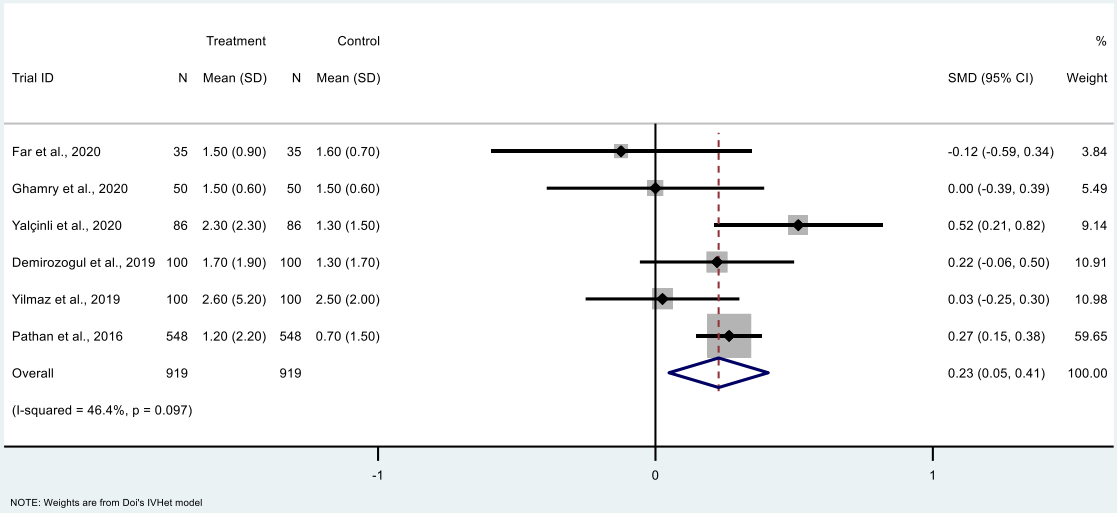
Forest plot of standardized mean difference of pain reduction at time 120 minutes

(Paracetamol compared to opioids)



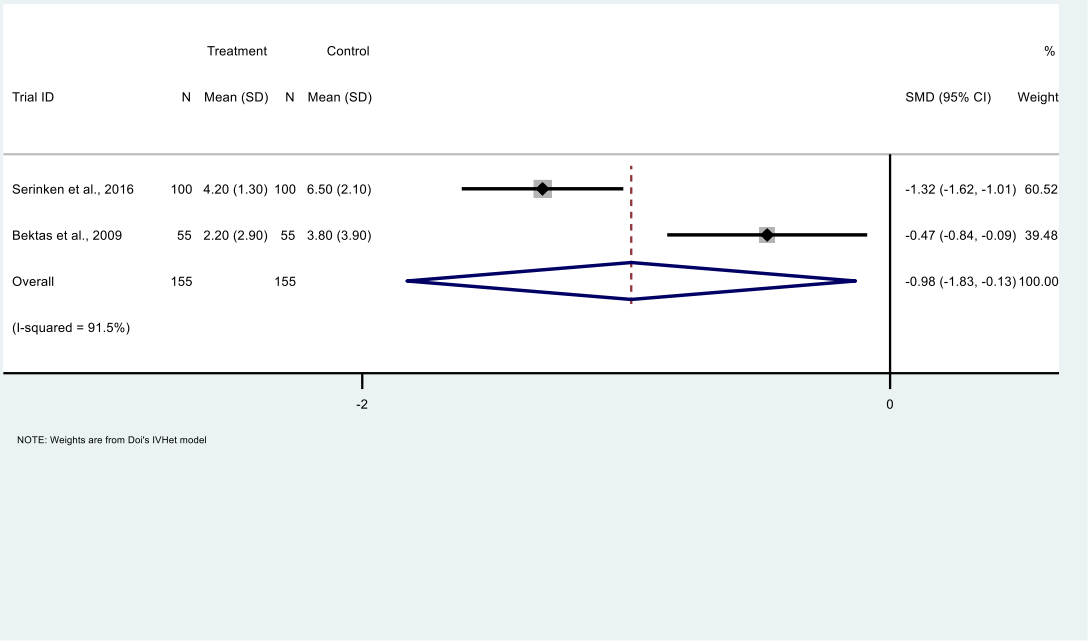
Forest plot of standardized mean difference of pain reduction at time 30 minutes

(Paracetamol compared to NSAIDs)



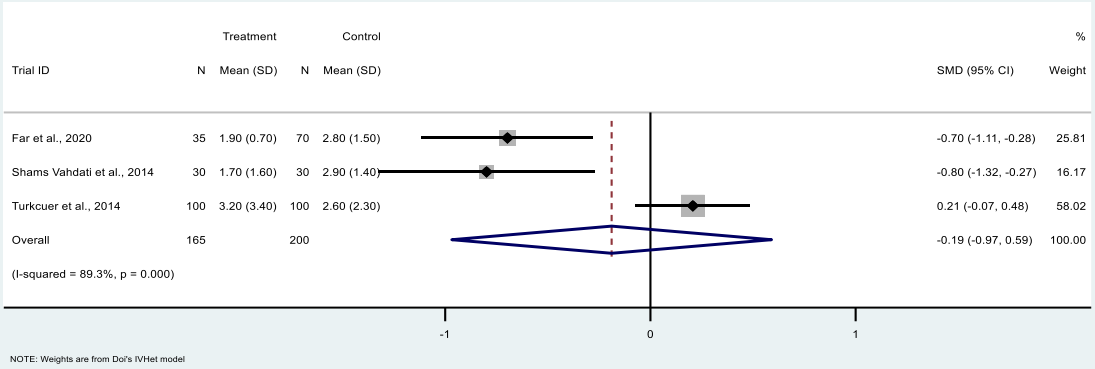
Forest plot of standardized mean difference of pain reduction at time 60 minutes

(Paracetamol compared to NSAIDs)

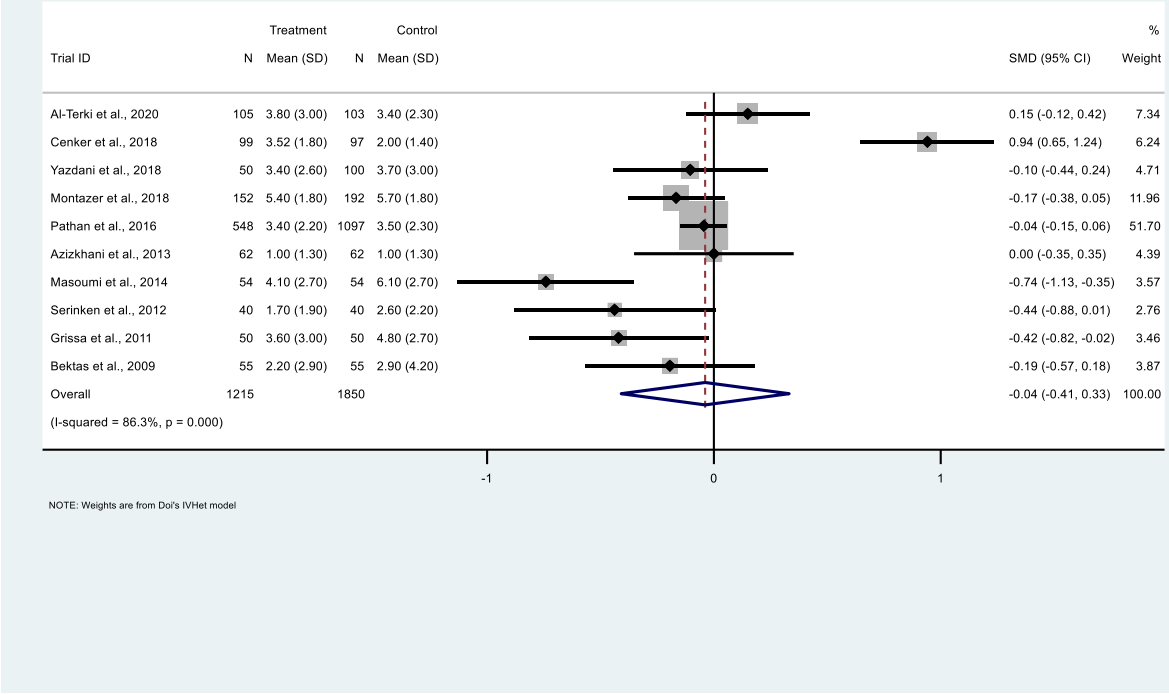


Forest plot of standardized mean difference of pain reduction at time 30 minutes

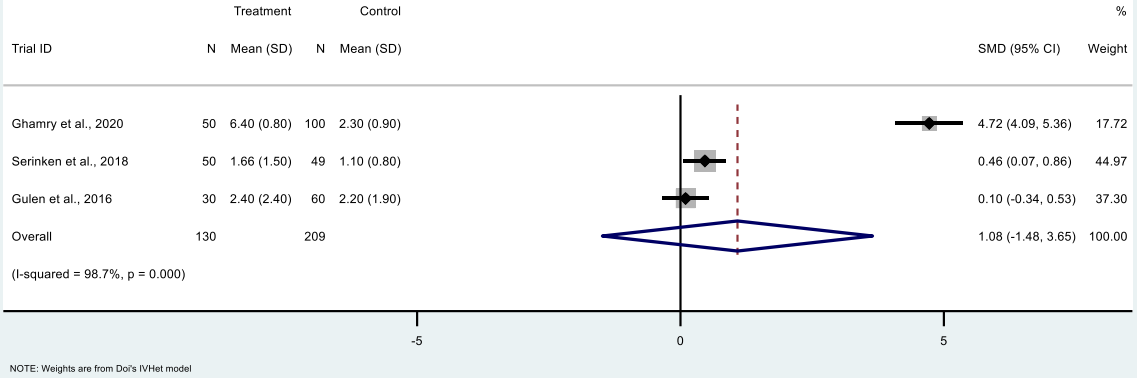
(Paracetamol compared to placebo)



