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REVIEW ARTICLE

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Monitoring, prevention and treatment of side effects of long-acting neuraxial opioids for post-cesarean analgesia

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ABSTRACT
Long-acting neuraxial opioids such as morphine and diamorphine, administered via spinal or epidural routes, are staple components of a multimodal approach to postoperative analgesia following cesarean delivery. The widespread use of neuraxial opioids is due largely to their significant analgesic efficacy and favorable safety profile. The most common side effects of neuraxial opioids are pruritus, nausea and vomiting. These symptoms appear to be dose-related. The most serious complication of neuraxial opioids is respiratory depression, which occurs in 0–0.9% of cases. Hypothermia has also been reported in association with neuraxial morphine use at cesarean delivery. This article will review recent advances in prophylaxis, treatment and monitoring of the side effects of long-acting neuraxial opioids.

Keywords: Opioids, neuraxial; Cesarean; Nausea; Vomiting; Pruritus; Hypothermia; Respiratory depression

Introduction

Anesthesia-related maternal mortality has steadily decreased from the late 1970s to the 2000s.[1,2] A decline in the rate of general anesthesia for cesarean delivery played a crucial role in this progress because most anesthesia-related complications occur during general anesthesia. The American Society of Anesthesiologists (ASA) practice guidelines for obstetric anesthesia suggest that neuraxial anesthesia should be considered in preference to general anesthesia for most cesarean deliveries.[3,4] Neuraxial anesthesia using neuraxial opioids in combination with local anesthetics provides superior intra-operative anesthesia and postoperative analgesia.[5–7] Compared with systemic opioids, neuraxial opioids reduce postoperative analgesic requirements and delay the time to first analgesic request.[8,9] Common side effects related to neuraxial opioids such as pruritus, nausea and vomiting, seem to be dose-dependent.[10–12] The most serious complication of neuraxial opioids is respiratory depression, which has an incidence of 0–0.9% when measured by intermittent respiratory rate assessments and pulse oximetry.[13–16] Neuraxial morphine may also contribute to peri-operative hypothermia.[17] The aim of this review is to discuss the incidence of these side effects and strategies for their prevention and treatment.

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Optimal dosing of neuraxial morphine

Neuraxial morphine is the "gold standard" analgesic method, and morphine is the most commonly used opioid for postoperative analgesia following cesarean delivery. Intrathecal doses ranging from 75–300 μg have been used in clinical practice[18] but an "analgesic ceiling" effect is reached at 100 μg, while higher doses are associated with an increased incidence and severity of side effects.[12] A meta-analysis by Sultan et al. comparing low-dose (50–100 μg) and high-dose (>100–250 μg) intrathecal morphine for cesarean delivery found that the higher dose was associated with more pruritus, nausea and vomiting but no difference in pain scores at 12 and 24 h and no difference in opioid consumption at 24 h post-delivery.[19] Epidural morphine can also provide effective post-cesarean analgesia, with 3 mg considered to be an adequate dose to balance analgesia and side effects.[20] A study by Palmer et al.[21] reported an analgesic ceiling effect at 3.75 mg epidural morphine.

Pruritus

Pruritus is one of the most common side effects associated with neuraxial opioid use. Pregnant women are

particularly susceptible and show an incidence as high as 60–100%.[10,22–25] Despite this, one study by Carvalho et al. suggested that for women undergoing cesarean delivery avoiding pain, nausea and vomiting is more important than avoiding pruritus.[26] Pruritus is typically present in the trigeminal distribution (around the eyes and nose) and is usually localized to the facial areas due to the trigeminal nerve being rich in opioid receptors.[27] The exact etiology of opioid-induced pruritus is unclear but several mechanisms have been suggested. These include the presence of an "itch center" in the central nervous system and modulation of the serotonergic pathway.[28] In the medulla a high density of 5-hydroxytryptamine subtype 3 (5HT3) receptors and μ-opioid receptors are present in the superficial layers of the dorsal horn and in the spinal trigeminal nucleus.[28] The latter is thought to be an integrative center for sensory input from the face and the "itch center." At the spinal level the presence of "itch-selective" afferent C-fibers has been demonstrated in animal models.[29] It is postulated that nociception-specific neurons of the dorsal horn inhibit these spinal itch neurons and that, if the inhibition is disrupted, the itch neurons become active. Spinal triggering of itching can be observed by activation of mu-opioid receptors.[29]

Pruritus associated with intrathecal morphine can be a bothersome side effect and no single agent has been shown to be completely effective in its treatment.[10] Although most women receiving neuraxial opioids will experience pruritus, not all require treatment. This may be due to a genetic component that impacts the severity of pruritus. Tsai et al. and Wong et al. examined the genetic variation of the μ-opioid receptor gene (OPRM1) and found a higher incidence of pruritus among parturients carrying the 118AA allele compared with the 118GG and 118AG alleles.[30,31]

Prophylaxis (Table 1)

Several classes of medications have been examined for their efficacy in the prevention of opioid-induced pruritus. These include opioid receptor antagonists, opioid receptor agonist-antagonists, antihistamines, 5HT3 receptor antagonists and dexamethasone.

