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REVIEW ARTICLE

Systemic adjunct analgesics for cesarean delivery: a narrative review

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ABSTRACT
It is critical to adequately treat postoperative cesarean delivery pain. The use of parenteral or neuraxial opioids has been a mainstay, but opioids have side effects that can be troubling and the opioid crisis in the United States has highlighted the necessity to utilize analgesics other than opioids. Other analgesic options include neuraxial analgesics, nerve blocks such as the transversus abdominis plane block, and non-opioid parenteral and oral medications. The goal of this article is to review non-opioid systemic analgesic adjuncts following cesarean delivery, focusing on their efficacy and side effects as well as their impact on reduction of opioid requirements after surgery.

Keywords: Opioids; Analgesia; Postoperative pain; Analgesic adjuvants; Cesarean delivery

Introduction

Postoperative pain arises both from direct tissue injury caused by an operation and the inflammation that surrounds the healing process afterwards.[1] Because the pain itself has multiple facets, the treatment should be multimodal. Pain after cesarean delivery (CD) is often reported to be worse than after vaginal delivery but it is quite variable.[2] While neuraxial opioids have consistently been shown to be superior to other routes of opioid administration when treating post-CD pain, many patients still require more pharmacologic pain relief[3] and reducing or eliminating opioid use should also be a goal.

The main issue with relying on opioids is their side effect profile. Neuraxial opioids lead to pruritus in 60–100% of cases and nausea or vomiting can occur in 70% of women after CD.[4] Constipation from opioids is not only bothersome but also leads to morbidity and increased cost of care.[5] While increased sedation and altered mental state are possible consequences of opioids, the feared complication of both neuraxial and systemic opioid is respiratory depression. However, this is very rare in this obstetric patient population. Furthermore, the morbidity associated with opioid analgesics does not end with discharge from hospital. Opioid-related deaths in the United States (US) have increased significantly, leading to mortality rates higher than deaths from motor vehicle accidents, suicides or firearms.[6] While pregnant women are less likely than their non-pregnant counterparts to abuse these medications,[7] Bateman et al. identified the rate of persistent opioid use among opioid-naïve women undergoing CD to be as high as 1 in 300.[8] While reducing opioid use is clearly an important goal, pain after CD can be significant and must be adequately treated. The goal of this narrative review is to evaluate systemic non-opioid analgesic drugs used to improve postoperative recovery after CD, with a focus on their efficacy in reducing pain and postoperative opioid requirements, as well as their impact on opioid-related side effects.

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Methods

We performed a literature search in March 2018 using the PubMed Database to identify prospective studies comparing non-opioid analgesics to placebo, other non-opioid or opioid regimens for post CD analgesia. We searched the PubMed Database (1966–2018), using the keywords 'cesarean delivery,' with the additional terms: 'postoperative analgesia', 'analgesia', 'acetaminophen', 'NSAIDS', 'ketamine', 'steroids', 'dexamethasone', 'gabapentinoids', 'gabapentin',

Table 1 Randomized controlled studies evaluating efficacy of acetaminophen for post cesarean delivery analgesia

Author (year)	Sample size	Anesthetic for CD	IT Morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Munishankar (2008)	78	NA	N	Group 1: acetaminophen 1000 mg PR and placebo PR Group 2: diclofenac 50 mg PR and placebo PR Group 3: combination	NS	Morphine consumption (mg): Group 3: 33.8 ± 23.8 Group 1: 54.5 ± 28.5 (P=0.02)	No significant difference in nausea or vomiting
Altenau (2017)	104	NA	Y	Group 1: acetaminophen 1000 mg IV q8h × 48 h Group 2: placebo	NS	Oxycodone consumption (mg): Group 1: 47 ± 39.1 Group 2: 65 ± 46.2 (P=0.032) across 48 h	No significant difference in nausea, vomiting, respiratory depression or constipation
Abu Omar (2011)	80	NA	Y	Group 1: acetaminophen 1000 mg IV q6h × 48 h Group 2: placebo	Median(range) 6 h: 1(0–6) vs 4(0–6) 12 h: 2(0–5) vs 3 (0–7) 24 h: 1.5(0–4) vs 3 (1–8) (P <0.05)	Patients requiring methadone (n,%) Group 1: 0 Group 2: 8 (25%) (P <0.05)	NR
Alhashemi (2006)	45	NA	N	Group 1: acetaminophen 1000 mg IV q6h and placebo PO × 48 h Group 2: placebo IV q6h and ibuprofen 400 mg PO q6h × 48 h	NS	NS	NR
Ozmete (2016)	60	GA		Group 1: acetaminophen 1000 mg IV 15 min prior to induction Group 2: placebo	Median VAS pain scores lower by 1–2 cm at all time points (1, 2, 4, 6, 12 h) except 24 h (P <0.003)	Morphine consumption (mg): mean (range) Group 1: 24 (14–31) Group 2: 38 (26–46) (P <0.0001)	No significant difference in nausea, vomiting or sedation

Towers (2018)	105	NA	Y	Group 1: acetaminophen 1000 mg IV 15 min prior to incision Group 2: placebo	NS		NR
Paech (2014)	111	NA	N	Group 1: parecoxib 40 mg IV followed by celecoxib 400 mg PO at 12 h Group 2: acetaminophen 2 g IV followed by acetaminophen 1 g PO q6h Group 3: combined parecoxib and acetaminophen regimens Group 4: placebo	NS	No significant difference in PCEA pethidine consumption. Incidence of women requiring a secondary breakthrough analgesic (tramadol) (n, %) Group 3: 6 (23%) Group 1: 21 (70%) Group 2: 18 (58%) Group 4: 11 (48%) (P=0.004)	No significant difference in nausea or sedation

*All analgesics are administered postoperatively unless otherwise indicated. **All visual analogue scale scores are reported as group 1 versus (vs.) group 2 as mean ± standard deviation (SD) in centimeters (cm) unless otherwise specified. ***Unless specified, the reported benefits are listed as mean ± standard deviation (SD) in milligrams (mg) and occur over the first 24 hour after cesarean delivery.; PR: per rectum. CD: cesarean delivery. PO: per os. IT: intrathecal. IV: intravenous. NA: neuraxial anesthesia. PRN: pro re nata. IM: intramuscular. NR: not reported. VAS: visual analogue scale. Y: yes. N: no. NS: not significant. GA: general anesthesia. PCEA: patient-controlled epidural analgesia.