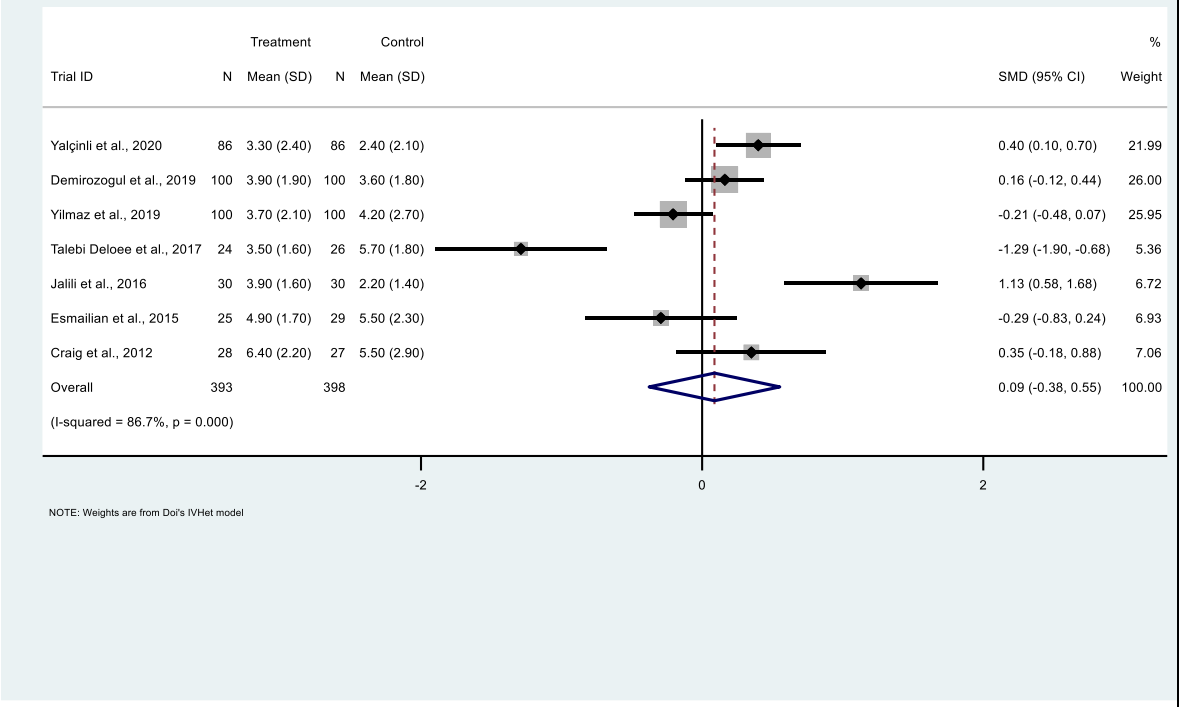
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with headache (Paracetamol compared to opioids or NSAIDs or combined group)



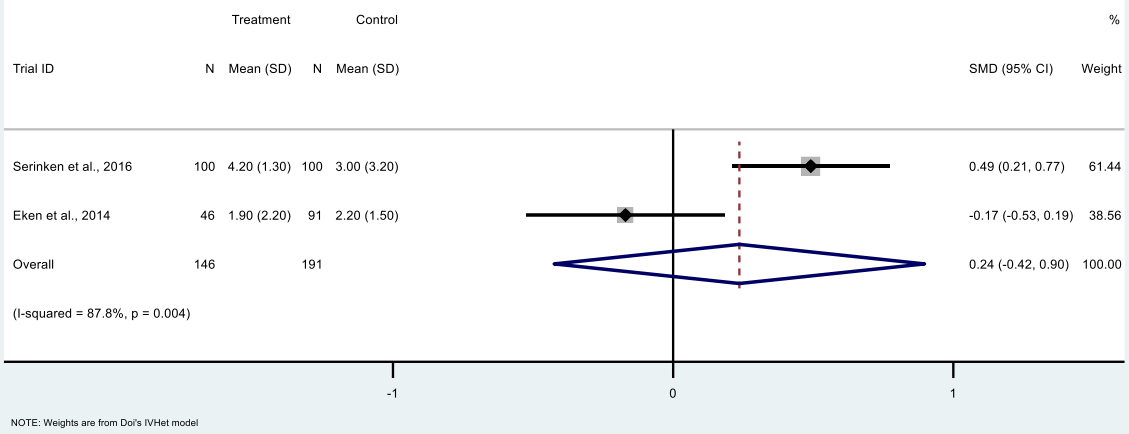
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with renal colic (Paracetamol compared to opioids or NSAIDs or combined group)



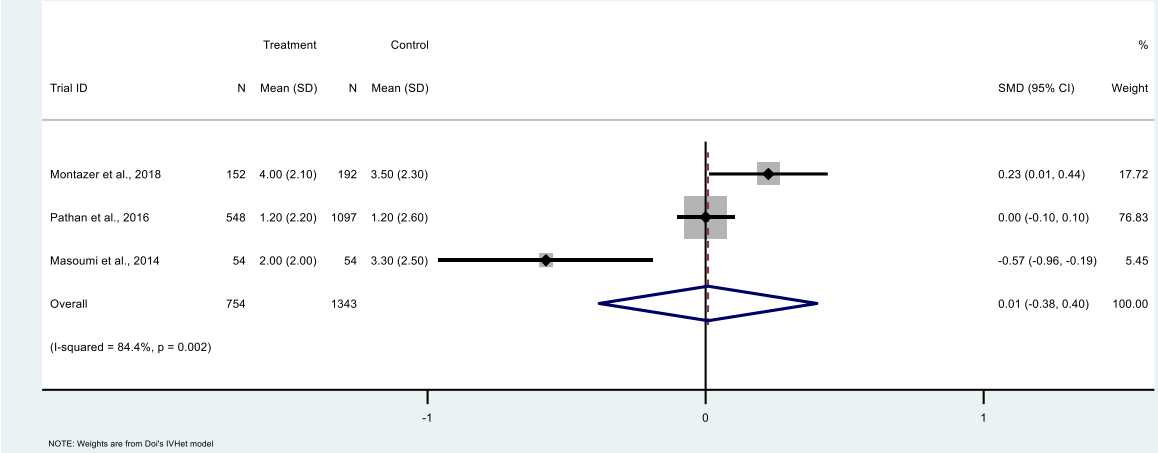
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with abdominal pain (Paracetamol compared to opioids or NSAIDs or combined group)



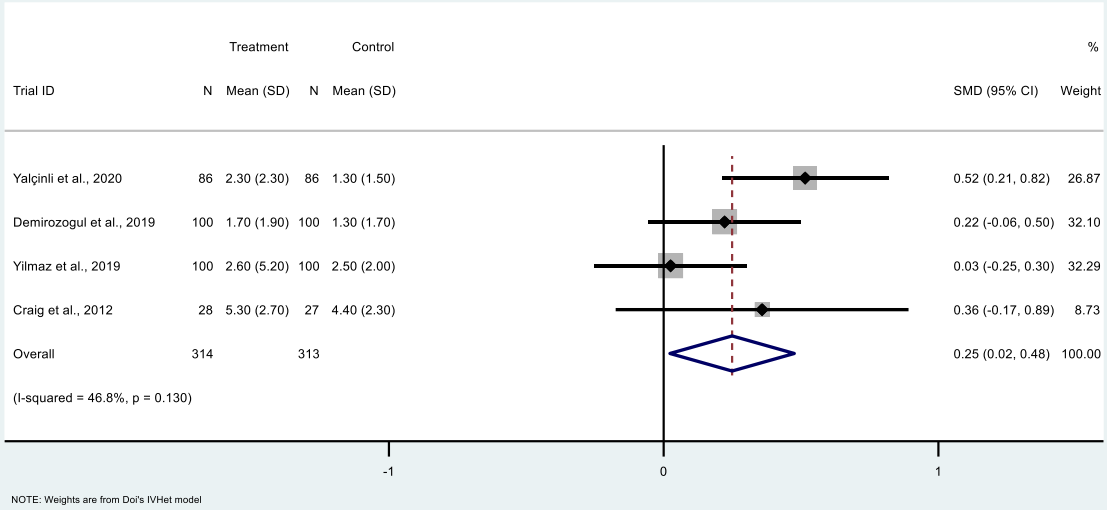
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with musculoskeletal injuries (Paracetamol compared to opioids or NSAIDs or combined group)



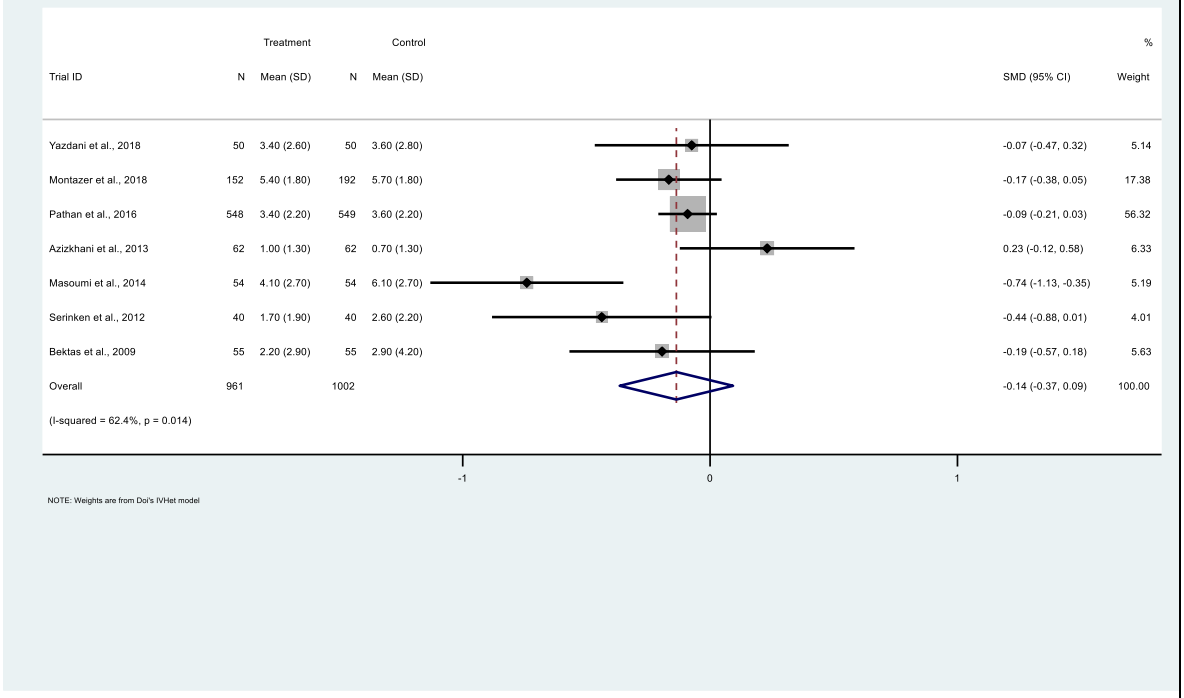
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with back pain (Paracetamol compared to opioids or NSAIDs or combined group)