Opioid receptor antagonists

Lockington et al. found that subcutaneous naloxone (0.4 mg) administered at the end of a cesarean delivery was ineffective for reducing the incidence of pruritus or need for treatment in patients receiving spinal anesthesia that included 25 μg intrathecal fentanyl and 150 μg intrathecal morphine.[32] On the other hand, Luthman et al. found that a naloxone infusion at 0.1 mg/h intravenously (IV) significantly reduced the incidence of intrathecal morphine-induced pruritus compared with control (28% vs. 90.5%, $P<0.001$).[33] Jeon et al. randomized women undergoing elective cesarean delivery to receive a continuous infusion of 6 mg epidural morphine in 0.1% bupivacaine, with or without 1.2 mg of naloxone at 2 mL/h, after receiving an epidural bolus of morphine 4 mg in the post-anesthesia care unit.[34] The incidence of pruritus was significantly lower in the naloxone group compared to the morphine-only group (47% vs. 82%, $P=0.003$). The morphine-only group also had more severe itching compared to the naloxone group ($P=0.001$). Pain scores did not differ significantly between the two groups.[34] The safety of epidural naloxone administration has not, however, been established and it has not been approved for use via this route. A systematic review of randomized trials by Kjellberg et al. found that naloxone, naltrexone and nalbuphine were effective in the prevention of opioid-induced pruritus.[35] Four randomized studies involving IV naloxone were analyzed for dose-responsiveness: the doses of naloxone examined in these four studies were 0.6 μg/kg/h, 0.25 and 1.0 μg/kg/h, 400 μg IV followed by 2.4 μg/kg/h, and 2 μg/kg/h. No graphical evidence of dose-responsiveness was found for IV naloxone doses from 0.25 to 2.4 μg/kg/h.[35] However, the combined data concluded that naloxone was effective compared to control in preventing pruritus, with a number-needed-to-treat (NNT) of 3.5. In this same review, the authors examined two randomized studies investigating oral naltrexone, which demonstrated dose-responsiveness for the anti-pruritic effects. Oral naltrexone 3 mg was not significantly different from control but 6 mg and 9 mg doses were significantly more efficacious than control. With both 6 mg and 9 mg, the average duration of analgesia was shortened compared with control and the 9 mg dose resulted in significantly less satisfactory analgesia compared with 6 mg.[35]

Opioid receptor agonist-antagonists

Opioid receptor agonist-antagonists have also been investigated for the prevention of intrathecal morphine-induced pruritus. Wu et al. reported that IV butorphanol administered as a 1 mg bolus followed by a 24-h infusion (at 0.2 mg/h) reduced the incidence of pruritus compared with placebo (13% vs. 49%, $P<0.001$).[36] Pentazocine is a κ-opioid receptor agonist and μ-receptor partial agonist. Animal studies suggest that activation of k-opioid receptors may attenuate opioid-induced pruritus.[37] Hirabayashi et al. investigated the efficacy of IV pentazocine 15 mg as a bolus in the prevention of intrathecal morphine-induced pruritus, comparing it to normal saline administered after delivery in 119 women who had received 100 μg intrathecal morphine.[38] The IV pentazocine reduced the overall incidence of pruritus within the first 24 h compared to normal saline (estimated relative risk (RR) 0.69, $P=0.007$) and also reduced the severity of pruritus. There were no significant differences in nausea, vomiting or postoperative pain scores between the two groups.[38]

Table 1 Prophylaxis for opioid-induced pruritus

Intervention (number of studies)	Relative risk (95% CI) (number of patients)	Number needed-to-treat (95% CI)
Effective Interventions		
Naloxone infusion[35] (4) 0.25–2.4 μg/kg/h IV infusion	0.43 (0.28 to 0.66) (195)	3.5 (2.4 to 6.3)
Naltrexone[35]		
6 mg oral (2)	0.29 (0.15 to 0.59) (55)	1.9 (1.3 to 3.3)
9 mg oral (1)	0.36 (0.17 to 0.74) (30)	1.7 (1.1 to 3.0)
Nalbulphine[35] (3) 40 mg/12 h IV infusion, 60 μg/kg/h IV infusion and 20–80 μg/mL epidural	0.58 (0.38 to 0.89) (181)	4.2 (2.7 to 9.9)