'pregabalin', 'magnesium sulfate', 'alpha$_2$-agonist', 'dexmedetomidine', 'clonidine', 'non-opioid analgesics', and their combinations in all fields.

The title and abstract of all articles were reviewed. Inclusion criteria were randomized studies that reported the analgesic efficacy of non-opioid analgesics following CD. Non-English language and non-CD studies, as well as case reports, were excluded. The references of retrieved articles were searched to identify additional articles of relevance (Table 1).

Data collected were the type of anesthetic and post-operative analgesic method used, the analgesia outcomes (e.g. the reduction in postoperative analgesic medications administered or pain scores, and reported side effects). Results are described using mean and standard deviation (SD) unless otherwise specified.

Acetaminophen (paracetamol)

Acetaminophen is now the most commonly utilized analgesic worldwide and is recommended by the World Health Organization for the initial treatment of all types of pain.[9] Acetaminophen has fewer side effects compared with its nonsteroidal anti-inflammatory drug (NSAID) counterparts due to its unique mechanism of action. Similar to NSAIDs, acetaminophen inhibits the cyclo-oxygenase (COX)-1 and -2 pathways leading to analgesic and anti-pyretic effects, however its anti-inflammatory impact is significantly less than other NSAIDs. This may be because acetaminophen only inhibits prostaglandin formation centrally and not peripherally.[10] While this may limit acetaminophen's efficacy for treating inflammatory-mediated pain, it offers the benefit of not blocking thromboxane's platelet activating functions, which may be a benefit in the immediate postoperative setting. Other proposed mechanisms of action include interference with the descending serotonergic pain pathways, weak binding of cannabinoid receptors by an active metabolite and/or inhibition of N-methyl-D-aspartate (NMDA)-receptor activation, which in turn inhibits nitric oxide formation in the spinal cord and modulates nociceptive transmission.[10]

Acetaminophen has been found to reduce the dose of opioids required after major surgery,[11] including after CD.[12] It is already a staple component of post-CD analgesic regimens at many institutions due to its safety record at regular doses,[13] lack of breastmilk penetration[14] and the improved quality of analgesia, especially when it is combined with NSAIDs.[15,16] Intravenous (IV) acetaminophen has become more popular for postoperative patients as it can be utilized regardless of fasting status or digestive tract function immediately after a procedure.

In 2011, Abu-omar et al. compared postoperative IV acetaminophen 1000 mg every six hours with placebo in women undergoing CD with neuraxial anesthesia and intrathecal (IT) morphine. No women in the

intervention group required additional opioids (meperidine) for breakthrough pain compared with 25% of those in the placebo group.[17] More recently, in a randomized controlled trial with 80 women undergoing CD with a spinal anesthetic including IT morphine, Altenau et al. demonstrated a significant reduction in oxycodone use at 48 h (47 mg vs 65 mg, P=0.034) versus placebo when IV acetaminophen 1000 mg was dosed every eight hours.[12] Even a single pre-operative dose of acetaminophen may be beneficial when general anesthesia is given for the CD. Ozmete et al. compared 1000 mg IV acetaminophen with placebo administered 15 min prior to induction of general anesthesia and found both a reduction in postoperative morphine use (24 mg vs 38 mg, P <0.001) and a reduction in median pain scores over the first 12 h.[18] However, a single pre-procedure dose was not found to be efficacious when administered prior to CD under spinal anesthesia including IT morphine.[19]

When comparing acetaminophen 1000 mg IV and ibuprofen 400 mg per os (PO) every six hours in women undergoing CD with spinal bupivacaine without IT morphine, Alhashemi et al. was unable to find a difference in post-CD morphine usage (98 ± 37 mg vs 93 ± 33 mg, P=0.628) or pain scores over 48 h.[20] Munishankar et al. similarly found no difference in post-CD morphine use between acetaminophen 1000 mg and diclofenac 50 mg per rectum (PR) with regularly scheduled dosing, however, the combination of acetaminophen and diclofenac was associated with a 38% reduction in morphine use over the first 24 h as compared with acetaminophen alone.[16] Paech et al. compared epidural pethidine requirements after CD performed with spinal anesthesia without IT morphine across four groups: acetaminophen only, parecoxib/celecoxib only, combination of both and placebo. They found no statistically significant difference in patient-controlled epidural analgesia (PCEA) pethidine use at 24 h. There was however a reduction in the number of women who required supplemental oral tramadol in the combination group as compared to the other three groups (23% in the combined group vs 58%, 70% and 48% in the acetaminophen, NSAID, and control groups respectively, P=0.004).[21]

One of the limitations of investigating the impact of acetaminophen on post-CD analgesia may be the almost doubling of the plasma clearance of acetaminophen seen in pregnant women immediately after delivery when compared with that at 10–15 weeks postpartum.[22] If clearance is increased, then the dosing schedule may need to be adjusted and perhaps more acetaminophen may be required. Siddik et al. compared oral diclofenac 100 mg eight-hourly with IV acetaminophen 2000 mg six-hourly, a combination of the two medications, and a placebo. They found a 57% reduction in opioid use in the combination group and a 46% reduction in the acetaminophen alone group, compared with just an 8.2% reduction in the NSAID monotherapy arm compared with placebo.[23] While to date there are no studies comparing oral versus IV acetaminophen after CD, in other post-surgical patient populations the analgesic and opioid-sparing effects are similar[24] (Table 1).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The NSAIDs' analgesic, anti-pyretic and anti-inflammatory effects result from inhibition of the COX pathway of prostaglandin and thromboxane formation. The enzyme COX-1 is found in every cell and is responsible for many hemostatic activities, while COX-2 is more localized and upregulated in response to toxic mediators and stress signals.[25] There are more than 20 different NSAIDs commercially available and they differ in their mode and level of inhibition of the COX enzyme. However, the level of analgesia provided does not appear to match target affinity.[26] The NSAIDs are a mainstay of post-CD pain regimens. Among anesthesiologists responding to a survey in 2009, 82% reported routine use of NSAIDS, this being greater than use of any other adjunct.[27] While the choice of non-selective NSAID may not matter, regimens based on dosing at a fixed time interval have been shown to improve efficacy and satisfaction compared with on-demand dosing.[28]

