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Comparison of different nonsteroidal anti-inflammatory drugs for cesarean section: a systematic review and network meta-analysis

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Background: Cesarean section is associated with moderate to severe pain and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed. The optimal NSAID, however, has not been elucidated. In this network meta-analysis and systematic review, we compared the influence of control and individual NSAIDs on the indices of analgesia, side effects, and quality of recovery.

Methods: CDSR, CINAHL, CRCT, Embase, LILACS, PubMed, and Web of Science were searched for randomized controlled trials comparing a specific NSAID to either control or another NSAID in elective or emergency cesarean section under general or neuraxial anesthesia. Network plots and league tables were constructed, and the quality of evidence was evaluated with Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis.

Results: We included 47 trials. Cumulative intravenous morphine equivalent consumption at 24 h, the primary outcome, was examined in 1,228 patients and 18 trials, and control was found to be inferior to diclofenac, indomethacin, ketorolac, and tenoxicam (very low quality evidence owing to serious limitations, imprecision, and publication bias). Indomethacin was superior to celecoxib for pain score at rest at 8–12 h and celecoxib + parecoxib, diclofenac, and ketorolac for pain score on movement at 48 h. In regard to the need for and time to rescue analgesia COX-2 inhibitors such as celecoxib were inferior to other NSAIDs.

Conclusions: Our review suggests the presence of minimal differences among the NSAIDs studied. Nonselective NSAIDs may be more effective than selective NSAIDs, and some NSAIDs such as indomethacin might be preferable to other NSAIDs.

Keywords: Analgesia; Cesarean section; Non-steroidal anti-inflammatory agents; Obstetrical anesthesia; Postoperative pain; Systematic review.

Introduction

Cesarean section is one of the most common operations performed worldwide. It is, however, associated with moderate to severe pain in almost four fifths of women [1] and, when compared to many other surgical procedures, it has been reported to be the ninth most painful operation on the first postoperative day [2]. Pain during and following ce-

sarean section has been demonstrated to be of greatest concern to women [3], and inadequate pain relief has been related to negative effects on breastfeeding and infant care [1], maternal dissatisfaction [4], postpartum depression [5], and chronic pain [5,6].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used as part of a multimodal strategy in the perioperative period, and provide analgesia by the inhibition of cyclooxygenase enzymes that are involved in the formation of hyperalgesic prostaglandins [7]. In a meta-analysis that compared control to NSAIDs, NSAIDs decreased the pain score at rest at 12 h and 24 h and on movement at 24 h, lowered opioid consumption, and reduced the risk of sedation, the latter a recognized side effect of opioids [8]. Given this, the procedure specific postoperative pain management (PROSPECT) recommendations for elective cesarean section include the intraoperative use of intravenous NSAIDs and postoperative use of oral or intravenous NSAIDs [9]. It is still not clear, however, which NSAID is most effective in the setting of cesarean section. Different NSAIDs may produce varying pain relief efficacy and have differing side effect profiles, and hence a comparative analysis of NSAIDs is important. Several randomized trials investigating NSAIDs have been published recently [10,11], and a contemporary review would update the available evidence for the use of NSAIDs in cesarean section.

Our aim in this network meta-analysis and systematic review was to compare the influence of control and individual NSAIDs such as diclofenac and ibuprofen on the indices of analgesia, side effects, and quality of recovery. We hypothesized that we would establish the overall efficacy of NSAIDs in cesarean section, and potentially uncover differences among the NSAIDs studied.

Materials and Methods

We prospectively registered the protocol for the systematic review and network meta-analysis with PROSPERO (CRD42021264209), and our findings have been presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. The following databases, CDSR, CINAHL, CRCT, Embase, LILACS, PubMed, and Web of Science, were searched from inception to May 27, 2021, for free text keywords and subject headings associated with different permutations of terms related to cesarean section, obstetric analgesia, NSAIDs in general, and specific NSAID drug names (Supplementary Material 1).

Once duplicate citations were discarded, two authors (IM and ND) independently screened the titles and abstracts of the remaining citations against the inclusion and exclusion criteria in Rayyan (Qatar Computing Research Institute, 2016, Doha, Qatar) [13]. Inclusion criteria were defined as randomized controlled trials that compared a specific NSAID to either control or another NSAID in the context of elective or emergency cesarean section under general or neuraxial anesthesia. The timing of NSAID administration could be preoperative, intraoperative, and/or postoperative, and trials that investigated more than one NSAID, either combined or in more than one arm, were included. Exclusion criteria included trials in which regional anesthesia or wound catheters were utilized postoperatively. Trials that included intraoperative local anesthetic infiltration and single-shot transversus abdominis plane block, for example, were included, but those that used postoperative infusions of local anesthetic through catheters into the epidural space, transverse abdominis plane, or wound were excluded. No limits were placed on the language of publication. Cases of disagreement were resolved by a third author (BC). If a trial was thought to be eligible for inclusion, then we carried out a full text review to confirm this. In order to seek further trials not identified by our search strategy, one author (AC) searched the reference lists of included trials and previously published systematic reviews.

Data extraction was conducted and checked by five authors (IM, AC, PS, JO, and ND). The following characteristics of trials were extracted: number of patients in each group; nature of cesarean section; mode of anesthesia; intraoperative regional anesthesia and systemic analgesia; dose, route, and timing of NSAID administration; regular postoperative analgesia; and management of postoperative breakthrough pain. The primary outcome was the cumulative intravenous morphine equivalent consumption at 24 h, and the MCID was prespecified at 10 mg. It is the opinion of the authors that this outcome is particularly important as it provides a measure of pain and need for rescue analgesia on the first postoperative day, and increased opioid consumption has been associated with side effects such as nausea and vomiting, urinary retention, constipation, and sleep disturbance that can lead to distress and interfere with postoperative recovery [14]. In a systematic review, the clinician perceived the MCID estimate for this primary outcome in the setting of total hip and knee arthroplasty was 10 mg and, in the absence of evidence-based and patient-rated MCIDs, we concurred with this [15]. Secondary outcomes included: pain score at rest and on movement at 8–12 h, 24 h, and 48 h; need for rescue analgesia and time to first analgesic request; cumulative intravenous morphine consumption at 8–12 h, 48 h, and in-hospital; incidence of postoperative nausea and/or vomiting, pruritus, and sedation at 24 h, 48 h, and in-hospital; quality of recovery-15 (QoR-15) [16] at 24 h and 48 h; and hospital length of stay. No other secondary outcomes were considered. We extracted dichotomous data as numbers and continuous data as

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means and standard deviations. If data were presented as medians, these were assumed to be equal to the means, and the standard deviations were calculated by dividing the interquartile range by 1.35 or the range by 4 as per guidance from the Cochrane Collaboration [17]. In cases where data were presented only in graphical format, PlotDigitizer™ (Version 2.1, Free Software Foundation, USA) was utilized in order to facilitate numerical extraction. Opioid conversion was performed with reference to the British National Formulary [18] and Faculty of Pain Medicine [19]. Where the data were not published or unclear, the authors were emailed up to three times for clarification.