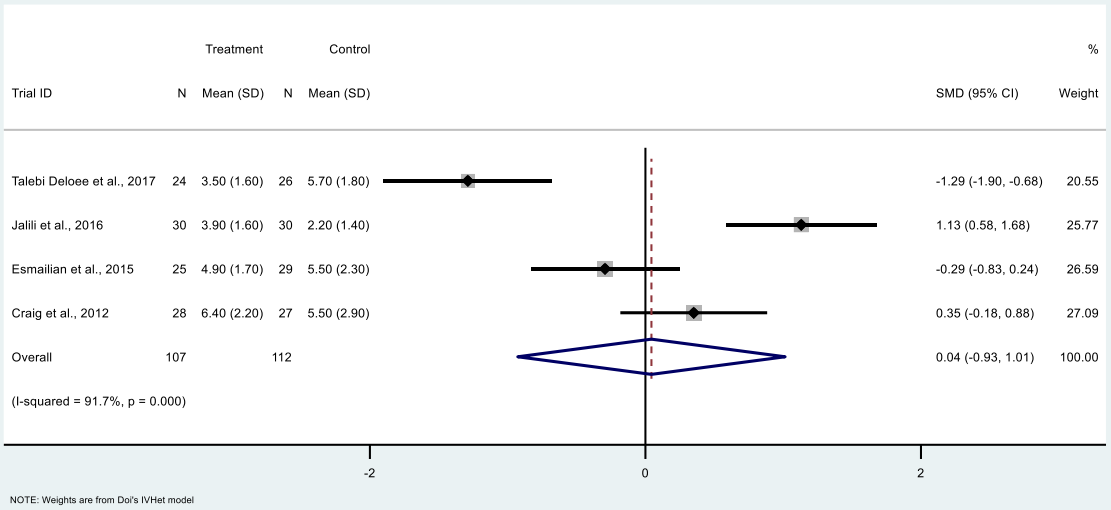
Forest plot of standardized mean difference of pain reduction at time 60 minutes among patients with renal colic (Paracetamol compared to opioids or NSAIDs or combined group)



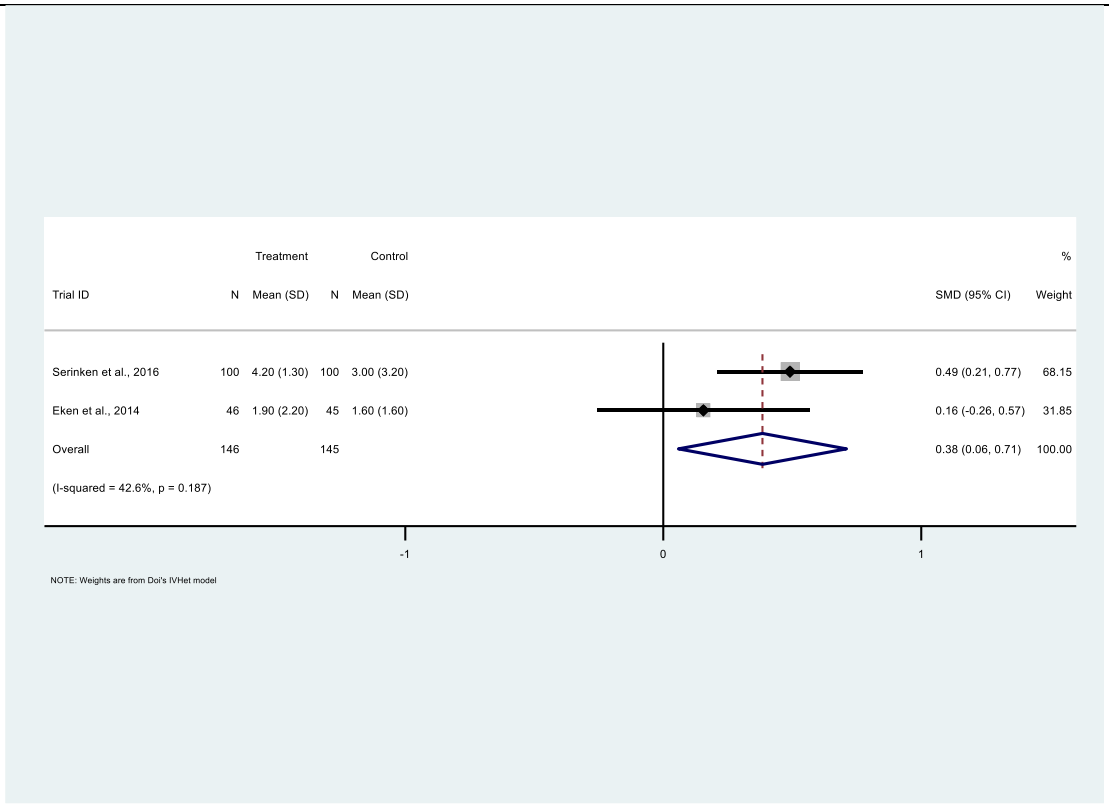
Forest plot of standardized mean difference of pain reduction at time 60 minutes among patients with musculoskeletal injuries (Paracetamol compared to opioids or NSAIDs or combined group)



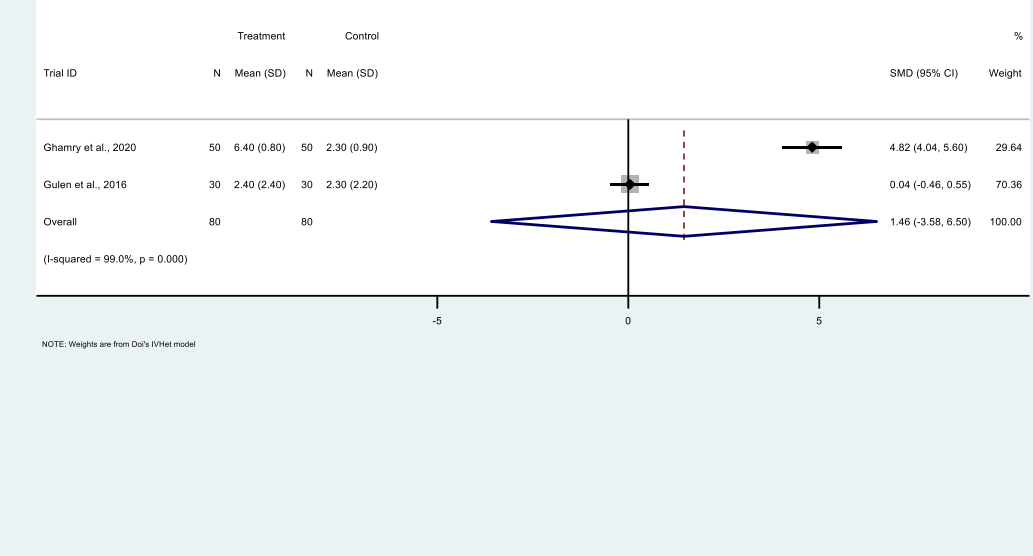
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with renal colic (Paracetamol compared to opioids)



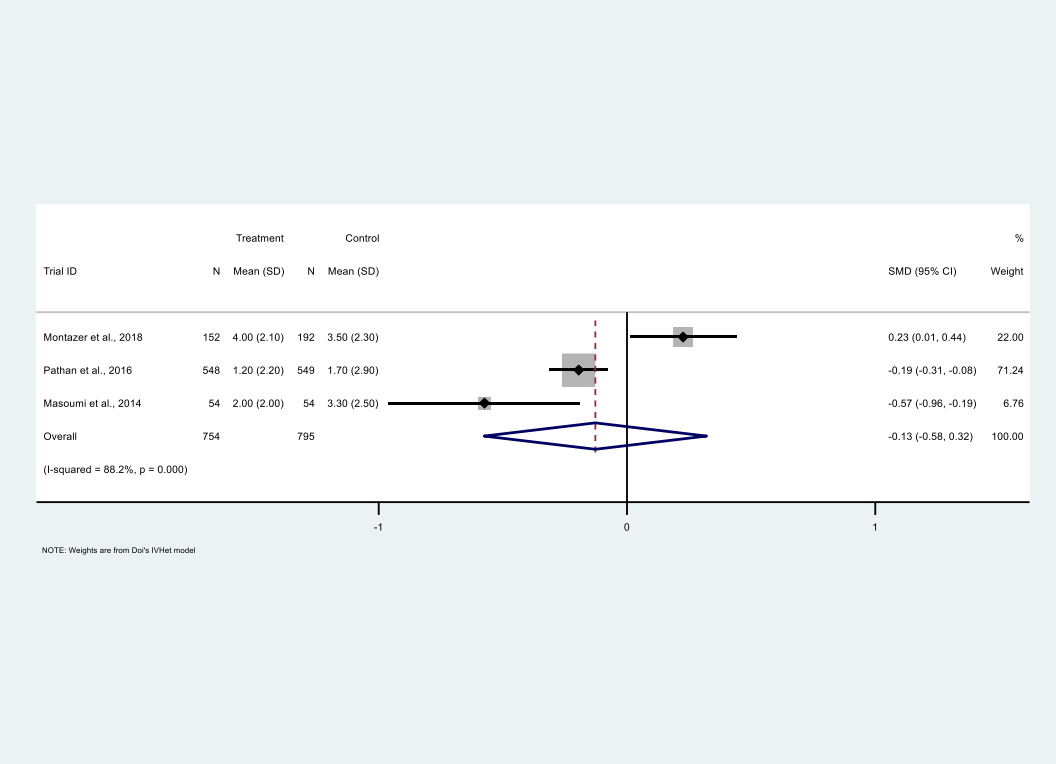
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with musculoskeletal injuries (Paracetamol compared to opioids)



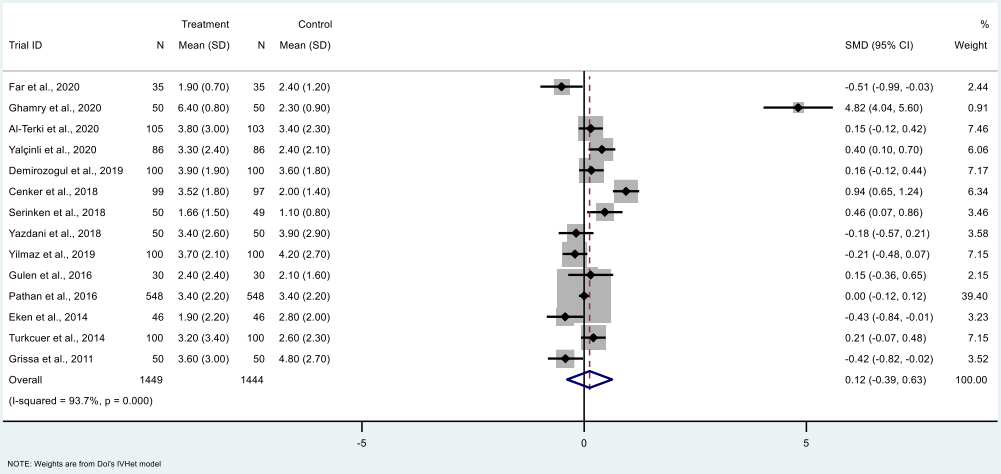
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with back pain (Paracetamol compared to opioids)