Ketorolac has become a popular post-surgical option in the US as it can be given IV, intramuscularly (IM) or orally. Intravenous ketorolac 30 mg is reported to provide similar analgesia to morphine sulfate 10 mg IV but without the risk of respiratory depression.[29] When compared to placebo, an intra-operative dose of 30 mg IV ketorolac followed by two more doses at six and 12 h post procedure reduced the use of opioids administered by PCEA (28.1 ± 3.35 mg vs 41.6 ± 4.25 mg morphine equivalents, P=0.008) and reduced pain from two to 24 h after CD (P=0.033).[30] The authors did not comment on opioid-related side effects. Of note, while ketorolac carries a US Food and Drug Administration 'black box' warning about prostaglandin inhibition and its possible deleterious impact on the neonate, ketorolac has very low breastmilk transfer[31]and is listed by the American Academy of Pediatrics as safe to use during breastfeeding.[32]

Naproxen has been evaluated specifically in the setting of post-CD analgesia. When compared with placebo, Angle et al. found that giving 500 mg per rectum (PR) naproxen during CD under neuraxial anesthesia with IT morphine, followed by six doses of 550 mg of oral naproxen 12-hourly, reduced incisional sitting pain at 36 h post CD. The median time to request for opioid for breakthrough pain was 22 h in the intervention group compared with nine hours in the placebo group (P=0.0006). The total amount of opioid consumed over

72 h was significantly less after naproxen at all time points between zero and 72 h (P <0.01), although the extent of the reduction was not reported. There was no difference between groups in relation to opioid-related side effects.[33] Sammour et al. compared post-CD pain over 48 h in 120 women who received oral naproxen 500 mg six-hourly or tramadol 100 mg six-hourly, with either fixed schedule or on-demand dosing. They did not find a statistically significant difference between groups in pain scores at time points throughout the first 48 h but the need for supplemental analgesics was reduced in the naproxen groups. There were significantly more adverse events such as nausea, vomiting and sedation in the tramadol group compared with the naproxen group (30% vs 15%, P=0.049).[34]

Diclofenac is another useful NSAID for post CD analgesia as it has multiple routes of administration, including IV, IM, PO, transdermal and PR. Surakarn et al. randomized 80 women undergoing CD with neuraxial anesthesia and IT morphine to receive either two doses of IM diclofenac 75 mg (once at delivery and then 12 h later) or placebos. They found that pain scores were lower at 6, 12 and 24 h in the study group and that none of the patients enrolled in the intervention group requested tramadol breakthrough medication, compared with 20% of those in the control group (P <0.05).[35] Olofson et al. randomized 50 women who underwent CD with a spinal anesthetic without IT morphine to diclofenac 50 mg PR eight-hourly for three doses, or placebo, and noted a 39% reduction in ketobemidone patient-controlled analgesia (PCA) dose (30.9 ± 3.3 mg vs 47.6 ± 3.1 mg, P <0.01) in the first 24 post-operative hours. The PCA demand activations were also fewer in the intervention group, however, pain scores were only significantly lower during the first three hours of the study period.[36] In a randomized trial of 40 women, Rashid et al. compared a regimen of diclofenac 100 mg PR once, followed by 50 mg PR after 12 h and 100 mg PR at 36 h, with placebo, and similarly found an opioid-sparing effect. The total pethidine dose consumed by all group members over 48 h was 280 mg in the study group vs 520 mg in the placebo group (P <0.05). Constipation was reported to be less frequent in the intervention group but nausea rates were unchanged.[37] Lim et al. investigated the effect of a peri-operative single dose of diclofenac 100 mg PR vs placebo on post-procedure PCEA use after CD with spinal bupivacaine without IT morphine. They found that even a single dose reduced the amount of PCEA volume required in the first 24 h (52.8 ± 17.8 mL vs 74 ± 25 mL, P <0.005).[38]

Theoretically, selective COX-2 inhibitors should be ideal for post-CD analgesia since they have fewer side effects than non-selective NSAIDS. When compared to naproxen, celecoxib provides non-inferior analgesia while significantly reducing the risk of gastrointestinal bleeding in individuals with chronic pain.[39] Celecoxib also does not impact platelet aggregation as do non-selective NSAIDS when tested in healthy adults.[40] Given the increase in the percentage of parturients who are placed on pharmacological thrombo-embolic prophylaxis post CD, selective COX-2 inhibitors should be considered. In a letter to the editor, Fong et al. presented a prospective blinded randomized placebo-controlled trial in which 60 parturients were either given celecoxib 400 mg PO 30 min prior to spinal anesthesia, celecoxib 400 mg PO during wound closure, or placebos. Morphine equivalents were reduced in both the pre-procedure and post-procedure celecoxib groups compared to placebo (13 ± 6.2 mg, 12 ± 5.4 mg and 27 ± 7.2 mg respectively, P <0.05). The time to first breakthrough opioid dosing was only significant longer when the celecoxib was given pre-procedure (421 ± 92 min vs 334 ± 56 min and 261 ± 46 min respectively, P <0.05).[41] Matsota et al. found no significant differences in PCEA ropivacaine 0.2% and fentanyl 2 μg/mL requirements or demand attempts when celecoxib 200 mg PO was given post CD under spinal anesthesia, without IT morphine, as compared to placebo. However, pain scores both at rest and with movement were reduced at 24 h post procedure (P=0.009) in the celecoxib group, although only by approximately 10 mm on a 0–100 mm scale.[42] Lee et al. compared 200 mg celecoxib given immediately after delivery to placebo at CD under spinal anesthesia with 300 μg IT morphine. The primary outcome was the incidence of pruritus and secondary outcomes were pain and rescue opioid requirements. Neither the primary nor secondary outcomes were significantly different among 60 patients. To date, there are no studies comparing selective COX-2 inhibitors to non-selective NSAIDs for pain management after CD (Table 2).