Intervention (number of studies)	Relative risk (95% CI) (number of patients)
Ineffective interventions	
Propofol[35] (3) 10 mg IV bolus, 10 mg IV bolus + 30 mg/24 h IV infusion and 30 mg/h IV infusion	0.89 (0.69 to 1.15) (179)
Dexamethasone[46] (6) 2.5 –10 IV	0.98 (0.84 to 1.15) (520)
5HT3 receptor antagonists[42] (5) ondansetron 4 mg and 8 mg IV tropisetron 5 mg IV granisetron 3 mg IV	0.94 (0.81 to 1.09) (536)

Results compiled from meta-analyses by Allen et al.[46], George et al.[42], and Kjellberg et al.[35]; IV: intravenous; CI: confidence interval; 5HT3: 5-hydroxy-tryptamine$_3$.

Peripheral opioid receptor antagonists

Peripheral opioid receptor antagonists have been investigated for the prevention of intrathecal opioid-induced pruritus. Paech et al. randomized parturients undergoing elective cesarean delivery with 100 μg of intrathecal morphine to receive either subcutaneous methylnaltrexone 12 mg or saline during skin closure.[39] Of the 137 patients who completed the study, the primary outcome of the incidence and severity of pruritus was not significantly different between the methylnaltrexone and placebo groups. However, secondary outcomes including the percentage of moderate to severe pruritus and the number of patients requiring treatment for pruritus were lower in the methylnaltrexone group compared with the placebo group.[39]

Antihistamines

Historically, antihistamines have been used as first line agents for histamine-related causes of pruritus but have had little to no effect on opioid-induced pruritus. Diphenhydramine 30 mg IV bolus administered immediately after delivery was not effective in the prevention of opioid-induced pruritus compared with placebo (80% vs. 85%) in women receiving 150 μg intrathecal morphine.[40]

Serotonin receptor antagonists

The 5HT3 antagonists such as ondansetron have been investigated for the prevention of neuraxial opioid-induced pruritus, with mixed results. Bonnet et al. performed a systematic review of 15 randomized controlled trials and found that treatment with a single IV bolus of a 5HT3 antagonist significantly reduced the incidence and severity of pruritus after neuraxial opioid administration.[41] This meta-analysis was not, however, restricted to women undergoing cesarean delivery. A more recent systematic review by George et al. examined nine randomized controlled trials totaling 1152 women undergoing cesarean delivery.[42] The 5HT3 receptor antagonists examined in these studies were tropisetron, granisetron and ondansetron. Eight trials used a fixed dose of drug (tropisetron 5 mg IV bolus, granisetron 1 mg and 3 mg IV bolus, and ondansetron 4 mg and 8 mg IV bolus) and one trial used an ondansetron 0.1 mg/kg IV bolus, this being included with the 8 mg IV bolus for the meta-analysis. George et al. found that the incidence of

pruritus was not reduced with IV 5HT3 receptor antagonist prophylaxis compared with placebo (80.7% vs. 85.8%) but that these drugs reduced the incidence of severe pruritus and the need for treatment of pruritus.[42]

There is an abundance of 5HT3 receptors in the medulla and dorsal horn of the spinal cord. Therefore, epidural 5HT3 receptor antagonists may be effective in the prophylaxis of neuraxial opioid-induced pruritus. Han et al. performed a randomized controlled trial to investigate the efficacy of epidural ondansetron compared with IV ondansetron in the prophylaxis of opioid-induced pruritus in elective cesarean delivery.[43] The first portion of the study was an animal study investigating the safety of epidural ondansetron administered to male Sprague-Dawley rats. Behavioral and histological studies did not reveal any significant change in the rats receiving epidural ondansetron compared with epidural saline. The clinical portion of the study randomized women undergoing elective cesarean delivery who had received 7 mg epidural morphine in 100 mL of 0.3% ropivacaine to receive 8 mg ondansetron epidurally or IV (at 0.167 μg/h) for 48 h. The overall incidence and severity of pruritus was significantly lower in the epidural ondansetron group compared to the IV group at 24 h (0% vs. 10% moderate pruritus) and 48 h (15% vs. 30% mild pruritus) postoperatively (P <0.05).[43] Further studies are needed to confirm the safety of epidural ondansetron in humans and its use via this route is not approved.