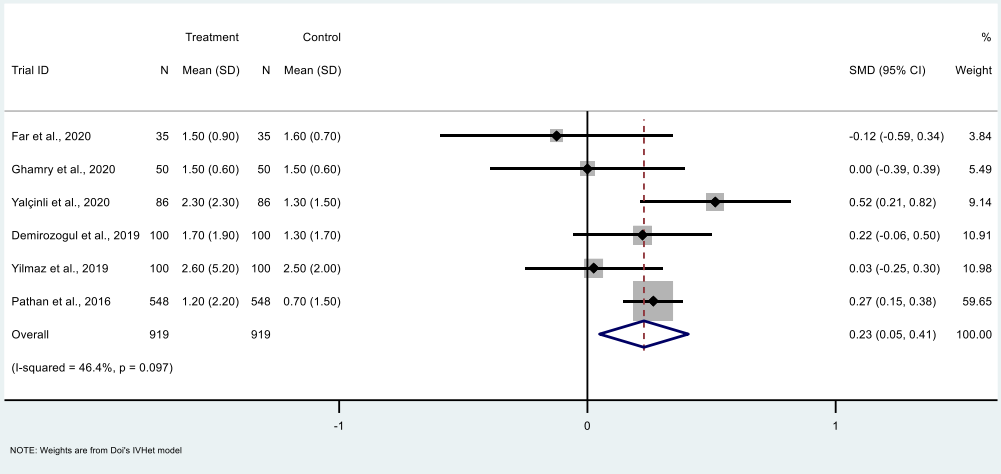
Forest plot of standardized mean difference of pain reduction at time 30 minutes among patients with abdomen pain (Paracetamol compared to opioids)



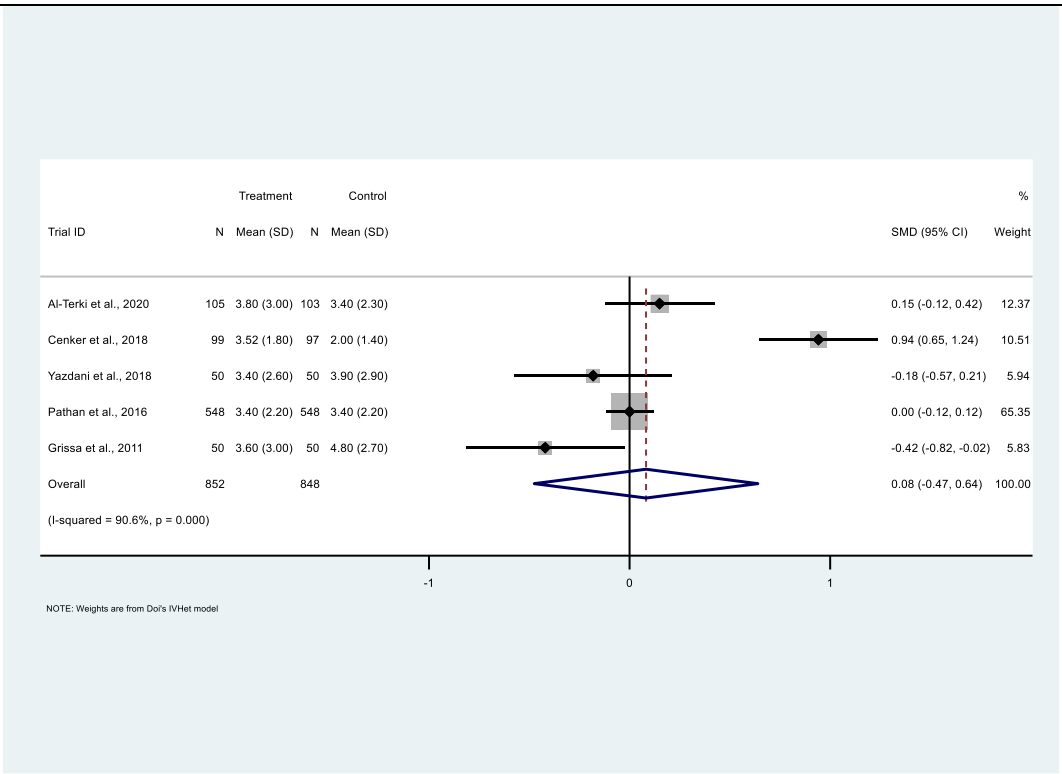
Forest plot of standardized mean difference of pain reduction at time 60 minutes among patients with renal colic (Paracetamol compared to opioids)



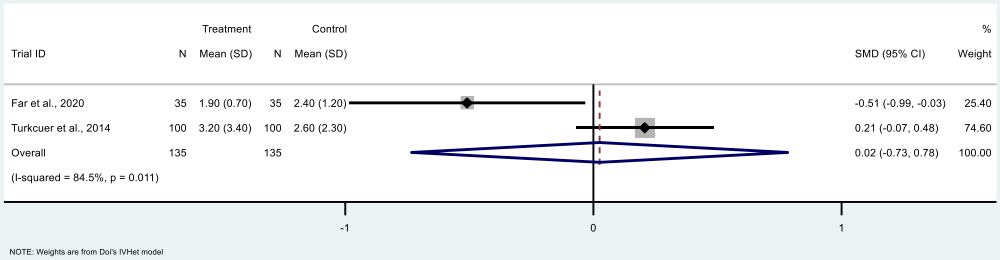
Forest plot standardized mean difference of pain reduction at time 30 minutes (paracetamol compared to NSAIDs)



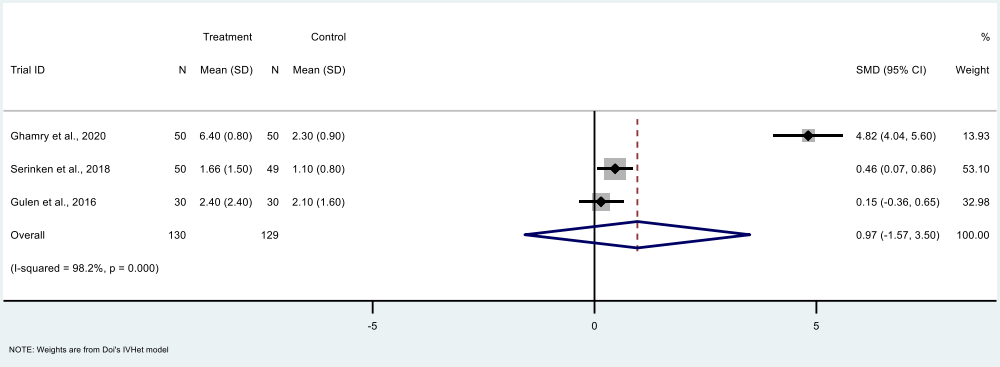
Forest plot standardized mean difference of pain reduction at time 60 minutes (paracetamol compared to NSAIDs)



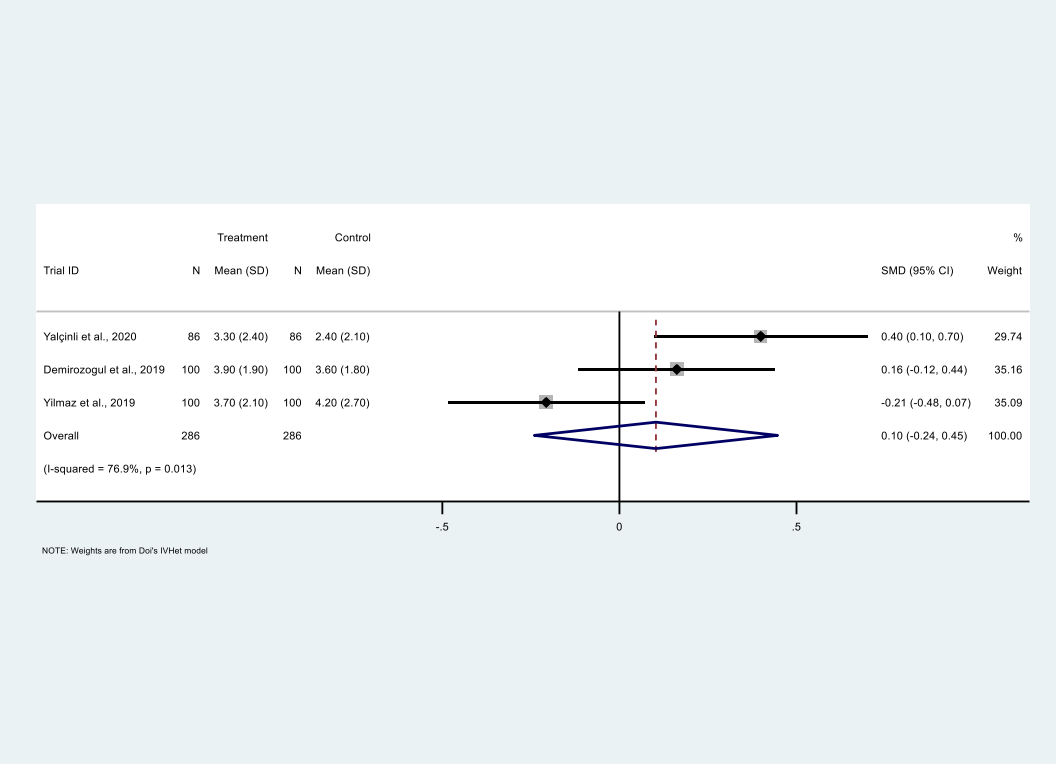
Forest plot standardized mean difference of pain reduction at time 30 minutes among patients with renal colic (paracetamol compared to NSAIDs)