Steroids

Steroids reduce pain by inhibiting the synthesis of arachidonic acid, the precursor in the COX pathway of prostaglandin formation.[10] Dexamethasone has been shown to decrease the transcription of COX-2 receptors in response to stress.[43] Because steroids mostly work through changes in transcription, they often have a delayed onset, with a peak effect at 45–60 min.[44]

Dexamethasone prevents postoperative nausea and vomiting (PONV) and reduces pain after CD under neuraxial anesthesia. In a 2010 meta-analysis, Allen et al.[45] identified eight randomized controlled trials (four at CD and four at abdominal hysterectomy) involving 768 women anesthetized with spinal anesthesia and IT morphine for postoperative analgesia. In the CD trials, 2.5–10 mg IV dexamethasone reduced pain scores minimally across the first 24 h (−0.3, 95% CI −0.46 to −0.13). While this reduction is not clinically relevant, the need

Table 2 Randomized controlled studies evaluating efficacy of nonsteroidal anti-inflammatory drugs for post-cesarean delivery analgesia

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Angle (2002)	80	NA	Y	Group 1: naproxen 500 mg PR once intra-operatively followed by naproxen 550 mg PO q12h for 6 doses Group 2: Placebo	36 h 3.82 ± 2.6 vs 5.14 ± 2.57 (P=0.05)	Median (range) time to first breakthrough opioid (h): Group 1: 9 (1–49) Group 2: 22 (1–50) (P=0.003) Total mg oral codeine reduced by ~50% across all time points from 0 to 72 h (graphically represented) (P <0.01)	No significant differences in pruritus, nausea or vomiting, maternal sedation or respiratory rates
Sammour (2011)	120	NA and 5 cases of GA	NR	Group 1: naproxen 500 mg PO q6h scheduled Group 2: naproxen 500 mg PO q6 prn Group 3: tramadol 100 mg PO q6h scheduled Group 4: tramadol 100 mg PO q6h prn	NS	Overall opioid consumption not compared between groups. Dose of additional doses of trial medications (tablet count): Group 1: 2.1 ± 1.47 Group 2: 1.50 ± 1.38 (P=0.027)	Increased incidence of side effects (nausea, sedation) in tramadol groups (30% vs 15%, P=0.049)
Surakarn (2009)	80	NA	Y	Group 1: diclofenac 75 mg IM q12h for 2 doses Group 2: tramadol prn (dose/time not specified)	Median (range) 6 h: 1(0–6) vs 4 (0–6) (P=0.002) 12 h: 2 (0–5) vs 3 (0–7) (P=0.031) 24 h: 1.5 (0–4) vs 3 (1–8) (P <0.0001)	Incidence of rescue tramadol: n (%) Group 1: 0 (0%) Group 2: 8 (20%) (P <0.05)	NR
Bourlert (2005)	64	NR		Group 1: diclofenac IM (dose/frequency not specified) Group 2: placebo	NS	Morphine consumption (mg): Group 1: 21.69 + 9.78 Group 2: 27.41 + 11.09 (P=0.016)	

Rashid (2000)	40	GA		Group 1: diclofenac 100 mg PR intra-operatively followed by 50 mg PR at 12 h then 100 mg PR at 36 h Group 2: no intervention	Median pain scores (range) 12 h: 2.3 vs 3.9 ($P < 0.05$) 18 h: 2 vs 3.6 ($P < 0.05$) 24 h: 1.3 vs 3.2 cm ($P < 0.05$)	Pethidine consumption over 48 h: Total mg for all group members: Group 1: 280 mg Group 2: 520 mg ($P < 0.05$)	Incidence of constipation: Group 1 vs. Group 2 25% vs 75% ($P < 0.05$) Incidence of sedation: n(%) 6 h: 6(30) vs 18(90) 12 h: 4(20) vs 12(60) 24 h: 0(0) vs 6(30) ($P < 0.05$) No difference in nausea or vomiting
Siddik (2001)	80	NA	N	Group 1: diclofenac 100 mg PR q8h × 24 h Group 2: acetaminophen 2000 mg IV q6h × 24 h Group 3: combined diclofenac and acetaminophen regimens Group 4: placebo	Group 3 vs 4: 2 h at rest: 2.7 ± 2 vs 4: 6 ± 3 ($P < 0.05$) 24 h at rest: 1.5 ± 1.3 vs 3.2 ± 2.7 ($P < 0.05$)	Morphine consumption mean ± SD (% morphine reduction compared to placebo) Group 1: 36 ± 18 (46%) Group 2: 61.1 ± 23 (8%) Group 3: 28.3 ± 15.8 (57%) Group 4: 66.7 ± 20 mg (NA) ($P < 0.05$, except Group 2 vs 4)	No significant difference in sedation, respiratory rate, nausea, vomiting
Lim (2001)	48	NA	N	Group 1: diclofenac 100 mg PR Group 2: no intervention	NS	PCEA (ropivacaine 0.2% + fentanyl 2 μg/mL) demand doses over 24 h (mL): Group 1: 52.8 ± 17.8 Group 2: 74 ± 25 ($P < 0.005$)	NR
Olofsson (2000)	50	NA	N	Group 1: diclofenac 50 mg PR q8h × 3 doses Group 2: placebo	VAS scores reduced in group 1 vs group 2 for first 3 h only (P=0.025) (graphically represented)	Ketobemidone consumption: (20 h) Group 1: 30.9 ± 3.3 Group 2: 47.6 ± 3.08 ($P < 0.01$) PCA attempts: Group 1: 72.6 ± 7.55 Group 2: 43.6 ± 5.8 ($P < 0.004$)	NR

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Table 2 (*continued*)

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Fong (2008)	60	NA	NR	Group 1: celecoxib 400 mg PO 30 min prior to anesthetic Group 2: celecoxib 400 mg PO after wound closure Group 3: placebo	VAS scores reported as reduced at 6 and 12 h and lower in group 1 and 2 compared to group 3 (specific values not reported)	Morphine consumption (mg): Group 1: 13 ± 6.2 Group 2: 12 ± 5.4 Group 3: 27 ± 7.2 ($P < 0.05$ Group 1 and Group vs Group 3) Time to first breakthrough opioid dose (min): Group 1: 421 ± 92 Group 2: 334 ± 56 Group 3: 261 ± 46 ($P < 0.05$ for group 1 vs 3 only)	No significant difference in opioid-related side effects (side effects not specified)
Matsota (2013)	64	NA	N	Group 1: celecoxib 200 mg PO once post procedure Group 2: No intervention	VAS pain scores reduced both at rest and with movement at 6 and 24 h in Group 1 compared to Group 2 (graphically represented)	NS	No significant differences in nausea, pruritus or respiratory depression between groups
Lee (2004)	60	NA	Y	Group 1: celecoxib 200 mg PO once after delivery Group 2: placebo	NS	NS	No significant difference in pruritus

*All analgesics are administered postoperatively unless otherwise indicated.**All visual analogue scale (VAS) scores reported as Group 1 vs Group 2 are mean ± standard deviation (SD) in cm unless otherwise specified.***Unless specified, the reported benefits are listed as mean ± standard deviation (SD) in mg and occur over the first 24 h after cesarean delivery.; PR: per rectum. CD: cesarean delivery. PO: per os. IT: intrathecal. IV: intravenous. NA: neuraxial anesthesia. PRN: pro re nata. IM: intramuscular. NR: not reported. VAS: visual analogue scale. Y: yes. N: no. NS: not significant. GA: general anesthesia. PCEA: patient-controlled epidural analgesia.