Propofol

Sub-hypnotic doses of propofol have been investigated for the prevention of neuraxial opioid-induced pruritus, with conflicting results. Torn et al. found a decrease in the incidence of pruritus associated with a sub-hypnotic dose of propofol (10 mg IV bolus followed by 30 mg/24 h infusion) administered after spinal anesthesia in an orthopedic surgical population, while Warwick et al. found that a sub-hypnotic dose of propofol (10 mg IV bolus) administered after delivery did not prevent pruritus in an obstetric population.[44,45]

Dexamethasone

In a systematic review by Allen et al., six studies examining the incidence of pruritus associated with neuraxial morphine in patients receiving IV dexamethasone or placebo found that dexamethasone did not significantly reduce the incidence of pruritus.[46] Intrathecal dexamethasone has been shown to be effective in the prevention of neuraxial opioid-induced pruritus by Abdel-Aleem et al.[47] They reported that 8 mg intrathecal dexamethasone reduced the risk of itching in women undergoing cesarean delivery and receiving 200 μg intrathecal morphine, with a NNT of 4.35.[47] The safety of intrathecal dexamethasone, however, needs to be established and its administration by this route has not been approved.

Treatment (Table 2)

Opioid receptor antagonists

Opioid receptor antagonists and mixed agonist-antagonists have been investigated for the treatment of opioid-induced pruritus. A study by Charuluxananan et al. reported that the opioid receptor agonist–antagonist nalbuphine, at a dose of 3 mg IV bolus, was more effective than a propofol 20 mg IV bolus for the treatment of moderate to severe intrathecal morphine-induced pruritus (incidence 61% vs 83% P <0.001).[22] Intravenous nalbuphine was also more effective than IV diphenhydramine for the treatment of pruritus (incidence 43% vs 83%, P <0.01).[48] In a dose–response study, Somrat et al. reported that IV nalbuphine in doses of 2, 3 and 4 mg was effective for the treatment of intrathecal morphine-induced pruritus but that there was some reversal of analgesia with the 4 mg dose. The authors concluded that 2–3 mg might be the optimal nalbuphine dose for the treatment of pruritus.[49] Butorphanol given as an IV loading dose of 1 mg followed by infusion of 0.2 mg/h for 24 h was also more effective than placebo in reducing the incidence (13% vs. 48.9%, P <0.001) and severity of pruritus in women who had received spinal anesthesia including 100 μg intrathecal morphine.[36]

Antihistamines

The efficacy of antihistamines in treating neuraxial morphine-induced pruritus is questionable.[50] A randomized clinical trial by Alhashemi et al. comparing IV nalbuphine (5 mg and 10 mg) and IV diphenhydramine (25 mg and 50 mg) found that treatment of intrathecal morphine-induced pruritus was more successful with IV nalbuphine (incidence 43% vs 83%, P<0.01).[48] Antihistamines such as diphenhydramine and hydroxyzine produce sedation and any presumed effect on pruritus may be related to inducing sedation and sleep as opposed to decreasing the severity of pruritus.[51]

Serotonin receptor antagonists

Studies investigating 5HT3 receptor antagonists' efficacy for the treatment of opioid-induced pruritus have produced mixed results. Charuluxananan et al. reported that 4 mg IV ondansetron was significantly more effective than normal saline for the treatment of intrathecal morphine-induced pruritus (36% vs 80%, P <0.001).[24] Tamdee et al. found that 15 mg IV pentazocine was more effective against opioid-induced pruritus than was 4 mg IV ondansetron (80.8% vs. 96.1%, P=0.001); and that recurrence after treatment with IV pentazocine was less likely (12% vs. 32.1%, P=0.001).[25] Siddik-Sayyid et al. reported that 4 mg IV ondansetron was comparable to 25 mg IV diphenhydramine in the treatment success of moderate to severe intrathecal morphine-induced pruritus. The recurrence of pruritus following treatment with either drug was also similar,

Table 2 Treatment for opioid-induced pruritus

Investigator	Intervention (number of patients)	Success rate (%)	*P*-value
Charuluxananan et al.[22]	nalbuphine 3 mg IV bolus (91) vs. propofol 20 mg IV bolus (90)	83% vs. 61%	<0.001
Alhashemi et al.[48]	nalbuphine 5–10 mg IV bolus (40) vs. diphenhydramine 25–50 mg IV bolus (40)	83% vs. 43%	<0.01
Wu et al.[36]	butorphanol 1 mg IV bolus + 0.2 mg/h infusion (46) vs. saline (45)	87% vs. 51%	<0.001
Charuluxananan et al.[24]	ondansetron 4 mg IV bolus (41) vs. saline (39)	80% vs. 36%	<0.001
Tamdee et al.[25]	pentozocine 15 mg IV bolus (104) vs. ondansetron 4 mg IV bolus (104)	96.1% vs. 80.8%	0.001
Siddik-Sayyid et al.[52]	ondansetron 4 mg IV bolus (57) vs. diphenhydramine 25 mg IV bolus (56)	70% vs. 70%	0.79