Subsequent to data extraction, the data were transferred from Microsoft Excel® (Microsoft, USA) into Stata (Version 16.1, StataCorp LLC, USA) by one author (ND) and then checked by a second author (IM). We conducted this network meta-analysis with a frequentist method on any outcome of interest if three or more competing interventions could be connected into a network through direct comparisons between the trials [20,21]. Network plots were produced for all outcomes subjected to network meta-analysis with a common heterogeneity parameter and multivariate methods. In these network plots, the nodes depicted the interventions and the connecting lines represented the direct comparisons between the interventions. If interventions were not directly compared within trials, indirect comparisons via a common comparator were mathematically derived using results from the various direct intervention effects. Consistency was locally and globally assessed between direct and indirect estimates by the Separating Indirect from Direct Evidence technique and with the design-by-treatment interaction test, respectively. The results of comparisons between the different interventions were presented in network league tables as mean differences and 95% CIs for continuous outcomes and odds ratios and 95% CIs for dichotomous outcomes. If serious imprecision was not present for a particular outcome, competing interventions were ranked in order. We performed pairwise meta-analysis in Review Manager® (Version 5.3, The Nordic Cochrane Centre, Denmark) for those outcomes that were not analyzable by network meta-analysis but were reported by two or more randomized controlled trials. Heterogeneity was calculated with predetermined thresholds for low (25%–49%), moderate (50%–74%), and high (≥ 75%) levels [22], and the fixed and random effects model used for low and moderate or high heterogeneity, respectively. Tests were two-tailed and statistical significance was represented at the 5% level. The results were presented as mean differences and 95% CIs for continuous outcomes and risk ratios and 95% CIs for dichotomous outcomes.

The quality of evidence for every outcome was evaluated by two authors (IM and ND) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [23] and with the CINeMA software® (Institute of Social and Preventative Medicine, University of Bern, Switzerland). Fundamental components of quality include: risk of bias, indirectness, imprecision, inconsistency, and publication bias. Risk of bias was determined by two authors (JO and DO) using the Cochrane Risk of Bias 2 (RoB 2) tool [24] to examine the following: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Cases of disagreements were resolved by a third author (ND). Publication bias was examined with a comparison-adjusted funnel plot and the Egger's linear regression test.

Results

In all, we included 47 trials in this review [10,11,25–69] and details of the screening process are illustrated in Fig. 1. The following interventions were compared: control vs. celecoxib in two trials [35,46]; control vs. celecoxib + parecoxib in one trial [57]; control vs. diclofenac in 24 trials [11,25–34,36–43,65–69]; control vs. diclofenac vs. indomethacin in one trial [44]; control vs. diclofenac vs. ketoprofen in one trial [45]; control vs. ibuprofen vs. ketorolac in one trial [47]; control vs. indomethacin in one trial [48]; control vs. ketorolac in six trials [10,49–53]; control vs. naproxen in one trial [54]; control vs. parecoxib in one trial [55]; control vs. tenoxicam in six trials [56,58–62]; diclofenac vs. ketoprofen in one trial [63]; and ketorolac vs. parecoxib in one trial [64]. The findings of the risk of bias assessment are presented in Fig. 2. Overall, only four trials were deemed to be at low risk of bias [10,54,55,68], and 30 and 13 of the remaining trials were evaluated to have some concerns [25,27–35,37,38,43–45,47,49,52,53,57–67] or be at high risk of bias [11,26,36,39–42,46,48,50,51,56,69], respectively. Many of the concerns were related to the randomization process, measurement of the outcome, and the selection of the reported result. Of the 21 authors we emailed to clarify on methodology or results, nine responded with the requested information [38,42,43,50,53,55,61,62,65].

Characteristics of the trials are presented in Table 1. In regard to the nature of the cesarean section, it was elective, elective or emergent, and not specified in 30 [10,26,29,31–35,37,38,45,48–51,53–58,60–62,64–69], six [11,30,40–43], and 11 [25,27,28,36,39,44,46,47,52,59,63] trials, respectively. The mode of anesthesia was spinal, combined spinal-epidural (CSE), epidural, or general anesthesia in 27 [10,11,29,32–35,37–39,41–44,46,48,50,54–56,60–64,68,69], two [51,57], three [49,66,67], and 11 [25–28,30,31,47,53,58,59,65] trials, respectively. Of the remaining trials, one performed spinal or epidural anesthesia [45], two used neuraxial or