Table 3 Randomized controlled studies evaluating efficacy of steroids or ketamine for post cesarean delivery analgesia

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Naghibi (2013)	99	NA	N	Group 1: bupivacaine 0.5% 3 mL IT with 2 mg IT betamethasone and IV placebo Group 2: bupivacaine 0.5% 3 mL IT with IT placebo and 2 mg IV betamethasone Group 3: bupivacaine 0.5% 3 mL IT with IT placebo and IV placebo	Group 1 vs 2 vs 3 4 h: 3.18 ± 1.2 vs 4 ± 1.3 vs 6 ± 2 (P <0.0001) 6 h: 2.5 ± 1 vs 4 ± 1.8 vs 7.7 ± 1.8 (P <0.0001) 12 and 24 h: NS	Diclofenac consumption for breakthrough pain (mg): Group 1: 163.3 ± 82 Group 2: 227.2 ± 103 Group 3: 293.9 ± 82 (P <0.0001) Mean time to rescue (min): Group 1: 336.8 ± 86 Group 2: 312 ± 106 Group 3: 245.4 ± 93 (P <0.0001)	Increased incidence of nausea in placebo group compared to IT or IV groups (57% vs 27% vs 19% for placebo, IT, IV respectively, P <0.05)
Ituk (2018)	52	NA	Y	Group 1: dexamethasone 8 mg IV after umbilical cord clamping Group 2: placebo	12 h at rest: Median(range) 1(0–1) vs 2(1–3) (P=0.014) 6, 24 h at rest: NS 6, 12, 24 h with movement: NS	NS	No significant difference in pruritus, nausea or vomiting or need for rescue anti-emetic
Bauchat (2011)	188	NA	Y	Group 1: ketamine 10 mg IV after delivery Group 2: placebo	NS	NS	No significant difference in pruritus nausea or vomiting.
Rahmanian (2015)	160	NA	N	Group 1: ketamine 0.25 mg/kg IV after delivery Group 2: placebo	2 h: 3.92 ± 1.33 vs 5.38 ± 1.06 6 h: 3.90 ± 1.7 vs 6.16 ± 0.27 12 h: 3.19 ± 0.67 vs 4.64 ± 0.47 (P <0.001)	Pethidine consumption in doses of 50 mg: Group 1: 0.44 ± 0 vs Group 2: 1.62 ± 2 (P <0.001) Percentage of women who required any pethidine Group 1: 1.2% Group 2: 57%	No significant difference in pruritus and nausea. Vomiting: Group 1: 35% Group 2: 18.8% (P=0.02) Hallucinations: Group 1: 22.5% Group 2: 10% (P=0.032)

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Table 3 (*continued*)

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Menkiti (2012)	60	NA	N	Group 1: ketamine 0.15 mg/kg IV after delivery Group 2: placebo	Percentage of patients with VAS scores greater than 3: 60 min: 0 vs 61% (P <0.001) 90 min: 43% vs 100% (P <0.001) 120 min: 57% vs 100% (P <0.001)	Pentazocine consumption (mg) Group 1: 109 ± 18.6 Group 2: 150 ± 20 (P <0.001) no difference from 24 to 48 h	No significant difference in nausea, vomiting, shivering, headache, hallucinations
Reza (2010)	60	GA		Group 1: ketamine 0.5 mg/kg IV 5 min prior to induction Group 2: placebo	NS	Morphine consumption: 2 h (mg): Group 1: 4.8 ± 2.5 Group 2: 8.1 ± 4.2 (P=0.01) No significant difference from 2 to 24 h	No significant difference in nausea or vomiting
Bilgen (2012)	140	GA		Group 1: ketamine 0.25 mg/kg IV 5 min prior to induction Group 2: ketamine 0.5 mg/kg IV 5 min prior to induction Group 3: ketamine 1 mg/kg IV 5 min prior to induction Group 4: placebo	NS	NS	No significant difference in nausea, vomiting, nystagmus, diplopia, sedation or hallucinations

*All analgesics are administered postoperatively unless otherwise indicated.**All visual analogue scale (VAS) scores are reported as Group 1 vs Group 2 as mean ± standard deviation (SD) in cm unless otherwise specified.***Unless specified, the reported benefits are listed as mean ± standard deviation (SD) in mg and occur over the first 24 h after cesarean delivery.; PR: per rectum. CD: cesarean delivery. PO: per os. IT: intrathecal. IV: intravenous. NA: neuraxial anesthesia. PRN: pro re nata. IM: intramuscular. NR: not reported. VAS: visual analogue scale. Y: yes. N: no. NS: not significant. GA: general anesthesia. PCEA: patient-controlled epidural analgesia.

for rescue analgesia was almost 30% less in the dexamethasone groups as compared with placebo (27% vs 38%, RR 0.76, 95% CI 0.62 to 0.93). There were no reported side effects (such as delayed wound healing or increased infection risk) in the dexamethasone-exposed cohort.[45]

In a randomized controlled trial comparing IV betamethasone 2 mg with placebo for post-CD analgesia in 99 women having spinal anesthesia without IT morphine, Naghibi et al.[46] found a 2 cm reduction in visual analog scale (VAS) pain scores at 4 h (6 ± 2 vs 4 ± 1.3, $P < 0.0001$) and an almost 4 cm reduction at 6 h (7.7 ± 1.8 vs 4 ± 1.8, $P < 0.001$) from betamethasone. However, pain scores at 12 h and 24 h were not significantly different. While the time to first breakthrough pain relief only increased by approximately an hour (245.4 ± 93 min vs 312.4 ± 106 min, $P < 0.001$), the total dose of diclofenac given for breakthrough pain was about 25% less in the dexamethasone group (293.9 ± 82 mg vs 227.2 ± 103 mg, $P < 0.0001$.).[46] More recently Ituk et al. investigated whether a single dose of 8 mg IV dexamethasone would reduce opioid consumption over the first 24 h in women undergoing CD with a spinal anesthetic and IT morphine. They reported no difference from placebo in opioid dose requirements, time to breakthrough medication or opioid-related side effects[47] (Table 3).