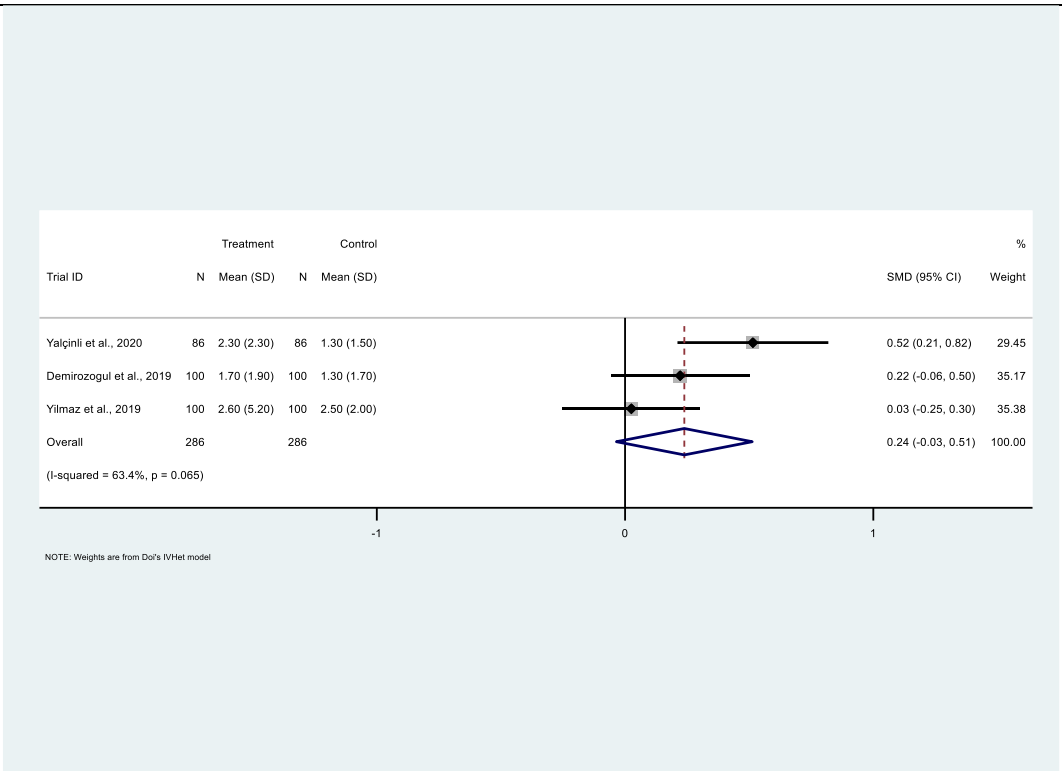
Forest plot standardized mean difference of pain reduction at time 30 minutes among patients with headache (paracetamol compared to NSAIDs)



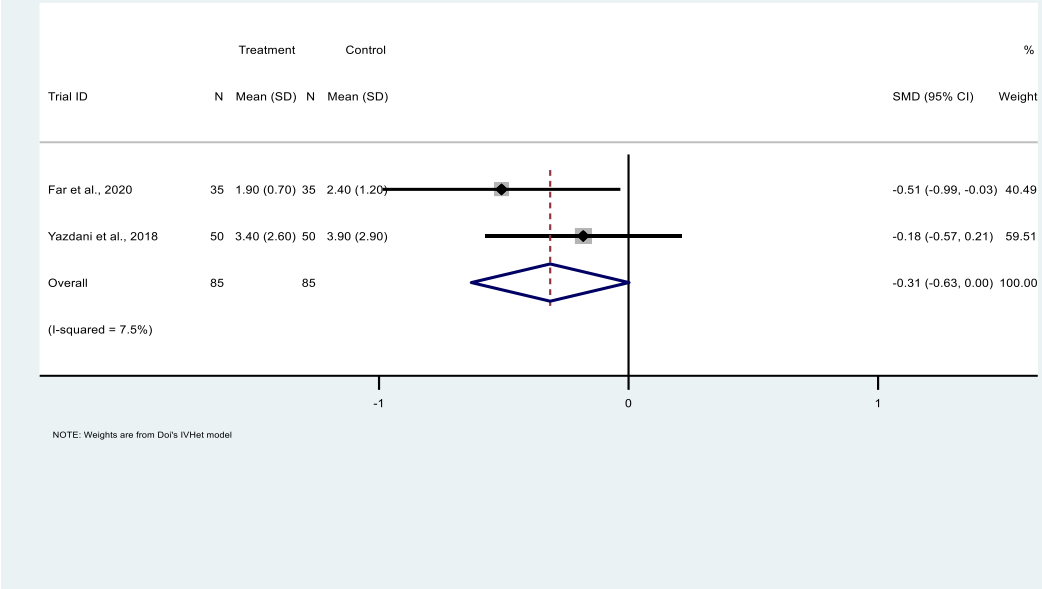
Forest plot standardized mean difference of pain reduction at time 30 minutes among patients with abdominal pain (paracetamol compared to NSAIDs)



Forest plot standardized mean difference of pain reduction at time 30 minutes among patients with musculoskeletal injuries (paracetamol compared to NSAIDs)

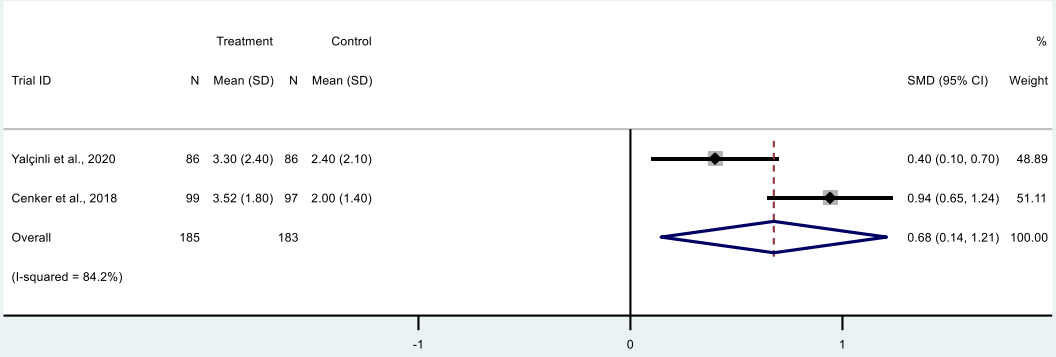


Forest plot standardized mean difference of pain reduction at time 60 minutes among patients with musculoskeletal injuries (paracetamol compared to NSAIDs)



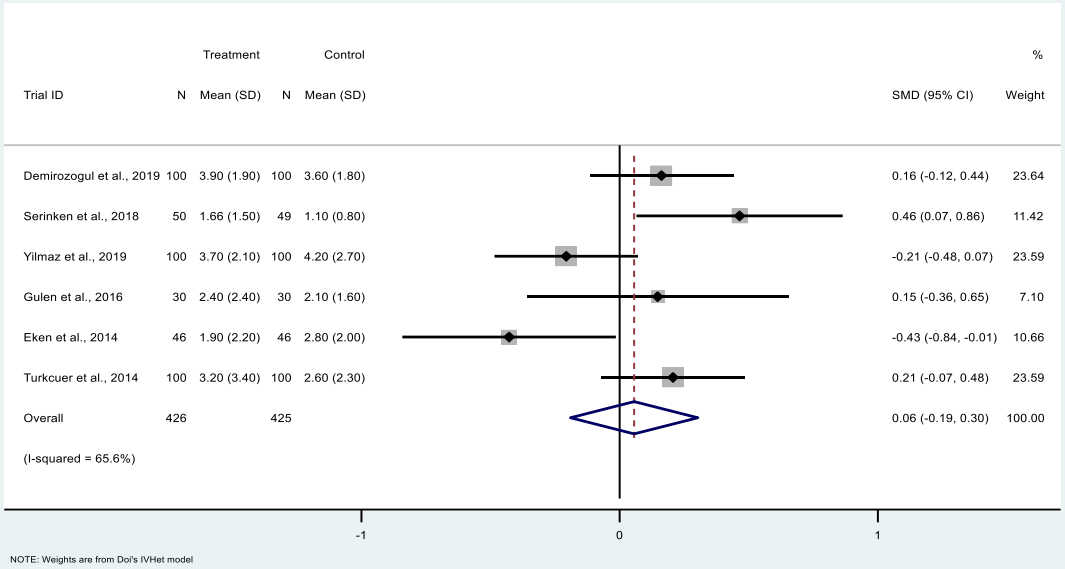
Forest plot standardized mean difference of pain reduction at time 30 minutes

(paracetamol compared to Ketorolac)



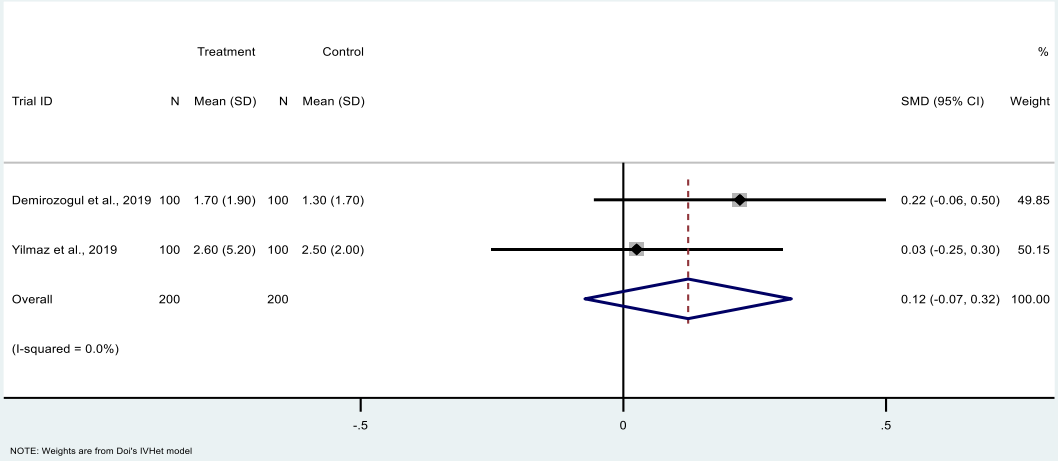
Forest plot standardized mean difference of pain reduction at time 30 minutes

(paracetamol compared to Ibuprofen)



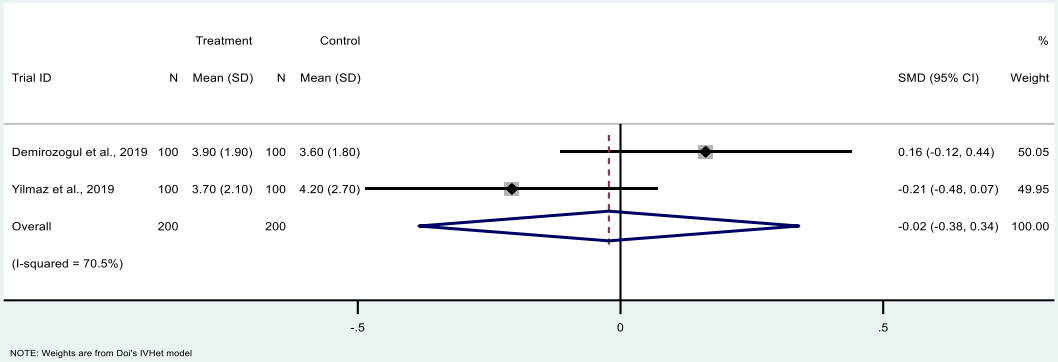
Forest plot standardized mean difference of pain reduction at time 30 minutes