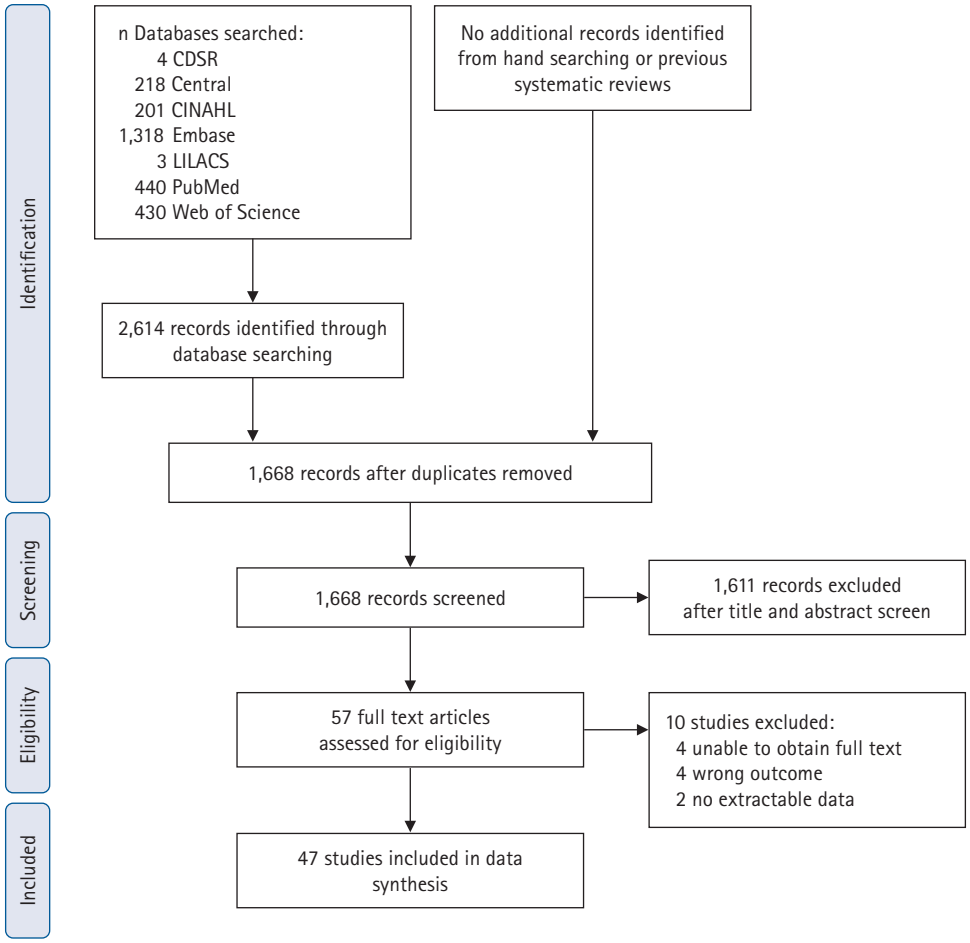

Fig. 1. PRISMA flow diagram summarizing the retrieved, included, and excluded randomized controlled trials. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

general anesthesia [40,52], and one did not specify the type of anesthesia [36]. Single-shot transversus abdominis plane block was utilized in one trial [11]. In addition to NSAIDs, women received propacetamol or paracetamol in four trials [32,33,37,57]. The route of administration of NSAIDs was as follows: oral in two trials [35,46]; intramuscular in 13 trials [25,27,28,31,34,36,38,40,43,49,65–67]; intravenous in 16 trials [10,11,39,45,50–53,55,56,58–62,64]; rectal in 11 trials [26,29,30,32,33,41,42,44,48,68,69]; oral or intramuscular in one trial [47]; intravenous and oral in one trial [57]; intramuscular or intravenous in one trial [63]; and rectal and oral in two trials [37,54]. In 21 trials, just one dose of NSAIDs was administered [10,11,26,35,36,39,46,49,55,56,58–63,65–69] and in further 21 trials, more than one dose or an infusion of NSAIDs was given [25,29–33,37,38,40,42–45,48,50–54,57,64]. Some trials provided NSAIDs only when the pain was reported to be at least moderate in intensity [34,41], or the pain score was greater than or equal to seven on a scale of zero to 10 [27,28] or higher than or equal to 60 on a scale of zero to 100 [47].

Our primary outcome, the cumulative intravenous morphine equivalent consumption at 24 h, was evaluated in 1,228 patients and 18 trials [27–29,32–34,37,39,44–46,50,52,55,58,61,62,64]. In the network plot, nine direct and 12 indirect comparisons were established between seven interventions (Fig. 3). With an MCID of 10 mg, control was clinically and statistically inferior to diclofenac, indomethacin, ketorolac, and tenoxicam (Table 2). No other statistical differences were demonstrated between the various NSAIDs. Evidence for local or global inconsistency was not found and the standard deviation of between-trials heterogeneity was 11.08. Inspection of the comparison-adjusted funnel plot (Supplementary Fig. 1) and the results of Egger's test (P = 0.011) revealed the presence of publication bias. The quality of evidence was graded as very low (Supplementary Material 2), and the network ranking of interventions was not performed in view of the serious imprecision (Supplementary Material 3).

Details of the results of the secondary outcomes are presented

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Fig. 2. Risk of bias assessment of included trials using the revised Cochrane tool.

in Table 3 and Supplementary Material 3, and information related to their network plots, inconsistency plots, contribution plots, predictive interval plots, and comparison-adjusted funnel plots is provided in Supplementary Material 4. Differences between NSAIDs were shown for some of these outcomes. For the pain score at rest at 8–12 h, indomethacin was clinically and statistically superior to celecoxib, and for the pain score on movement at 48 h, indomethacin was clinically and statistically superior to celecoxib + parecoxib, diclofenac, and ketorolac. In regard to the need for rescue analgesia, ketoprofen was clinically and statistically superior to celecoxib + parecoxib, and with respect to the time for rescue analgesia, diclofenac, ibuprofen, indomethacin, and ketorolac were clinically and statistically superior to celecoxib. In terms of side effects, ketoprofen was clinically and statistically su-

Table 1. Characteristics of the Included Trials

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs celecoxib										
Lee et al. 2004 [35]	Control (30) Celecoxib (30)	Anaesthesia	English	Hong Kong	Elective; Pfannensteil approach	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine with morphine 300 μg	P.O. celecoxib 200 mg, once only, following delivery of neonate	Not specified	P.O. paracetamol and dextropropoxyphene
Fong et al. 2008 [46]	Control (20) Celecoxib (40)	British Journal of Anaesthesia	English	Taiwan, Republic of China	Not specified	Spinal	Not specified	P.O. celecoxib 400 mg, once only, either 30 min before spinal anesthesia or following surgical wound closure	I.V. morphine PCA	Not specified
Control vs celecoxib and parecoxib										
Paech et al. 2014 [57]	Control (55) Celecoxib and parecoxib (56)	Anaesthesia and Intensive Care	English	Australia	Elective; Pfannensteil approach	CSE	CSE: 2.1–2.5 0.5% hyperbaric bupivacaine with fentanyl 15 μg Systemic: I.V. paracetamol 2 g in only some groups	I.V. parecoxib 40 mg following delivery of neonate and P.O. celecoxib 400 mg at 12 h	P.O. paracetamol 1 g at 6, 12, and 18 h in only some groups. Patient-controlled epidural analgesia with bolus of pethidine 20 mg and lockout interval of 15 min	P.O. tramadol
Control vs diclofenac										
Bush et al. 1992 [65]	Control (25) Diclofenac (23)	Anaesthesia	English	United Kingdom	Elective; Pfannensteil approach	General anesthesia	Systemic: I.V. papaveretum 0.3 mg/kg	I.M. diclofenac 75 mg, once only, prior to discontinuation of general anesthesia	I.V. papaveretum PCA	Opioid, otherwise not specified
Sun et al. 1992 [66]	Control (58) Diclofenac (59)	Anesthesia and Analgesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 2 mg in only some groups subsequent to delivery of placenta	I.M. diclofenac 75 mg, once only, on arrival to recovery	Not specified	I.M. pethidine
Sun et al. 1993 [67]	Control (20) Diclofenac (20)	Anesthesia and Analgesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 4 mg subsequent to delivery of placenta	I.M. diclofenac 75 mg, once only, on arrival to recovery	Not specified	I.M. pethidine
Luthman et al. 1994 [68]	Control (23) Diclofenac (27)	International Journal of Obstetric Anesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.75 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 100 mg, once only, at the end of surgery	I.V. morphine PCA	Not specified