Ketamine

Ketamine's analgesic, anesthetic and antidepressant effects are multifactorial. The primary mechanism is likely to be inhibition of postsynaptic N-methyl-D-aspartate (NMDA) receptors by binding the phencyclidine (PCP) site inside the ion channel, blocking the release of the inhibitory neurotransmitter gamma-amino butyric acid (GABA), and thus increasing the amount of the excitatory neurotransmitter glutamate released presynaptically.[48] Other targets of ketamine may be the 5-hydroxytriptamine-$_2$ serotonin, dopamine-$_2$ and sigma-$_1$ receptors. Ketamine may also potentiate the effects of opioids at the μ-opioid receptor, has been shown to potentiate fentanyl's effect at lower doses, to increase the duration of action of opioids by keeping the μ-opioid receptors in an active state, and double the speed of re-sensitization such that the receptors can fire more frequently.[49]

The use of subanesthetic doses of ketamine for analgesia after CD has been evaluated in several studies but with mixed results. When a bolus of 10 mg of IV ketamine was given in conjunction with spinal anesthesia including IT morphine, Bauchat et al. found that pain scores and opioid consumption across the first 24 h were unchanged compared with controls. More patients in the ketamine group were drowsy (−1) or restless (+1) on the Richmond Agitation-Sedation Scale (RASS) when compared with a saline group during infusion of the medication, but none reported nightmares.[50] Rahmnanian et al. used a larger dose of 0.25 mg/kg IV ketamine administered after delivery of the baby at CD performed under spinal anesthesia without IT morphine. While the pain scores were only 1 –2 cm lower (on a 0–10 scale) at two, four, six and 12 h, and the time to first opioid request was only prolonged by a mean of one hour, there was a large difference in total opioid use during the first 24 h. Fewer than 50% of those in the ketamine group requested pethidine for breakthrough pain in comparison with 98.8% in the control group. There was no difference in pruritus and nausea between the groups but the incidence of vomiting was reduced (18.8% vs 35%, $P=0.02$) and the incidence of hallucinations was increased in the ketamine group (22.5% vs 10%, $P=0.032$).[51] Menkiti et al. used 0.15 mg/kg of ketamine for CD under spinal anesthesia without IT morphine and found that the ketamine group used less pentazocine than the placebo group during the first 24 h (109 ± 18.6 mg vs 150 ± 20 mg, $P < 0.001$). There was no significant difference between groups in the incidence of nausea, vomiting, headache, sedation or headaches; and no hallucinations were reported in either group.[52]

When general anesthesia was utilized for CD, Reza et al. reported that a pre-induction bolus of 0.5 mg/kg of ketamine decreased immediate postoperative morphine use by only 3 mg and did not significantly reduce use between two and 24 h. Rates of nausea and vomiting were similar between the groups but two of 30 women in the ketamine group reported hallucinations compared with to none in the control group.[53] Bilgen et al. compared multiple doses of pre-induction ketamine, ranging from 0.25–1 mg/kg, administered for CD under general anesthesia. They found no difference in postoperative pain or opioid consumption at any time points through 48 h when compared with placebo. There were also no reported differences in nausea, vomiting, vision changes, sedation or hallucinations.[54] Helmy et al. randomized 60 women to receive either 0.3 mg/kg of ketamine, 30 mg/kg of magnesium sulfate or placebo 10 min prior to induction of general anesthesia for CD and reported less pethidine use in the first 24 h in the ketamine group compared with the placebo group (82 ± 33 mg vs 140 ± 38 mg, $P < 0.05$). There was no difference in the reported rate of nausea or sedation.[55]

A 2015 meta-analysis by Heesen et al. evaluated 953 women undergoing CD in 12 studies, seven of which were performed under general anesthesia and five under neuraxial anesthesia. The authors found a morphine dose reduction of 5 mg across the first 24 h after ketamine versus placebo in the neuraxial anesthesia group (−5.12 mg, 95% CI −1.9 to −0.17), but no significant difference if general anesthesia had been used. There were no significant differences observed in maternal hemodynamics, the rates of nausea, vomiting, pruritus,

visual changes, headaches or psychomimetic adverse events in either the general anesthesia or regional groups (Table 3).[56]

Gabapentinoids

Designed to mimic GABA as a treatment against seizures,[57] gabapentin and pregabalin have been repurposed as leading analgesics against neuropathic pain, especially when combined with other analgesics such as opioids.[58] While the exact mechanism of action is still a subject of research, gabapentinoids are known to interfere with neuroplasticity after nerve injury that may lead to upregulation of pain. Other research suggests inhibition of NMDA receptors as well.[57]

In a randomized double-blinded placebo-controlled trial, Moore et al. assigned 46 women to receive a single dose of gabapentin 600 mg PO or placebo one hour prior to their CD, which included IT morphine. The visual analogue scale pain scores were 20 mm lower in the intervention group during the first 24 h (21 mm vs 41 mm, P=0.001) but the total dose of IV morphine and the number of women who required a breakthrough dose was not significantly different. The incidence of PONV and of pruritus was similar between groups; and while the amount of mild maternal sedation, measured on a self-reported four-point scale was similar to controls, there was a 20% incidence of 'severe' sedation in the gabapentin group but none among controls (P=0.04). Postoperative pain at three months did not significantly differ between the groups.[59] Short et al. conducted a similarly designed study with three groups; 600 mg or 300 mg of gabapentin or placebo given one hour prior to CD. They found no statistically significant differences in pain scores, breakthrough opioid requirements or side effects, including nausea, vomiting, pruritus, sedation or severe sedation.[60] Monk et al. randomized 204 women to gabapentin 600 mg PO one hour before incision followed by gabapentin 200 mg eight-hourly for five doses across 48 h, or to placebo, in women undergoing CD under spinal anesthesia with IT morphine. No difference in postoperative opioid requirements was found and the difference in pain scores at 24 h (40 vs 47 mm, P=0.047) was considered clinically unimportant. Nausea, vomiting and pruritus did not significantly differ but sedation (self-reported on a four-point scale) was greater in the gabapentin group (55% vs 40%, P=0.026), as was severe sedation (8% vs 2%, P=0.018).[61] Further limiting gabapentin's role in post-CD analgesic regimens are the relatively high placental and breastmilk transfer ratios (Table 4).[14]