Table compiled from studies by Charuluxananan et al.[22], Alhashemi et al.[48], Wu et al.[36], Charuluxananan et al.[24], Tamdee et al.[25], and Siddik-Sayyid et al.[52]; IV: intravenous.

and up to 50% of patients in the study required rescue treatment with 0.04 mg IV naloxone because of either treatment failure or the recurrence of pruritus.[52] Another study by Kung et al. randomized parturients into three groups: prophylaxis, treatment or control.[53] The prophylaxis group received ondansetron 8 mg IV bolus at cord clamping and normal saline 4 mL IV bolus for treatment of pruritus in the post-anesthesia care unit; the treatment group received normal saline 4 mL IV bolus at cord clamping and ondansetron 8 mg IV bolus as required in the post-anesthesia care unit; the control group received normal saline 4 mL IV bolus at both time points. This study was terminated early at an interim analysis due to no observed differences between the groups in the rate or severity of pruritus or in the request for treatment.

Nausea and vomiting

Nausea and vomiting after cesarean delivery under regional anesthesia are common symptoms and their etiology is multifactorial. Nausea and vomiting associated with neuraxial opioid use are thought to be a result of vascular uptake of opioids and are dose-related.[50] Central nervous system control of nausea and vomiting is predominantly via the medulla in two distinct areas: the chemoreceptor trigger zone located in the area postrema on the floor of the fourth ventricle where the blood-brain barrier is poorly developed; and the vomiting center in the lateral reticular formation.[54] The chemoreceptor trigger zone is highly vascularized while the vomiting center integrates input from the gastrointestinal tract, higher cortex, chemoreceptor trigger zone, labyrinth and intracranial pressure receptors. These areas are densely populated with dopaminergic, muscarinic, serotonergic, histaminergic, neurokinin-1 and opioid receptors, and it has been postulated that blocking these receptors may be effective in preventing and/or treating opioid-induced nausea and vomiting.

Nausea and vomiting have an incidence of up to 60–80% in parturients receiving neuraxial morphine.[55–57] There is an analgesic ceiling dose above which intrathecal and epidural opioids increase nausea and vomiting with no further improvement in analgesia.[12] A meta-analysis by Sultan et al. compared the effects of different intrathecal morphine doses (low dose 50–100 μg vs. high dose >100–250 μg) and found a lower risk of nausea and vomiting in the lower-dose group (odds ratio [OR] 0.44,95% CI 0.27 to 0.73, P=0.002) but no difference in postoperative pain scores at 12 h and 24 h or in opioid consumption at 24 h.[19]

Prophylaxis (Table 3)

A number of pharmacologic agents have been investigated for the prevention of nausea and vomiting associated with neuraxial opioids.

Dexamethasone

The use of dexamethasone for the prophylaxis of postoperative nausea and vomiting (PONV) in this patient population has had mixed results. A systematic review by Allen et al. examined eight clinical trials using bolus IV dexamethasone in doses ranging from 2.5 to 8 mg; four studies were in women undergoing cesarean delivery and four in women having abdominal hysterectomy and receiving neuraxial morphine.[46] The authors found that IV dexamethasone reduced the incidence of postoperative nausea (RR 0.68, 95% CI 0.51 to 0.90), postoperative vomiting (RR 0.70, 95% CI 0.52 to 0.96), and use of rescue anti-emetic compared to placebo (RR 0.53, 95% CI 0.29 to 0.98) following cesarean delivery but that there was no apparent dose-response in its antiemetic effect. A Cochrane review by Griffith et al. examined the effect of IV dexamethasone on the prevention of PONV in women undergoing cesarean delivery.[58] Two studies involving 235 women were analyzed and no reduction was found in postoperative nausea (IV dexamethasone 2.5–10 mg, RR 0.75, 95% CI 0.52 to 1.07). Analysis of three studies involving 295 women found no effect on postoperative vomiting from IV dexamethasone in doses of 2.5–10 mg (RR 0.78, 95% CI 0.54 to

Table 3 Prophylaxis for opioid-induced nausea and vomiting

Intervention (number of studies)	Postoperative nausea (PON) RR (95% CI) (number of patients)	Postoperative vomiting (POV) RR (95% CI) (number of patients)
Effective interventions		
5HT3 receptor antagonists[58] (four studies for PON, five for POV) ondansetron 4 mg and 8 mg IV granisetron 1 mg and 3 mg IV	0.40 (0.25 to 0.64) (405)	0.50 (0.32 to 0.77) (565)
Dopamine antagonists[58] (five studies for PONB, six for POV) metoclopramide 10 mg, 20 mg and 0.15 mg/kg IV droperidol 0.5 mg, 0.625 mg and 1.25 mg IV	0.60 (0.40 to 0.91) (412)	0.57 (0.36 to 0.91) (472)
Antihistamines[58] (3) dimenhydrate 50 mg and 100 mg IV cyclizine 50 mg IV	0.38 (0.26 to 0.59) (365)	0.50 (0.30 to 0.86) (184)