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Dennis et al. 1995 [69]	Control (25) Diclofenac (25)	Anaesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	P.R. diclofenac 100 mg, once only, at the end of surgery	Not specified	P.O. paracetamol and dextropropoxyphene, and I.M. or I.V. morphine
Lee et al. 1997 [25]	Control (90) Diclofenac (90)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain and further doses every 12 h	I.V. pethidine or morphine PCA depending on group allocation	Not specified
Sia et al. 1997 [26]	Control (30) Diclofenac (30)	Singapore Medical Journal	English	Singapore	Elective; surgical approach not specified	General anesthesia	Systemic: I.V. morphine 10 mg	P.R. diclofenac 100 mg, once only, following induction of general anesthesia and prior to surgical incision	I.V. morphine at a rate of 1.5 mg/h	I.M. pethidine
Kim et al. 1999 [27]	Control (40) Diclofenac (40)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain equal to or greater than 7 out of 10 and further doses every 12 h	I.V. pethidine or morphine PCA	Not specified
Lee et al. 1999 [28]	Control (30) Diclofenac (30)	Korean Journal of Obstetrics and Gynecology	Korean	Korea	Not specified	General anesthesia	None	I.M. diclofenac 75 mg following incidence of postoperative pain equal to or greater than 7 out of 10 and further doses every 12 h	I.V. pethidine PCA	Not specified
Olofsson et al. 2000 [29]	Control (25) Diclofenac (25)	European Journal of Obstetrics Gynecology and Reproductive Biology	English	Sweden	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 50 mg at the end of surgery and two further doses in the first 24 h	I.V. ketobemidone PCA	I.V. ketobemidone
Rashid et al. 2000 [30]	Control (20) Diclofenac (20)	Saudi Medical Journal	English	Saudi Arabia	Elective or emergent; surgical approach not specified	General anesthesia	Not specified	P.R. diclofenac 100 mg at the end of surgery, 50 mg at 12 h, and 100 mg at 36 h	Not specified	I.M. pethidine
Al-Waili et al. 2001 [31]	Control (60) Diclofenac (60)	Archives of Medical Research	English	United Arab Emirates	Elective Surgical approach not specified	General anesthesia	Not specified	I.M. diclofenac 75 mg following incidence of postoperative pain and up to every 12 h thereafter	Not specified	I.M. pethidine

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Siddik et al. 2001 [32]	Control (40) Diclofenac (39)	Regional Anesthesia and Pain Medicine	English	Lebanon	Elective; surgical approach not specified	Spinal	Spinal: 1.6 ml 0.75% hyperbaric bupivacaine with fentanyl 12.5 μg. Systemic: I.V. propacetamol in only some groups	P.R. diclofenac 100 mg at the time of skin closure and further doses every 8 h in the first 24 h	I.V. propacetamol 2 g every 8 h in the first 24 h in only some groups. I.V. morphine PCA	I.V. morphine
Dahl et al. 2002 [33]	Control (42) Diclofenac (40)	International Journal of Obstetric Anesthesia	English	Norway	Elective; surgical approach not specified	Spinal	Spinal: 2.2–2.4 ml 0.5% hyperbaric bupivacaine	P.R. diclofenac 100 mg on arrival to recovery, 12 h, and 24 h	P.O. paracetamol 1 g every 6 h	I.V. morphine
Wilder-Smith et al. 2003 [34]	Control (60) Diclofenac (60)	Anesthesia and Analgesia	English	South Africa	Elective; surgical approach not specified	Spinal	Spinal: 1.8–2 ml 0.5% hyperbaric bupivacaine	I.M. diclofenac 75 mg following regression of sensory blockade to T10 and pain severity reported to be moderate	I.M. tramadol 100 mg as stat only in only some groups	I.V. morphine
Bourlert et al. 2005 [36]	Control (30) Diclofenac (34)	Journal of the Medical Association of Thailand	English	Thailand	Not specified if elective or emergent; Pfannensteil approach	Not specified	Not specified	I.M. diclofenac 75 mg, once only, postoperatively	I.M. morphine 10 mg as stat dose. I.V. morphine PCA	Not specified
Munishankar et al. 2008 [37]	Control (24) Diclofenac (25)	Anaesthesia	English	United Kingdom	Elective; surgical approach not specified	Spinal	Spinal: 2.25–2.5 ml 0.5% hyperbaric bupivacaine with fentanyl 12.5 μg	P.R. diclofenac 100 mg at the end of surgery followed by P.O. diclofenac 50 mg every 8 h	P.R. paracetamol 1 g. P.O. paracetamol 1 g every 6 h. I.V. morphine PCA	I.V. morphine
Surakarn et al. 2009 [38]	Control (40) Diclofenac (40)	Journal of the Medical Association of Thailand	English	Thailand	Elective; low midline approach	Spinal	Spinal: hyperbaric bupivacaine 10–12 mg with morphine 200 μg	I.M. diclofenac 75 mg within 2 h of the end of surgery and at 12 h	Not specified	I.M. tramadol
Thiengthong et al. 2012 [39]	Control (15) Diclofenac (14)	Acta Anaesthesiologica Taiwanica	English	Thailand	Not specified if elective or emergent; Pfannensteil approach	Spinal	Spinal: 2.2–2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	I.V. diclofenac 75 mg, once only, at 12 h	None	I.V. tramadol
Adamou et al. 2014 [40]	Control (80) Diclofenac (80)	Nigerian Medical Journal	English	Nigeria	Elective or emergent; surgical approach not specified	Neuraxial or general anesthesia	Determined by anesthesiologist	I.M. diclofenac 1 mg/kg following the end of surgery and every 12 h for 48 h	I.M. pentazocine 1 mg/kg every 6 h for 48 h	Not specified
Lotfalizade et al. 2015 [41]	Control (33) Diclofenac (33)	Iranian Journal of Obstetrics, Gynecology and Infertility	Persian	Iran	Elective or emergent; surgical approach not specified	Spinal	Spinal: 2.4 ml 0.5% hyperbaric bupivacaine with adrenaline 200 μg and fentanyl 20 μg	P.R. diclofenac 100 mg of unspecified frequency following pain severity reported to be moderate	Tramadol 100 mg of unspecified route	Not specified