Intravenous magnesium sulfate

Magnesium sulfate ($MgSO_4$) has been shown to bind to and inhibit the NMDA receptor and has therefore become a popular target of study for its impact on both chronic and acute pain.[62] As $MgSO_4$ IV infusions are already widely used for a number of indications in the obstetric population, it would seem an ideal agent to utilize for post-CD pain relief. There are some studies that show decreased opioid requirements when a low-dose $MgSO_4$ ($\leq$50 mg/kg) infusion is administered prior to induction of general anesthesia for CD. Rezae et al.[63] reported a very small 2 mg reduction in morphine consumption in the first 24 h (11.2 ± 6.3 mg vs 13.9 ± 3.9 mg, P=0.006) and Mireskandari et al.[64] reported a 3 mg reduction in 24 h (4.36 ± 1.4 mg vs 7.2 ± 1.9 mg, P <0.001) when 50 mg/kg was compared with placebo prior to induction. Neither group of investigators commented on opioid-related side effects. Elrahman et al. also found a reduction in morphine requirements over the first 24 h (6.2 ± 0.87 mg vs 10.1 ± 0.95 mg, P=0.001) when 50 mg/kg $MgSO_4$ (versus placebo) was added to a general anesthetic that included bilateral transversus abdominis plane (TAP) blocks for CD. No comment was made about opioid side effects.[65] Helmy et al. found no difference in morphine requirement compared with placebo when 30 mg/kg $MgSO_4$ was infused prior to induction of general anesthesia.[55]

When neuraxial anesthesia without IT morphine was employed for CD in 120 women, Paech et al. reported no difference in pain scores, time to first breakthrough analgesic dose or total meperidine (pethidine) consumption when $MgSO_4$ was given as a bolus followed by an infusion for 24 h post-procedure, as compared to placebo, either at high dose (50 mg/kg bolus then 2 g/h) or low dose (25 mg/kg bolus followed by 1 g/h). The median estimated blood loss was 15–20% greater in the $MgSO_4$ groups compared with placebo (475 mL vs 500 mL vs 400 mL for low dose, high dose and placebo respectively, P=0.005; Table 4).[66]

Alpha$_2$-agonists

The alpha$_2$-adrenergic receptor serves as part of a negative feedback loop that inhibits further release of catecholamines. The proposed analgesic effects are most likely a result of alpha$_2$-agonists blocking nociception and inhibiting substance P formation in the spinal cord, reducing the upregulation and transmission of pain.[67]

Nie et al. designed a three-arm, double-blinded randomized controlled trial to determine if adding IV dexmedetomidine to the postoperative analgesic regimen would reduce the amount of opioid used after CD under spinal anesthesia without IT morphine. All three groups had IV sufentanil PCA to control postoperative pain. One group received a placebo injection, another a single peri-operative dose of dexmedetomidine 0.5 μg/kg and the third the same dose but also dexmedetomidine added to the sufentanil PCA (basal rate of 45 ng/kg/h with PCA dose of 70 ng/kg every

Table 4 Randomized controlled studies evaluating efficacy of gabapentinoids, magnesium sulfate or intravenous lidocaine for post cesarean delivery analgesia

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Moore (2011)	46	NA	Y	Group 1: gabapentin 600 mg PO 1 h prior to scheduled procedure start time Group 2: placebo	24 h with movement Mean (95%CI) (mm): 21(13–29) vs 41 (32–51) (P=0.001) VAS score with movement at 6 and 12 h as well as VAS at rest at 6, 12 and 24 h were also significantly less (graphically represented)	NS	No significant difference in nausea, vomiting or pruritus. Overall sedation rates were similar between groups but the incidence of severe sedation on self-reported four-point scale was 19% Group 1 compared to 0% in Group 2 (P=0.04)
Short (2012)	132	NA	Y	Group 1: gabapentin 600 mg PO 1 h prior to scheduled procedure start time Group 2: gabapentin 300 mg PO 1 h prior to scheduled procedure start time Group 3: placebo	NS	NS	No significant difference in pruritus, nausea, vomiting or sedation, including severe sedation
Monk (2015)	204	NA	Y	Group 1: gabapentin 600 mg PO 1 h prior to CD followed by gabapentin 200 mg q8h for 5 doses (48 h) Group 2: placebo	Mean (95% confidence interval) (mm) 40(36–45) vs 47 (42–51) (P=0.047)	NS	No significant difference in nausea, vomiting or pruritus Percentage of women with sedation on self-reported four-point scale at 24 h: Group 1: 55% Group2: 40% (P=0.026) Severe sedation: Group 1: 8% Group 2: 2% (P=0.018)

(*continued on next page*)

Table 4 (*continued*)

Author (year)	Sample size	Anesthetic for CD	IT morphine	Analgesic regimens*	Effect on pain scores**	Opioid reduction***	Opioid-related side effects
Rezae (2014)	70	GA		Group 1: $MgSO_4$ 50 mg/kg IV over 10 min, 30 min prior to induction Group 2: placebo infusion	2 h: 3.2 ± 1.8 vs 4.9 ± 2.3 12 h: 2.8 ± 1.1 vs 3.6 ± 1.3 24 h: 1.8 ± 2.1 vs 2.9 ± 1.2 ($P < 0.003$)	Morphine consumption (mg): Group 1: 11.2 ± 6.3 Group 2: 13.9 ± 3.9 ($P = 0.006$)	NR
Mireskandari (2015)	50	GA		Group 1: $MgSO_4$ 50 mg/kg IV over 15 min, 30 min prior to induction Group 2: placebo infusion	VAS score in mm: 1 h: 48.9 ± 19.6 vs 74.7 ± 18.4 ($P < 0.001$) 6 h: 42.1 ± 0.9 vs 58.3 ± 16.5 ($P < 0.002$) 12 h: 25.2 ± 6.1 vs 30 ± 8.1 ($P < 0.05$)	Morphine consumption (mg): Group 1: 4.36 ± 1.4 Group 2: 7.2 ± 1.9 ($P < 0.001$)	NR
Helmy (2015)	60	GA		Group 1: $MgSO_4$ 30 mg/kg IV over 10 minutes prior to induction Group 2: ketamine 0.3 mg/kg IV over 10 minutes prior to induction Group 3: placebo infusion	Group 2 vs 3: Median (range) 2 h: 2.4(2–4) vs 4 (2–5) 6 h: 3(2–4) vs 4 (3–5) ($P < 0.05$) NS at 12 or 24 h NS at any time points between Groups 1 and 3	Pethidine consumption (mg): Group 2: 82 ± 33 Group 3: 140 ± 38 ($P < 0.05$) Time to first pethidine request (min): Group 2: 82 ± 12 Group 3: 33 ± 7 ($P < 0.05$) No significant difference between group 1 ($MgSO_4$) and placebo	No significant difference in sedation or nausea
Elrahman (2017)	60	GA and TAP blocks		Group 1: $MgSO_4$ 50 mg/kg IV over 20 min, 30 min prior to induction Group 2: placebo infusion	NS	Morphine consumption (mg): Group 1: 6.2 ± 0.87 Group 2: 10.1 ± 0.95 ($P = 0.001$)	NR