Intervention (number of studies)	Postoperative nausea RR (95% CI) (number of patients)	Postoperative vomiting RR (95% CI) (number of patients)
Ineffective interventions		
Dexamethasone[58] (three studies)* dexamethasone 2.5–10 mg IV	0.75 (0.52 to 1.07) (235)	0.78 (0.54 to 1.12) (295)
Nalbuphine[58] (one study) 4 mg IV	0.75 (0.39 to 1.45) (120)	1.25 (0.35 to 4.43) (120)
P6 stimulation[58] (three studies)	0.83 (0.68 to 1) (429)	0.69 (0.45 to 1.06) (429)

Results compiled from meta-analysis by Griffith et al.[58] *Meta-analysis by Allen et al.[46] found that dexamethasone was effective compared to placebo for PON: (23% vs. 41%, RR [95% CI] 0.68 [0.51 to 0.90]) and for POV: (20% vs. 36%, RR [95% CI] 0.70 [0.52 to 0.96]) in subgroup analysis for cesarean delivery.; IV: intravenous; RR: relative risk; CI: confidence interval; 5HT3: 5-hydroxy-tryptamine$_3$.

1.12). Given these wide confidence intervals, more studies are needed to investigate the anti-emetic effect of dexamethasone in this patient population.

5HT3 receptor antagonists

George et al. conducted a systematic review and meta-analysis of nine clinical trials involving 1152 women to examine the efficacy of 5HT3 receptor antagonists for the prevention of PONV in women receiving intrathecal morphine for cesarean delivery.[42] Clinical trials utilizing IV ondansetron in doses of 4 mg and 8 mg, IV granisetron 3 mg and IV tropisetron 5 mg were included. There was a significant reduction in the incidence of postoperative nausea (NNT 9) and need for rescue anti-emetic treatment (NNT 7) with 5HT3 receptor antagonists when compared to placebo. There was no difference in anti-emetic efficacy between ondansetron doses of 4 mg and 8 mg. A Cochrane review by Griffith et al. also confirmed these findings. Compared to placebo there was a significant reduction in postoperative nausea (four studies involving 405 women) and also in postoperative vomiting (five studies involving 565 women) associated with 5HT3 receptor antagonists.[58] One study in the analysis compared ondansetron 4 mg and 8 mg and did not identify a significant difference in PONV between the two groups.[58]

Dopaminergic antagonists

Studies investigating the efficacy of dopaminergic antagonists in the prevention of PONV have produced mixed results. A Cochrane review by Griffith et al. found that dopaminergic antagonists were effective in preventing postoperative nausea (five studies, 412 women) and vomiting (six studies, 472 women) compared to placebo.[58] Some of the studies included in this review, however, did not use contemporary anesthetic techniques, and did not involve the use of intrathecal morphine or investigated droperidol, the use of which has significantly declined following a United States of America Food and Drug Administration 'black box' warning. A randomized controlled trial by Habib et al. investigating the efficacy of metoclopramide alone or in combination with ondansetron, compared to placebo in women receiving 150 μg intrathecal morphine, found that metoclopramide alone was ineffective for PONV prophylaxis. Metoclopramide in combination with ondansetron reduced PONV only in the first two hours after surgery.[59]

Antihistamines

Antihistamines have been studied for their efficacy as prophylaxis against opioid-induced PONV. In a study by Nortcliffe et al. cyclizine 50 mg IV was compared

to dexamethasone 8 mg IV and placebo given at the completion of surgery in 99 women undergoing elective cesarean delivery and receiving 200 μg intrathecal morphine.[60] The incidence of nausea was significantly lower in patients receiving cyclizine compared to dexamethasone or placebo (33% vs. 60% and 67% respectively, $P < 0.05$). The severity of nausea and number of vomiting episodes were also reduced three to six hours postoperatively in the cyclizine group compared to the placebo group and at three hours compared to the dexamethasone group. A Cochrane review comparing antihistamines to placebo found them to be effective in the prevention of postoperative nausea (three studies, 365 women) and postoperative vomiting (two studies, 184 women).[58] This same analysis reported no difference in efficacy between antihistamines and dopaminergic antagonists for the prevention of postoperative nausea but a greater reduction in postoperative vomiting with antihistamines (one study, 119 women).[58]