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Olateju et al. 2016 [42]	Control (52) Diclofenac (64)	Middle East Journal of Anesthesiology	English	Nigeria	Elective or emergent; low midline or Pfannensteil	Spinal	Spinal: 0.5% hyperbaric bupivacaine of unspecified volume	P.R. diclofenac 100 mg at the end of surgery, 12 h, and 24 h	I.M. pentazocine 30 mg every 6 h for 24 h	I.M. tramadol
Egede et al. 2017 [43]	Control (70) Diclofenac (70)	Journal of Clinical and Diagnostic Research	English	Nigeria	Elective or emergent; Pfannensteil approach	Spinal	Not specified	I.M. diclofenac 75 mg within 1 h of the end of surgery and every 12 h for 24 h	I.M. pentazocine 30 mg every 4 h for 24 h	I.M. pentazocine
Kanta et al. 2021 [11]	Control (30) Diclofenac (30)	Indian Journal of Anaesthesia	English	India	Elective or emergent; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% hyperbaric bupivacaine with morphine 200 μg. TAP block: 1.5 mg/kg 0.75% ropivacaine on each side	I.V. diclofenac 75 mg following delivery of neonate	Not specified	I.M. diclofenac
Control vs diclofenac vs indomethacin										
Akhavanakbari et al. 2013 [44]	Control (30) Diclofenac (30) Indomethacin (30)	Perspectives in Clinical Research	English	Iran	Not specified if elective or emergent; surgical approach not specified	Spinal	Spinal: 1.5–2 ml hyperbaric 5% lidocaine	P.R. diclofenac 50 mg or indomethacin 50 mg at the end of surgery and every 6 h for 24 h	Not specified	I.M. pethidine
Control vs diclofenac vs ketoprofen										
Rorarius et al. 1993 [45]	Control (30) Diclofenac (29) Ketoprofen (30)	British Journal of Anaesthesia	English	Finland	Elective; surgical approach not specified	Spinal or epidural	Spinal: 2.5–2.8 ml 0.5% hyperbaric bupivacaine. Epidural: Up to 20 ml 0.5% bupivacaine with or without 1% prilocaine if needed	I.V. diclofenac 150 mg or ketorolac 200 mg started at the end of surgery as an infusion over 24 h	Not specified	I.M. oxycodone
Control vs ibuprofen vs ketorolac										
Pagnoni et al. 1996 [47]	Control (32) Ibuprofen (30) Ketorolac (30)	Clinical Drug Investigation	English	Italy	Not specified	General anesthesia	Systemic: I.V. fentanyl 0.1 μg/kg	I.M. ketorolac 30 mg or P.O. ibuprofen, once only, following incidence of postoperative pain equal to or greater than 60 out of 100	Not specified	I.M. ketoprofen
Control vs indomethacin										
Pavy et al. 1995 [48]	Control (15) Indomethacin (15)	Anaesthesia and Intensive Care	English	Australia	Elective; Pfannensteil approach	Spinal	Spinal: 1.2–1.4 ml 0.75% hyperbaric bupivacaine with fentanyl 10–15 μg and morphine 250–300 μg	P.R. indomethacin 200 mg at the end of surgery followed by P.R. indomethacin 100 mg every 12 h for 72 h	None	P.O. paracetamol and codeine, and parenteral opioids

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs ketorolac										
Tzeng et al. 1994 [49]	Control (30) Ketorolac (30)	Annals of the Academy of Medicine, Singapore	English	Taiwan, Republic of China	Elective; surgical approach not specified	Epidural	Epidural: 2% lidocaine with adrenaline 5 μg/ml of unspecified volume, followed by morphine 2 mg postoperatively	I.M. ketorolac 30 mg, once only, following incidence of postoperative pain	Not specified	I.M. pethidine
Cohen et al. 1996 [50]	Control (12) Ketorolac (13)	International Journal of Obstetric Anesthesia	English	United States of America	Elective; Pfannensteil approach	Spinal	Spinal: 1.6 ml 0.75% hyperbaric bupivacaine and morphine 100 μg Systemic: I.V. fentanyl 50–100 μg if needed	I.V. ketorolac 60 mg 1 h after spinal anesthesia followed by I.V. ketorolac 30 mg every 6 h for three doses	Not specified	I.V. pethidine
Pavy et al. 2001 [51]	Control (20) Ketorolac (24)	Anesthesia and Analgesia	English	Australia	Elective; surgical approach not specified	CSE	CSE: 2–2.5 0.5% hyperbaric bupivacaine with fentanyl 12.5 μg	I.V. ketorolac 15–30 mg after delivery of neonate followed by I.V. ketorolac 105–120 mg started in recovery as an infusion over 24 h	Patient-controlled epidural analgesia with bolus of pethidine 24 mg and lockout interval of 15 min	P.O. paracetamol and codeine
Lowder et al. 2003 [52]	Control (22) Ketorolac (22)	American Journal of Obstetrics and Gynecology	English	United States of America	Not specified if elective or emergent; Pfannensteil approach	Neuraxial or general anesthesia	Determined by anesthesiologist	I.V. ketorolac 30 mg at the end of surgery and two further doses at unspecified time interval	I.V. hydromorphone, pethidine, or morphine PCA	Not specified
El-Tahan et al. 2007 [53]	Control (45) Ketorolac (45)	International Journal of Obstetric Anesthesia	English	Egypt	Elective; Pfannensteil approach	General anesthesia	Systemic: I.V. fentanyl 1 μg/kg	I.V. ketorolac 15 mg before induction of general anesthesia followed by I.V. ketorolac as an infusion of 7.5 mg/hr until the end of surgery	None	I.V. tramadol
Khezri et al. 2018 [10]	Control (50) Ketorolac (50)	Caspian Journal of Internal Medicine	English	Iran	Elective; surgical approach not specified	Spinal	Spinal: 2.5 ml 0.5% bupivacaine of unspecified baricity	I.V. ketorolac 30 mg, once only, before spinal anesthesia	Not specified	I.V. paracetamol
Control vs naproxen										
Angle et al. 2002 [54]	Control (40) Naproxen (40)	Anesthesia and Analgesia	English	Canada	Elective Pfannensteil approach	Spinal	Spinal: 1.2–1.8 ml 0.75% hyperbaric bupivacaine with fentanyl 10–20 μg and morphine 200 μg	P.R. naproxen 500 mg 1 h at the end of surgery followed by P.O. naproxen 550 mg every 12 h for 72 h	Not specified	P.O. paracetamol and codeine, and I.M. pethidine or morphine
Control vs parecoxib										
Inthigood et al. 2017 [55]	Control (41) Parecoxib (41)	Journal of Obstetrics and Gynaecology Research	English	Thailand	Elective; low midline or Pfannensteil approach	Spinal	Spinal: 2 ml 0.5% hyperbaric bupivacaine with morphine 200 μg	I.V. parecoxib 40 mg, once only, 2 h following the end of surgery	Not specified	I.V. pethidine