Paech (2006)	120	NA	N	Group 1: $MgSO_4$ 50 mg/kg IV followed by infusion of 2 g/h for 24 h Group 2: $MgSO_4$ 25 mg/kg IV followed by infusion of 1 g/h for 24 h Group 3: Saline bolus/infusion	NS	NS	Estimated blood loss: Median (range) (mL) Group 1: 500 (200–1000) Group 2: 475 (100–1500) Group 3: 400 (100–1600) (P=0.005)
Nie (2014)	120	NA	N	Group 1: dexmedetomidine 0.5 μg/kg IV infusion Group 2: dexmedetomidine 0.5 μg/kg IV infusion followed by infusion at 45 ng/kg/h and PCA dose of 70 ng/kg q8min Group 3: placebo	Mean VAS scores reduced in Group 2 by ~ 1 cm at all points up to 24 h compared to placebo (P <0.05). No significant difference between group 1 and placebo (VAS scores graphically represented)	Sufentanil consumption (mcg): Group 1: 56.3 ± 20.6 Group 2: 43.9 ± 19.2 Group 3: 54.5 ± 23.9 (P=0.023 between Groups 2 and 3, NS for Groups 1 and 3)	No difference in nausea, vomiting or sedation
Fernandes (2018)	78	NA	Y	Group 1: clonidine 75 μg IT Group 2: clonidine 75 μg IV Group 3: placebo	NS	NS	Sedation level on Richmond Agitation/Sedation Scale: mean ± SD Group 1: −1 ± 0.53 Group 2: −0.73 ± 0.45 Group 3: −0.3 ± 0.47 (P <0.001)
Gholipour Baradari (2016)	100	GA		Group 1: Lidocaine 1.5 mg/kg bolus IV prior to induction Group 2: placebo	24 h: 3.8 ± 1.09 vs 4.7 ± 0.8 (P <0.001)	Morphine consumption (mg): Median(range) Group 1: 0(0–12) Group 2: 3.79(0–9) (P <0.001)	No difference in nausea

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eight minutes). The third group demonstrated decreased sufentanil requirements compared with the other sufentanil and placebo groups (43 ± 19 μg vs 56 ± 20 μg vs 54 ± 24 μg respectively, $P < 0.05$). While VAS pain scores were also significantly lower, the reduction of about 10 mm at each time point up to 24 h was not clinically relevant. Side effects including nausea, vomiting and sedation were not significantly different among groups.[68]

Fernandes et al. compared 75 μg of IT or IV clonidine with placebo in 78 women undergoing CD with IT morphine; and reported no difference in pain scores or tramadol use in the first 24 h. Both clonidine groups had more maternal sedation (Table 4).[69]

Lidocaine

The analgesic effects of IV lidocaine are likely a result of its interaction with intracellular voltage-gated sodium channels in peripheral and central nerve endings, leading to reduced pain sensitization and the hyperalgesia that may result from tissue damage. Other proposed mechanisms include increased release of central endogenous opioids via an increase in acetylcholine in the cerebrospinal fluid, directly or indirectly reducing depolarization of NMDA and neurokinin receptors, and possibly reducing localized tissue damage by decreasing cytokine release.[70]

In a prospective randomized double-blind study, Golipour Baradari et al. evaluated a single 1.5 mg/kg dose of IV lidocaine, administered immediately before induction of general anesthesia, on pain scores in 100 women undergoing CD. On a 10-point scale, the VAS pain scores were consistently lower at two, four, six, 12 and 24 h, with a mean ± SD score of 3.8 ± 1.1 cm in the lidocaine group compared with 4.7 ± 0.8 in the placebo group ($P < 0.001$). There was no significant difference between the groups in the use of rescue diclofenac for mild pain (score ≥ 3) but there was a difference in median morphine requirements (across the first 24 h) offered for moderate pain (score ≥ 5). Women in the lidocaine group received a median (range) of 0 (0–12) mg of morphine compared with controls 3.8 (0–9) mg ($P < 0.001$). There was no significant difference between groups in patient satisfaction, hospital length of stay, nausea or vomiting (Table 4).[71]

Conclusions and authors' recommendations

Due to the many opioid-related side effects in the postoperative period it is important to find non-opioid analgesic alternatives. The routine use of scheduled acetaminophen, in addition to NSAID, is recommended in post-CD analgesic regimens given the safety profile and proven efficacy. There is no evidence to suggest the superiority of IV acetaminophen over the oral equivalent and the IV formulation is more expensive. In our institution, we administer ketorolac 30 mg IV every six hours for 24 h, followed by ibuprofen 600 mg every six hours until hospital discharge. Concurrently, acetaminophen 975 mg PO is offered every six hours from the recovery room until discharge.

While the evidence that steroids result in opioid sparing is weak, they are often utilized to prevent PONV and are therefore easily included in a standardized post-CD analgesia regimen. There appears to be only a mild opioid-sparing effect when ketamine is used, often at the expense of increased side effects such as sedation or hallucinations. There is only one study evaluating the effect of IV lidocaine on post-CD analgesia and, while the results were encouraging, more research is needed before we recommend routine use. There is little evidence that gabapentinoids, $MgSO_4$ or alpha$_2$-agonists are efficacious for post-CD pain and all have side effects, including increased sedation and possibly increased bleeding from $MgSO_4$. Consequently, these adjuncts are not recommended for routine use in this patient population.

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