(paracetamol compared to dexketoprofen)

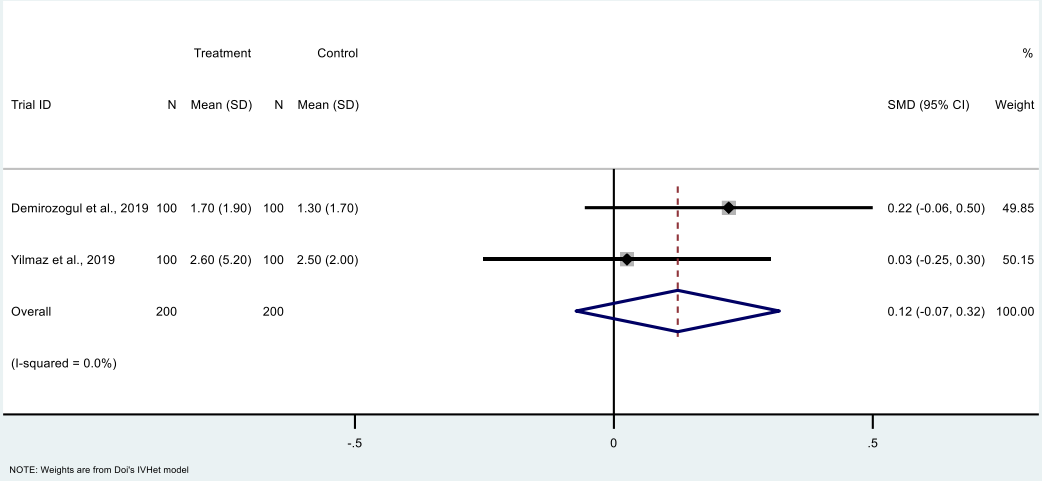


Forest plot standardized mean difference of pain reduction at time 60 minutes

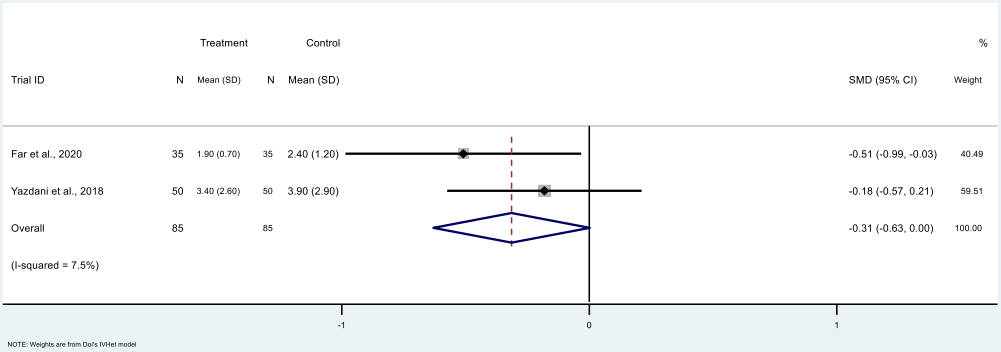
(paracetamol compared to dexketoprofen)



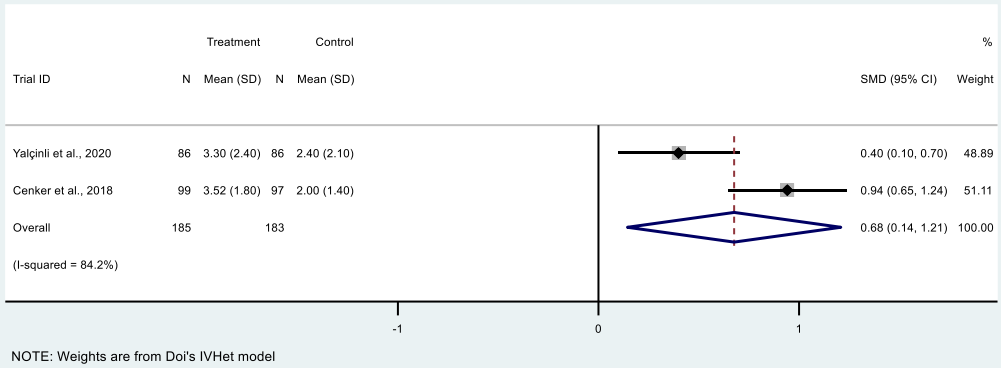
Forest plot standardized mean difference of pain reduction at time 30 minutes among patients with musculoskeletal injuries (paracetamol compared to dexketoprofen)



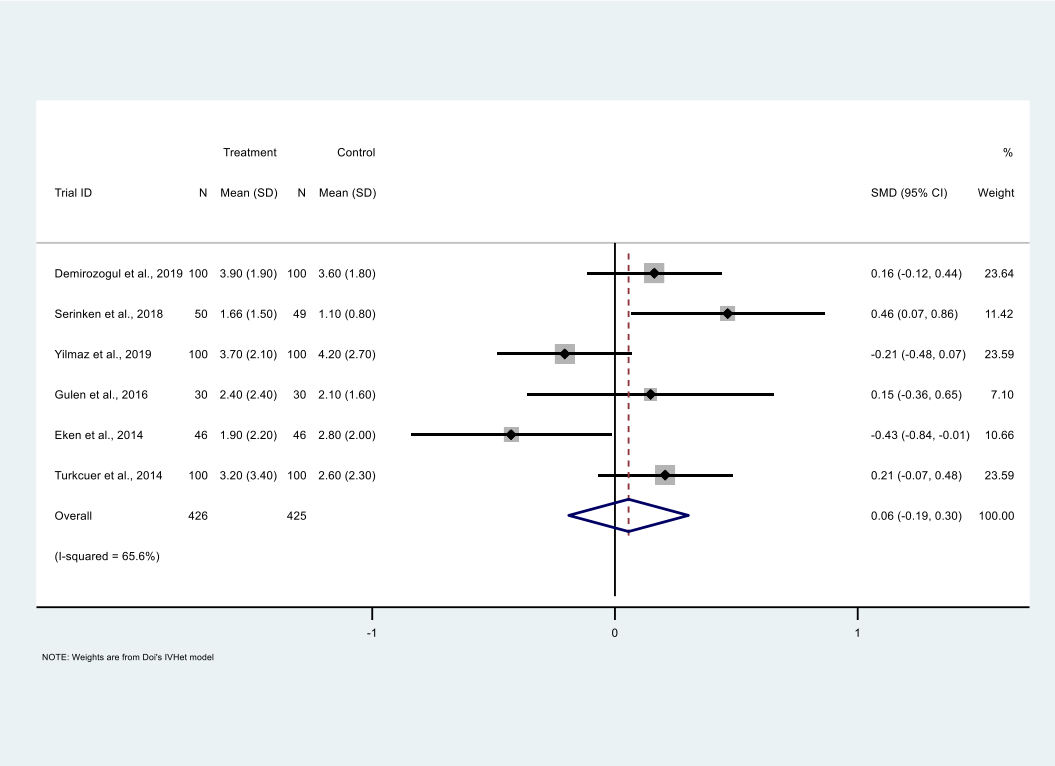
Forest plot standardized mean difference of pain reduction at time 60 minutes among patients with musculoskeletal injuries (paracetamol compared to dexketoprofen)



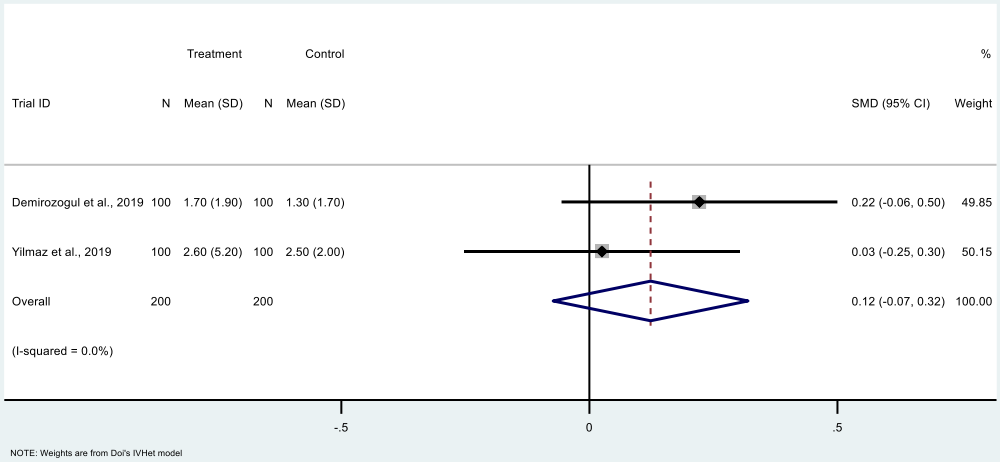
Forest plot standardized mean difference of pain reduction at time 30 (paracetamol compared to Ketorolac)



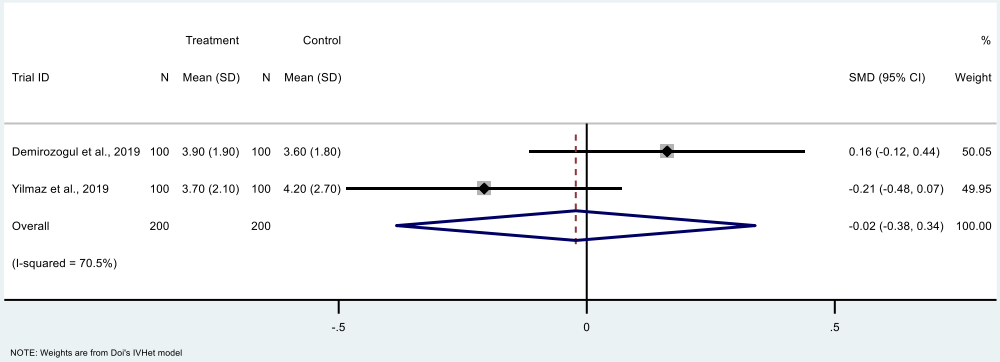
Forest plot standardized mean difference of pain reduction at time 30 (paracetamol compared to Ibuprofen)