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Table 1. Continued

Reference	Group (n)	Journal title	Language	Country of the enrolled patients	Nature of cesarean section	Mode of anesthesia	Intraoperative regional anesthesia and systemic analgesia	Dose, route, and timing of NSAID administration	Regular postoperative analgesia	Management of postoperative breakthrough pain
Control vs tenoxicam										
Belzarena 1994 [56]	Control (40) Tenoxicam (40)	Regional Anesthesia	English	Brazil	Elective; surgical approach not specified	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine	I.V. tenoxicam 20 mg, once only, before spinal anesthesia	Not specified	Paracetamol and codeine of unspecified route
Elhakim and Nafie 1995 [58]	Control (25) Tenoxicam (25)	British Journal of Anaesthesia	English	Egypt	Elective; surgical approach not specified	General anesthesia	Systemic: I.V. nalbuphine 0.25 mg/kg	I.V. tenoxicam 20 mg, once only, before induction of general anesthesia	None	I.M. nalbuphine
Ro et al. 1997 [59]	Control (20) Tenoxicam (20)	Korean Journal of Anesthesiology	Korean	Korea	Not specified	General anesthesia	None	I.V. tenoxicam 0.3 mg/kg, once only, before induction of general anesthesia	I.V. morphine 0.1 mg/kg bolus followed by infusion of 0.015 mg/kg/h	Not specified
Huang et al. 2002 [60]	Control (59) Tenoxicam (58)	Canadian Journal of Anaesthesia	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Spinal: 1.8–2.2 ml 0.5% hyperbaric bupivacaine with morphine 150 μg	I.V. tenoxicam 40 mg, once only, following clamping of umbilical cord	Not specified	I.M. pethidine
Hsu et al. 2003 [61]	Control (48) Tenoxicam (45)	Clinical Journal of Pain	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Spinal: 12.5 mg bupivacaine of unspecified baricity, concentration, and volume	I.V. tenoxicam 20 mg, once only, following clamping of umbilical cord	I.V. morphine PCA	Not specified
Yeh et al. 2005 [62]	Control (40) Tenoxicam (40)	Journal of the Formosan Medical Association	English	Taiwan, Republic of China	Elective; Pfannensteil approach	Spinal	Spinal: 1.8–2.2 ml 0.5% hyperbaric bupivacaine	I.V. tenoxicam 20 mg, once only, following clamping of umbilical cord	I.V. morphine PCA	Not specified
Diclofenac vs ketoprofen										
Hirahara et al. 2003 [63]	Diclofenac (22) Ketoprofen (22)	Revista Brasileira de Anestesiologia	English	Brazil	Not specified	Spinal	Spinal: 3 ml 0.5% hyperbaric bupivacaine with morphine 28 μg	I.M. diclofenac 75 mg or I.V. ketorolac 100 mg, once only, 90 min after spinal anesthesia	I.V. morphine PCA	Not specified
Ketorolac vs parecoxib										
Wong et al. 2010 [64]	Ketorolac (33) Parecoxib (33)	Acta Anaesthesiologica Taiwanica	English	Taiwan, Republic of China	Elective; surgical approach not specified	Spinal	Not specified	I.V. parecoxib 40 mg in recovery room and two further doses at 24 h and 48 h, or I.V. ketorolac 30 mg in recovery room followed by I.V. ketorolac in morphine PCA, administered at a rate of 0.36 mg/h and patient-controlled bolus of 1.8 mg with an unspecified time interval	I.V. morphine PCA	I.V. morphine

CSE: combined spinal-epidural, PCA: patient-controlled analgesia, PO: per oral, IV: intravenous, PR: per rectum, IM: intramuscular.

perior to celecoxib + parecoxib for the rate of in-hospital pruritus, and diclofenac was clinically and statistically superior to control for the rate of sedation at 24 h and in-hospital. The hospital length of stay was statistically but not clinically different between diclofenac and control.

Discussion

Our systematic review and network meta-analysis demonstrated that, compared to control, the administration of diclofenac, indomethacin, ketorolac, or tenoxicam led to a clinically significant decrease in the primary outcome, namely cumulative morphine consumption at 24 h, using an MCID of 10 mg. The quality of evidence, however, was very low due to serious limitations, imprecision, and publication bias. Differences between various NSAIDs were found, with indomethacin clinically superior to celecoxib and celecoxib + parecoxib, diclofenac, and ketorolac for the pain score at rest at 8–12 h and the pain score on movement at 48 h, respectively, when an MCID of 10 on a pain scale of 0–100 was applied. Indomethacin may be preferable, although it must be recognized that the evidence for other NSAIDs continues to emerge and is currently limited by the presence of imprecision.

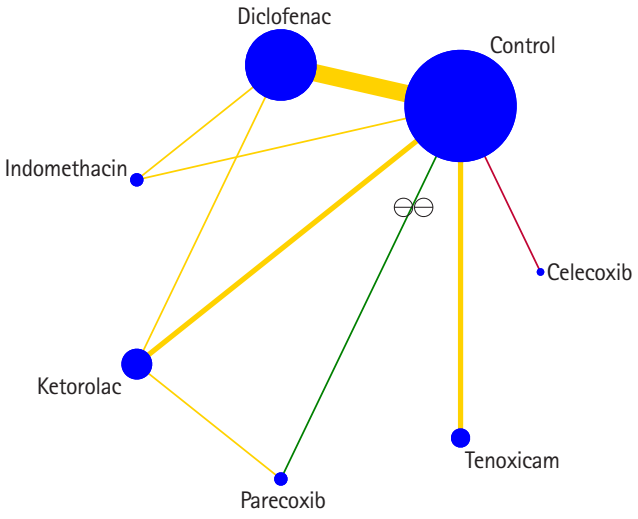

Fig. 3. Network plot in regard to the need for cumulative intravenous morphine equivalent consumption at 24 h. Each intervention is depicted by a circle that is proportional in size to the number of patients who were randomized to that intervention. Connecting lines between the circles indicate the direct comparisons of interventions, their width proportional to the number of trials evaluating the comparison, and their color representing the average risk of bias. Green: low risk, yellow: some concerns, red: high risk.