Non-pharmacologic techniques

Non-pharmacologic methods to manage nausea and vomiting in women undergoing cesarean delivery have gained some interest over the years. The findings from different studies have been inconsistent. In a systematic review by Allen and Habib, six randomized controlled trials involving 649 patients compared P6 stimulation with placebo in women undergoing cesarean delivery with neuraxial anesthesia. Neuraxial opioids were used in all but one study. Four of the studies reported on postoperative outcomes; one study reported a significant reduction in postoperative nausea and two studies reported a significant reduction in postoperative vomiting. One study reported a significant reduction in the need for rescue anti-emetic therapy.[61] A Cochrane review comparing acupressure or acupuncture with placebo included three studies involving 429 women and found no reduction in PONV from P6 stimulation.[58]

Combination anti-emetic therapy

Combination anti-emetic therapy has improved PONV prophylaxis in the general surgical population compared to monotherapy but there are very few studies in the obstetric population. Habib et al. found that combination therapy with metoclopramide 10 mg IV and ondansetron 4 mg IV was more effective than metoclopramide alone or placebo among women who received spinal anesthesia with 15 μg fentanyl and 150 μg morphine, and in whom blood pressure was maintained within 20% of baseline by a prophylactic phenylephrine infusion. However, efficacy was limited to the early postoperative period (two hours).[59] A study by Wu et al. found that the combination of dexamethasone 4 mg IV with droperidol 0.625 mg IV, and droperidol 1.25 mg IV alone, were more effective than dexamethasone 8 mg IV alone or placebo in reducing PONV in the first 24 h after surgery in women undergoing cesarean delivery with 200 μg intrathecal morphine.[62] Dexamethasone alone was not an effective anti-emetic in this study.

Treatment

While there are several studies evaluating prophylaxis against neuraxial opioid-induced nausea and vomiting, there is a scarcity of studies on its treatment. Research from the surgical population undergoing general anesthesia provides some general principles of treatment. In patients who have received anti-emetic prophylaxis, best evidence indicates that PONV occurring in the first six hours following the administration of the prophylactic anti-emetic should be treated with a drug working on a different receptor compared to the agent used for prophylaxis.[63–65] After six hours, the same agent used for prophylaxis can be repeated again for treatment, except if long-acting agents such as scopolamine, dexamethasone or aprepitant have been administered.[66] If the patient has received no prior prophylaxis, treatment with a low dose 5HT3 receptor antagonist might be considered as a first-line agent.[66] Anti-emetics that take some time to exert their anti-emetic effects such as dexamethasone, aprepitant and scopolamine are not appropriate for the treatment of established PONV.[64,66]

Respiratory depression

Although respiratory depression is a rare complication of neuraxial opioids, occurring in 0–0.9% of cases,[15,16] it can result in debilitating and/or devastating sequelae. Lee et al. performed a closed-claims analysis of postoperative opioid-induced respiratory depression in 357 acute pain claims and found that respiratory depression was "possible, probable or definite in 92 claims."[13] Although this analysis did not include any obstetric patients, neuraxial opioids were implicated in 36 of the 92 claims. More than 50% of the patients experiencing respiratory depression died and another 22% suffered severe brain damage. Anesthesia care was deemed to be less than appropriate in 40% of the claims and almost all the claims (97%) were judged as "probably or possibly preventable by better monitoring".[13] Pregnant women may be at lower risk of respiratory depression due to the physiological changes of pregnancy such as increased respiratory rate, secondary to a progesterone effect, and the fact that most are younger and have fewer comorbidities compared to the general surgical population.[50]

One of the challenges of discussing respiratory depression is the fact that a standard definition does not exist.[67] Respiratory rate and pulse oximetry are often used to determine the incidence of respiratory depression but other parameters include hypercarbia (>45 mmHg from arterial blood), low oxygen saturation (<92%), sedation, depressed ventilatory response to

hypoxia or hypercarbia, and the need for naloxone treatment.[68] The incidence of respiratory depression therefore depends on the definition used and there is wide variability between studies. In a systematic review of respiratory depression following cesarean delivery using neuraxial morphine and diamorphine, Sharawi et al. assessed the prevalence of clinically significant respiratory depression in obstetric patients who underwent cesarean delivery. Respiratory depression was defined as the presence of one or more of the following: an airway intervention, oxygen therapy, pharmacological therapy (i.e. opioid antagonists that reversed the effects) and/or excessive sedation requiring more than verbal stimulation to rouse the patient.[14] Of 18 452 patients analyzed, 11 patients had definite and clinically significant respiratory depression, equating to a rate of 5.96 per 10 000 (95% CI 2.2 to 11.3): all cases involved the administration of neuraxial morphine and none involved neuraxial diamorphine.[14]