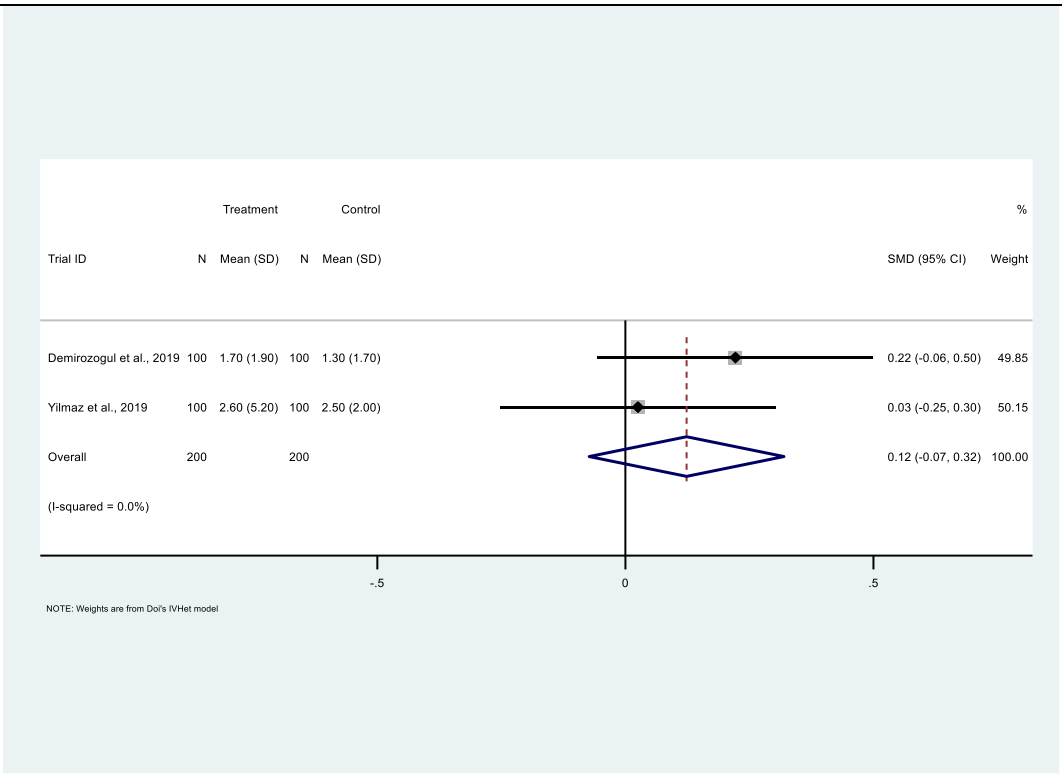
Forest plot standardized mean difference of pain reduction at time 30 (paracetamol compared to Dexketoprofen)



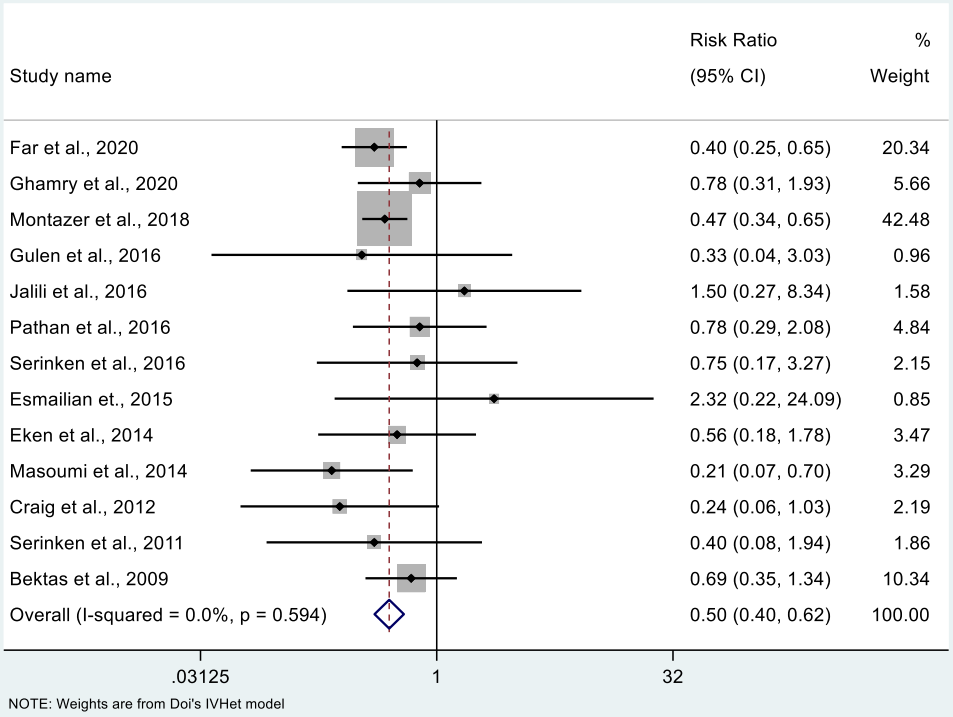
Forest plot standardized mean difference of pain reduction at time 60 (paracetamol compared to Dexketoprofen)



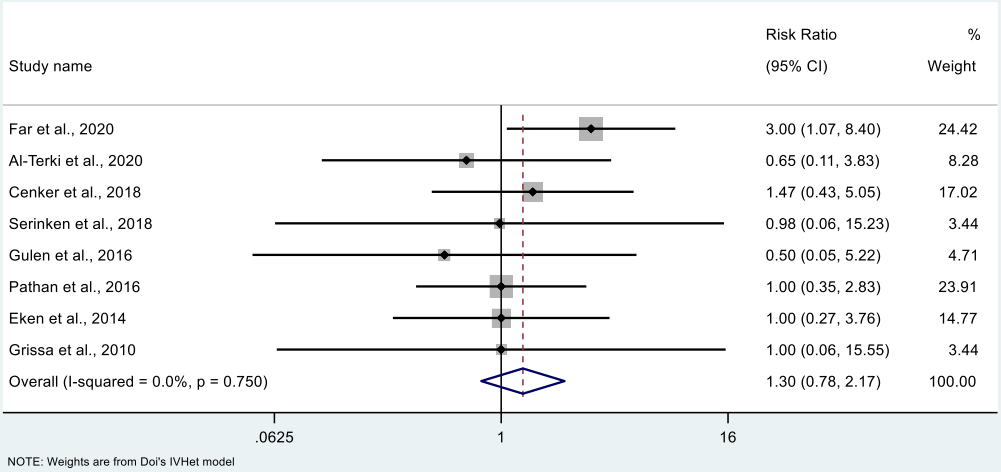
Forest plot standardized mean difference of pain reduction at time 30 (paracetamol compared to Dexketoprofen among patients with musculoskeletal injuries)



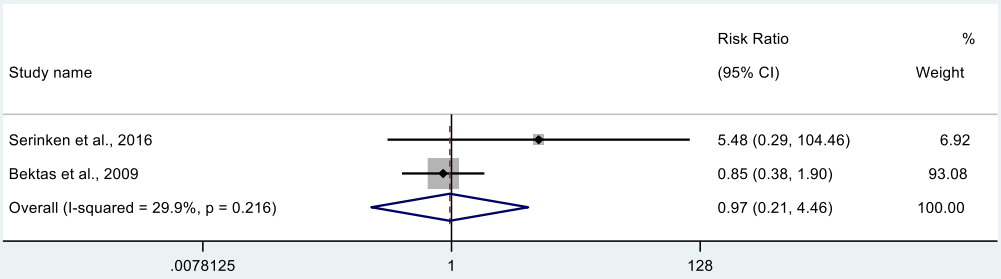
Forest plot standardized mean difference of pain reduction at time 60 (paracetamol compared to Dexketoprofen among patients with musculoskeletal injuries)



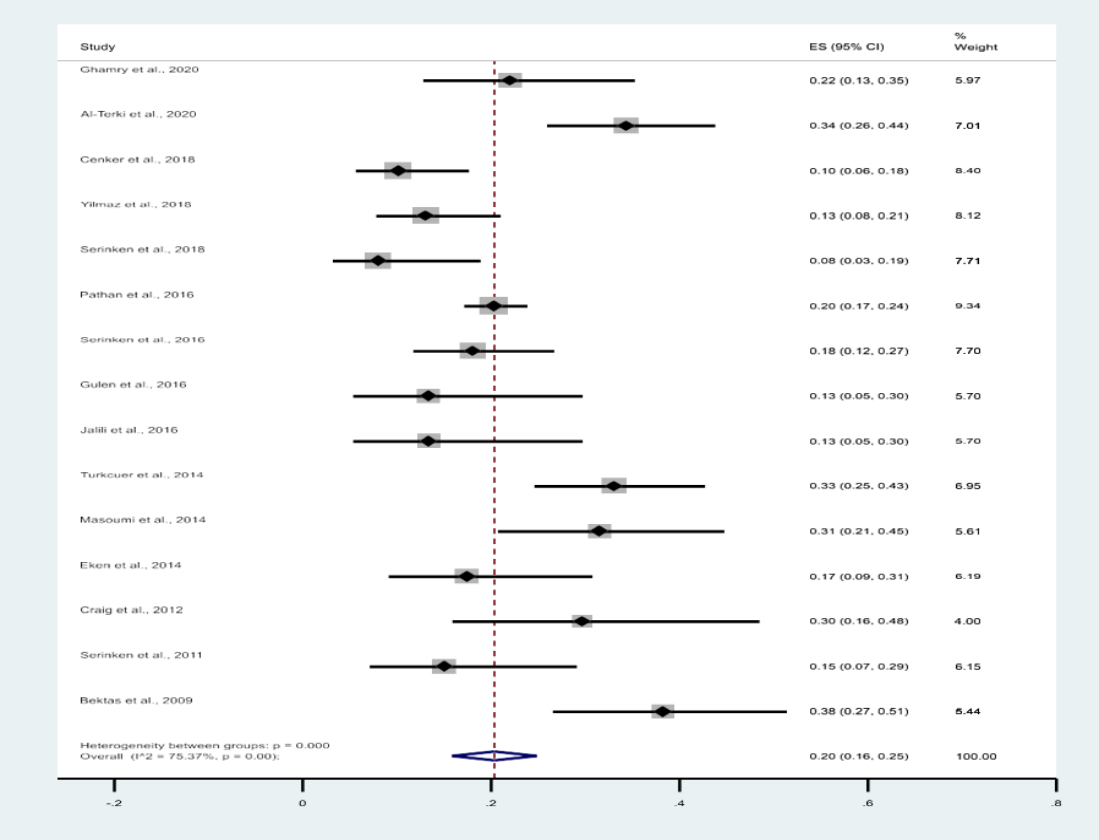
Forest plot of risk ratio of adverse events paracetamol compared to opioids