In contrast to diclofenac, indomethacin, ketorolac, and tenoxicam, control was not inferior to other NSAIDs such as celecoxib and parecoxib for the cumulative morphine consumption at 24 h. It is likely that this could be a reflection of the limited evidence base for these NSAIDs, resulting in imprecision and wide CIs, and the different dosing regimens employed in the included trials. In many trials that investigated diclofenac, indomethacin, and ketorolac, more than one dose of the NSAID was administered in 24 h [25,27–33,37,38,40,42–45,48,50–53]. Further, tenoxicam has a long mean elimination half-life of 67 h [70], explaining its beneficial effects on morphine consumption despite only being given once in the relevant trials [56,58–62]. Similarly, the various dosing strategies in the included trials may explain, at least in part, the superiority of ketoprofen to celecoxib + parecoxib in regard to the need for rescue analgesia and diclofenac, indomethacin, and ketorolac, but not ibuprofen, over celecoxib with respect to the time to rescue analgesia. Selective COX-2 inhibitors such as celecoxib have gained popularity as effective analgesics, particularly as they can produce fewer gastrointestinal side effects [71]. Their inferi-

Table 2. Network League Table for All the Interventions in regard to Cumulative Intravenous Morphine Equivalent Consumption at 24 h

Celecoxib						
−14.21 (−36.00, 7.58)	Control					
5.66 (−17.31, 28.64)	19.87 (12.56, 27.18)*	Diclofenac				
7.07 (−21.96, 36.10)	21.28 (2.09, 40.47)*	1.41 (−17.78, 20.59)	Indomethacin			
−1.68 (−26.32, 22.96)	12.53 (1.00, 24.05)*	−7.34 (−20.34, 5.65)	−8.75 (−30.94, 13.44)	Ketorolac		
−6.12 (−33.53, 21.30)	8.09 (−8.57, 24.75)	−11.78 (−29.74, 6.18)	−13.19 (−38.51, 12.14)	−4.44 (−21.26, 12.39)	Parecoxib	
0.46 (−24.86, 25.78)	14.67 (1.74, 27.59)*	-5.20 (−20.05, 9.64)	−6.61 (−29.75, 16.53)	2.14 (−15.18, 19.46)	6.57 (−14.51, 27.66)	Tenoxicam

Estimates are presented as mean differences with 95% CI in parentheses. Mean differences below 0 favor the column intervention and mean differences above 0 favor the row intervention. *Interventions which are significantly different since the 95% CI does not include 0.

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Table 3. Conclusion from the Results of the Analysis and GRADE Quality of Evidence Assessment for the Primary and Secondary Outcomes

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Analgesia								
Pain score at rest at 8–12 h (0–100) [11,23,25,26,34,35,37,42,43,45,47–49,57,59,61–63]	18	1,523	8	20	10	Control clinically and statistically inferior to diclofenac and indomethacin Indomethacin clinically and statistically superior to celecoxib No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 8–12 h (0–100) [11,25,30,42,47,52,57]	7	506	6	4	10	Control statistically inferior but clinically equivalent to diclofenac No statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score at rest at 24 h (0–100) [11,23,25,34,37,38,41–45,47–49,56,59,61–65,67]	22	1,790	9	19	10	Control clinically and statistically inferior to diclofenac Control statistically inferior but clinically equivalent to tenoxicam No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 24 h (0–100) [11,25,30,42,44,47,52,55,64]	9	582	5	10	10	Control clinically and statistically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score at rest at 48 h (0–100) [25,34,37,43,45,62]	6	571	3	3	10	No statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Pain score on movement at 48 h (0–100) [25,30,52,55]	4	235	4	6	10	Control clinically and statistically inferior to indomethacin No clinical or statistical difference between control and celecoxib + parecoxib Indomethacin clinically and statistically superior to celecoxib + parecoxib, diclofenac and ketorolac No other statistical differences between interventions, but, with MCID of 10, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

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Table 3. Continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Need for rescue analgesia (%) [23,25–28,32,37,40,43,47,51,53–55,57–60,63,66]	20	1,586	10	35	20%	Control statistically and clinically inferior to diclofenac, ketoprofen and tenoxicam Ketoprofen statistically and clinically superior to celecoxib + parecoxib No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision, and publication bias
Time to rescue analgesia (min) [10,11,24,30,40,46,49–52,54,55,57,58,60]	15	1,076	10	18	60 min	Control clinically and statistically inferior to diclofenac, ketorolac and naproxen Diclofenac, ibuprofen, indomethacin and ketorolac clinically and statistically superior to celecoxib No other statistical differences between interventions, but, with MCID of 60 min, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision, inconsistency, and publication bias
Cumulative intravenous morphine equivalent consumption at 8–12 h (mg) [26,33–35,39,55]	6	364	2	1	10 mg	Control clinically and statistically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Cumulative intravenous morphine equivalent consumption at 24 h (mg) [24,33–35,38–40,42,44,49,50,54,56,59,61,64,65,67]	18	1,228	9	12	10 mg	Control clinically and statistically inferior to diclofenac, indomethacin, ketorolac and tenoxicam No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Cumulative intravenous morphine equivalent consumption at 48 h (mg) [31,33,34]	3	320	-	-	10 mg	Pairwise comparison only Control clinically and statistically inferior to diclofenac (MD: -46.29, 95% CI [-60.71, -31.86], I^2 = 73%; P < 0.0001)	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Cumulative in-hospital intravenous morphine equivalent consumption (mg) [29,31,41,55,67]	5	404	3	3	10 mg	Control clinically and statistically inferior to diclofenac, ketorolac and parecoxib No other statistical differences between interventions, but, with MCID of 10 mg, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Side effects								
Rate of postoperative nausea and/or vomiting at 24 h (%) [10,29,36,39–41,44,48,53,55,61,64,67]	13	938	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision