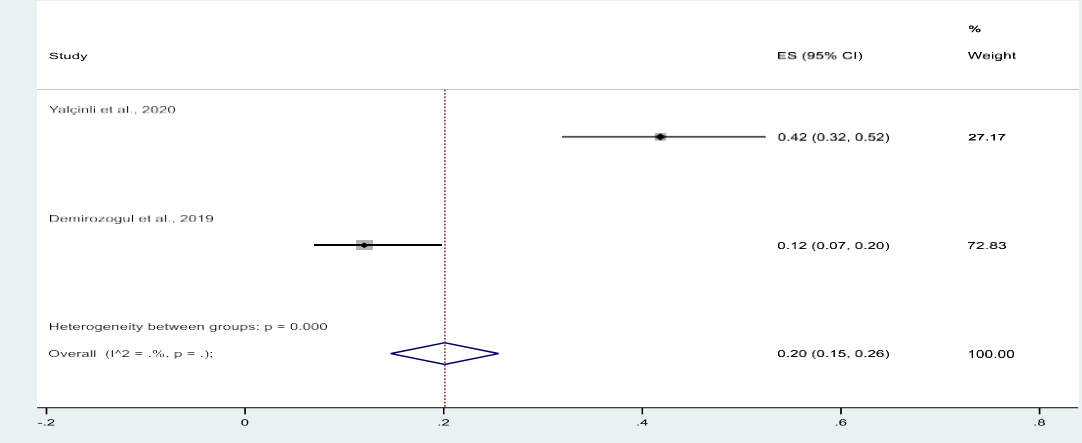
Forest plot of risk ratio of adverse events paracetamol compared to NSAIDs



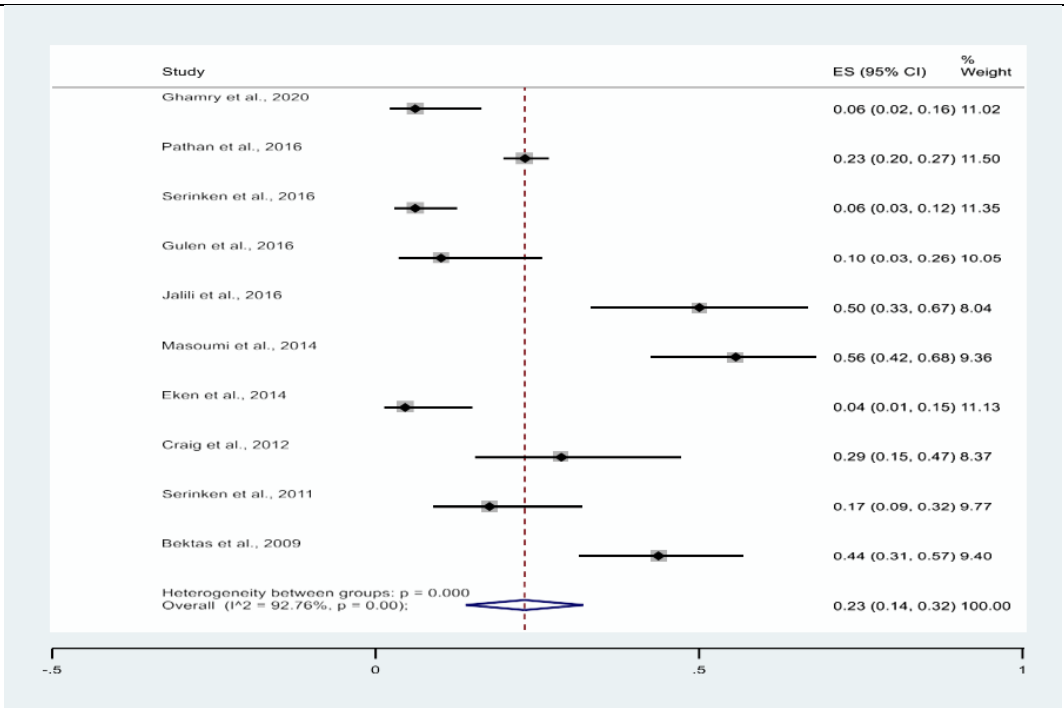
Forest plot of risk ratio of adverse events paracetamol compared to Placebo



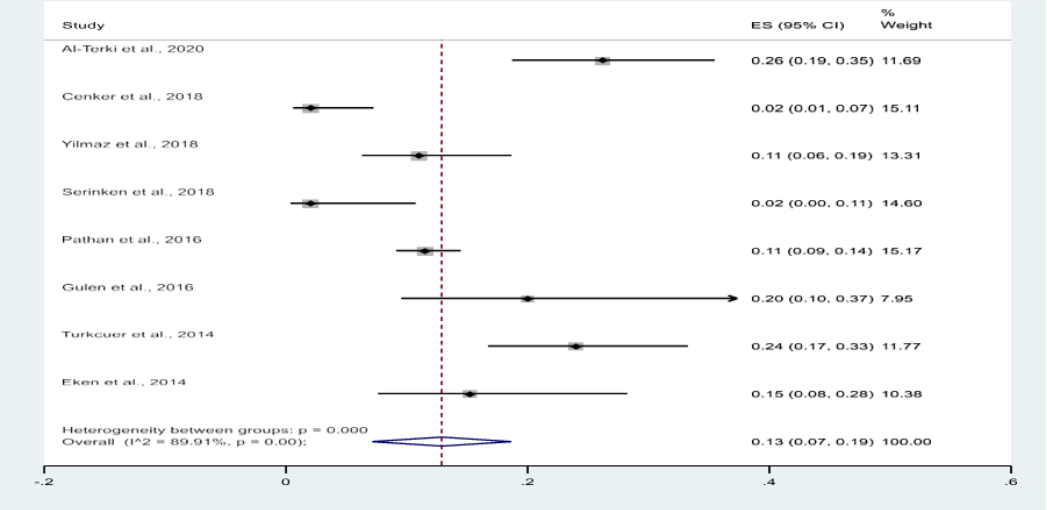
Forest plot of proportion of rescue analgesia in paracetamol group at time 30 minutes



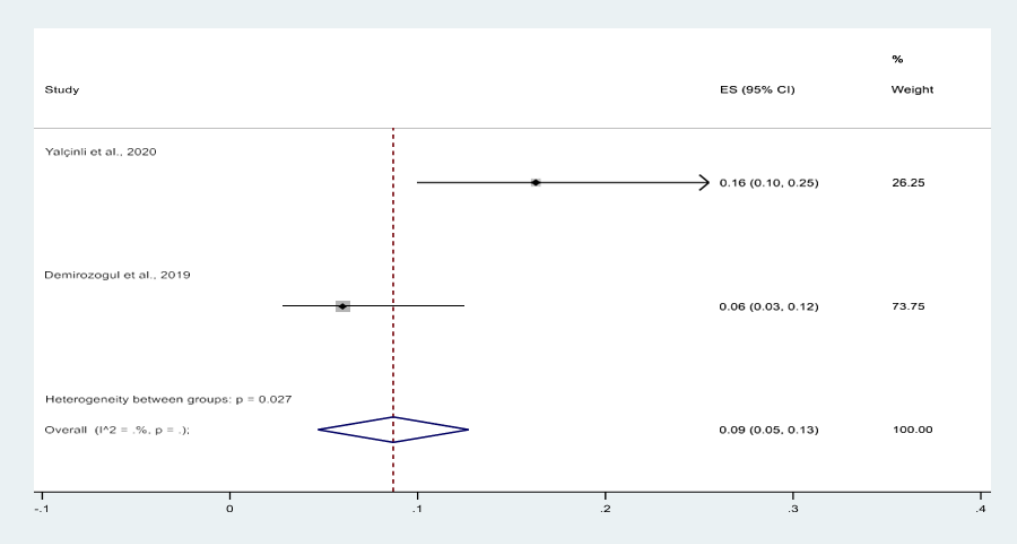
forest plot of proportion of rescue analgesia among paracetamol group at time 60 minutes



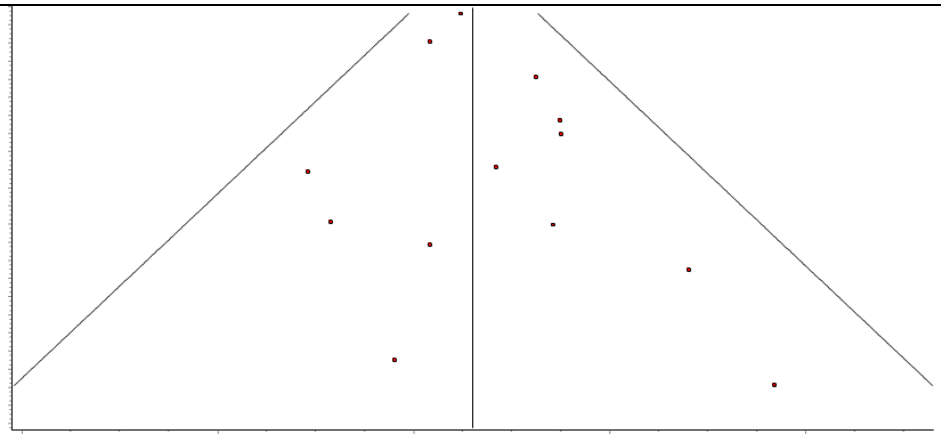
Forest plot of proportion of rescue analgesia among opioids group at time 30 minutes



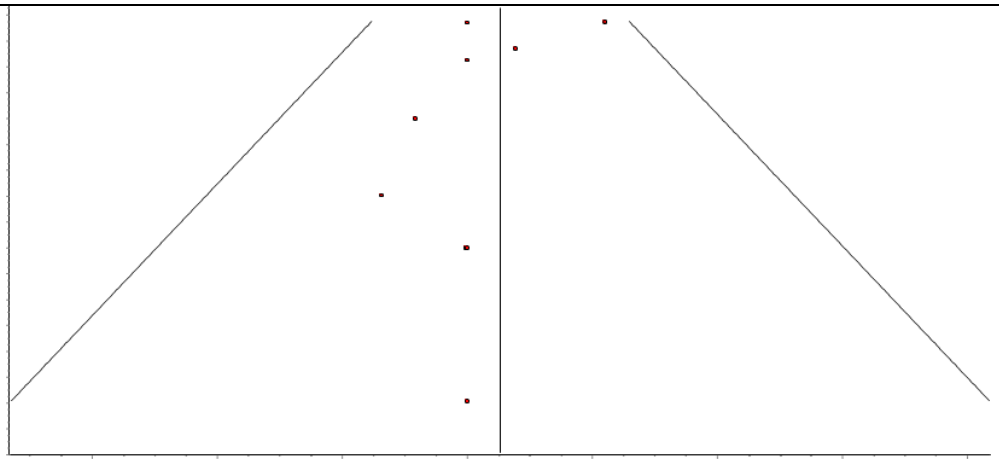
Forest plot of proportion of rescue analgesia in NSAIDs group at time 30 minutes.



Forest plot of proportion of rescue analgesia in NSAIDs group at time 60 minutes.



Funnel plot of Risk ratio of adverse events paracetamol compared to opioids



Funnel plot of Risk ratio of adverse events paracetamol compared to NSAIDs