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Table 3. Continued

Outcome	Number of trials	Total number of participants	Number of direct comparisons	Number of indirect comparisons	MCID	Conclusions	Quality of evidence	Comments
Rate of postoperative nausea and/or vomiting at 48 h (%) [52,55]	2	74	2	1	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Rate of in-hospital postoperative nausea and/or vomiting (%) [27,28,30–34,38,42,45,47,54,57,60,62,63,66]	17	1,387	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of pruritus at 24 h (%) [52,53,55,64,67]	5	293	4	6	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of pruritus at 48 h (%) [52,55]	2	74	2	1	20%	No statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Very low quality (⊕)	Downgraded for serious limitations, imprecision and publication bias
Rate of in-hospital pruritus (%) [23,25,27,28,30,31,34,36,38,54,60,62,63,66]	14	1,043	6	15	20%	Ketoprofen statistically and clinically superior to celecoxib + parecoxib No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of sedation at 24 h (%) [29,36,37,40,48,55,61,67]	8	630	4	6	20%	Control statistically and clinically inferior to diclofenac No other statistical differences between interventions, but, with MCID of 20%, clinical differences possible	Low quality (⊕⊕)	Downgraded for serious limitations and imprecision
Rate of sedation at 48 h (%) [55]	1	44	-	-	20%	In one trial, no statistical difference between control and ketorolac	-	-
Rate of in-hospital sedation (%) [31,33,34,38,45]	5	559	-	-	20%	Pairwise comparison only Control clinically and statistically inferior to diclofenac (RR: 0.43, 95% CI [0.26, 0.73], I^2 = 13; P = 0.002)	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations
Functional outcomes								
Hospital length of stay (h) [39,44,48,67]	4	317	-	-	6 h	Pairwise comparison Control statistically inferior but clinically equivalent to diclofenac (MD: -0.48, 95% CI [-0.88, -0.08], I^2 = 0%; P = 0.02) In one trial, no statistical difference between ketorolac and parecoxib	Moderate quality (⊕⊕⊕)	Downgraded for serious limitations

GRADE: grading of recommendations assessment development and evaluation, MCID: minimally clinically important difference, MD: mean difference, RR: risk ratio.

ority to other NSAIDs could be indicative of their slow absorption from the small intestine following oral administration [72], and their relatively homogenous distribution in body tissue in comparison to acetic acid derivatives with acidic functional groups such as diclofenac, ketorolac, and indomethacin. NSAIDs that are acetic acid derivatives as well as those with high protein binding can selectively accumulate and persist in areas of inflammation [72,73], and this may facilitate their increased analgesic effectiveness at sites of tissue injury subsequent to cesarean section. The superiority of indomethacin to other NSAIDs might be representative of its potential to act as a positive allosteric modulator at the type one cannabinoid receptor, modifying the endocannabinoid system and increasing its antinociceptive properties [74].

In terms of side effects, diclofenac compared to control resulted in decreased sedation at 24 h and in-hospital. This probably underlines its capacity to influence the pain score at 8–12 h and 24 h as well as the need for and time to rescue analgesia, hence reducing the cumulative morphine consumption and these secondary undesirable effects. Interestingly, in the absence of differences in the cumulative morphine consumption, ketoprofen decreased the rate of in-hospital pruritus compared to celecoxib + parecoxib. NSAIDs do not have any recognized direct antipruritic effects [75], and it is possible that the lack of difference in the cumulative morphine consumption was once again a reflection of imprecision rather than absence of true underlying differences.

Our findings corroborate and expand upon the systematic reviews and meta-analyses conducted to date. Consistent with what we have shown, in a prior meta-analysis of 22 randomized controlled trials, NSAIDs were reported to be superior to control in the context of cesarean section for the pain score at 12 h and 24 h and the cumulative morphine consumption [8]. NSAIDs have been compared in settings outside that of cesarean section in other systematic reviews [76–78]. In a previous network meta-analysis of 26 randomized controlled trials, etoricoxib was superior to celecoxib, ketoprofen, and tenoxicam for pain relief in ankylosing spondylitis [76], and in a prior systematic review of 76 randomized controlled trials, diclofenac, etoricoxib, and rofecoxib were ranked highest for the reduction of pain in hip and knee osteoarthritis [77].

We acknowledge the limitations related to this meta-analysis. First, there were a limited number of trials comparing different NSAIDs. Second, few trials were evaluated to be at low risk of bias, and concerns were present in the remaining trials in regard to the randomization process, measurements of the outcome, and the selection of the reported result. Third, the included trials investigated patients who had emergency and/or elective cesarean section under neuraxial, with or without intrathecal opioids, or general anesthesia. Moreover, the strategy of NSAID administration was inconsistent with varied dosing, route, and duration. Such variability introduces heterogeneity, although it increases the generalizability of the findings. Fourth, the standard practice of multimodal analgesia with paracetamol was, surprisingly, only used in a minority of trials. The combination of paracetamol and NSAIDs has been recommended due to their additive effect [79,80]. Fifth, a change in the pain score of 10 on a pain scale of 0–100, including in obstetrics, has been revealed to represent a clinically important difference in the intensity of pain [81]. It is likely, however, that the MCID for any individual patient may vary depending on the severity of the pain, with a greater MCID needed for more severe pain [82]. The MCID for many indices remains undetermined in cesarean section [83], and the authors thus used their experience in this systematic review to select the different thresholds for clinical significance. Sixth, concerns with respect to imprecision for most outcomes precluded the ranking of various NSAIDs. Last, we did not examine which NSAID was best in terms of minimizing transfer to breast milk and increasing safety in breastfeeding women. Those NSAIDs with low oral bioavailability, high protein binding, short half-life, and inactive metabolites as well as reassuring data on breast milk transfer and long record of safe use are likely to be optimal in this respect [80,84]. Interestingly, ibuprofen is thought to be the ideal NSAID for women who are breastfeeding, but our results do not provide sufficient data to confirm its superior properties in the context of cesarean section.

Our network meta-analysis and systematic review demonstrated that diclofenac, indomethacin, ketorolac, and tenoxicam compared to control decreased cumulative morphine consumption at 24 h. No differences were found between different NSAIDs in the cumulative morphine consumption at 24 h, and the quality of evidence was very low. Differences in the secondary outcomes between various NSAIDs were uncovered, with indomethacin clinically superior to celecoxib and celecoxib + parecoxib, diclofenac, and ketorolac for the pain score at rest at 8–12 h and the pain score on movement at 48 h. In light of this emerging but limited evidence, our review suggests the presence of minimal differences among the NSAIDs studied. Nonselective NSAIDs may be more effective than selective NSAIDs, and some NSAIDs such as indomethacin might be preferable to other NSAIDs. Further trials with designs relevant to modern obstetric anesthesia practice are required to increase the strength and quality of the evidence base and the recommendations related to the selection of NSAIDs in the setting of cesarean section.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Iona Murdoch (Data curation; Formal analysis; Writing – original draft)
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Pervez Sultan (Data curation; Writing – review & editing)
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Lindsay Blake (Data curation)
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Neel Desai (Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Material 1. Search Strategy.
Supplementary Material 2. GRADE quality of evidence assessment for each outcome.
Supplementary Material 3. Network league table for secondary outcomes.
Supplementary Material 4. Statistical analysis.
Supplementary Fig. 1. Comparison-adjusted funnel plot with respect to the network for cumulative morphine equivalent consumption at 24 h. Different colors correspond to particular comparisons of interventions. The red line indicates the null hypothesis that the comparison-specific pooled effect estimates do not differ from the respective trial-specific effect sizes.

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