Monitoring for respiratory depression

The American Society of Anesthesiologists (ASA) Task Force on Neuraxial Opioids Practice Guidelines recommend that "all patients receiving neuraxial opioids should be monitored for adequacy of ventilation, oxygenation, and level of consciousness and increased monitoring may be warranted in patients at increased risk of respiratory depression".[69] Failure to respond to hypercapnia (at a threshold of 50 mmHg in normal lung) is the most sensitive measure of respiratory depression. Hypercapnia is closely associated with hypoxemia and may be an earlier sign for respiratory depression, particularly in the setting of supplemental oxygen therapy where desaturation may not be observed on pulse oximetry.[70] Dalchow et al. used a transcutaneous carbon dioxide monitor (the Topological Oscillation Search with Kinematical Analysis or TOSCA) for the detection of respiratory depression, defined as oxygen saturation <90%, transcutaneous carbon dioxide levels >7 kPa (52.5 mmHg) for more than two minutes or the need for medical intervention for clinically significant respiratory depression, in women who received 300 μg of intrathecal diamorphine (equivalent to 100 μg intrathecal morphine). They found a higher incidence of respiratory depression using TOSCA (17.8%) compared to using respiratory rate or pulse oximetry (0%).[71] Subsequently, Bauchat et al. used the TOSCA monitor to estimate the incidence of respiratory depression (defined as transcutaneous carbon dioxide >50 mmHg for ≥2 min) in women who received 150 μg intrathecal morphine for post-cesarean analgesia. They reported an incidence of respiratory depression of 32%.[68] This did not appear to be clinically relevant, however, since no medical intervention was required in either TOSCA study. Weiniger et al. conducted a prospective study to investigate the number of apneic events (defined as end-tidal carbon dioxide <5 mmHg for 30–120 s) using continuous capnography and pulse oximetry in women who underwent cesarean delivery with 150 μg intrathecal morphine.[72] Of the 80 women enrolled, 53% had an apneic event and the 198 events detected by capnography lasted on average 57 s. No events were observed by hourly nursing observation of respiratory rate and a rate >14 breaths per minute was recorded at all times in all women. Of note, however, none of the events observed led to a clinically relevant respiratory adverse event.[72]

The ASA Taskforce recommends monitoring of patients following neuraxial opioids but a preferred modality is not specified.[69] The taskforce concluded that current literature is insufficient to determine whether continuous monitoring with pulse oximetry, electrocardiogram or ventilation is associated with improved detection of respiratory depression or hypoxemia in patients administered neuraxial opioids. The recommendations include using the lowest effective dose of neuraxial opioid and monitoring for adequacy of ventilation, oxygenation and level of consciousness. Increased monitoring if there is concurrent use of parenteral opioids and other sedatives (e.g. benzodiazepines, magnesium) is suggested. The current recommendation for neuraxial morphine monitoring is every hour for the first 12 h and then every two hours for the next 12 h, for a minimum of 24 h.[69] The guidelines also recommend identification of patients at increased risk of respiratory depression, such as those with obstructive sleep apnea, as these patients may need additional monitoring. It is important to note that these guidelines address the general surgical population and are not specific to the obstetric population.

In order to specifically address the obstetric population, the Society of Obstetric Anesthesia and Perinatology (SOAP) has produced consensus statement recommendations for the prevention and detection of respiratory depression associated with neuraxial morphine in women undergoing cesarean delivery.[73] As the majority of parturients are young, low-risk, relatively healthy and receive a single dose of neuraxial morphine in a non-sedated setting, the SOAP Taskforce suggested that the frequency of monitoring recommended by the ASA guidelines may be overly aggressive for the obstetric population. Therefore, the SOAP Taskforce recommends that after ultra-low dose neuraxial opioid (intrathecal morphine <50 μg or epidural morphine ≤1 mg), no additional monitoring beyond routine institutional monitoring is required. For low-dose morphine (intrathecal morphine >50–150 μg or epidural morphine >1–3 mg), the Taskforce recommends monitoring of respiratory rate and sedation scores every two hours for 12 h in addition to routine institutional monitoring. For high-dose morphine (intrathecal morphine >150 μg or epidural morphine >3 mg), the Taskforce

agrees that it is reasonable to monitor based on ASA guidelines. Finally, the SOAP Taskforce recommends risk stratification and identification of at-risk patients to tailor the intensity, frequency and duration of respiratory monitoring.

Hypothermia

Hypothermia during cesarean delivery is very common and several mechanisms may contribute to its occurrence. For instance, local anesthetics used in neuraxial anesthesia are believed to be associated with hypothermia by causing vasodilation below the level of sensory blockade, leading to increased radiant heat loss, by decreasing vasoconstriction due to obtunded afferent input, and decreasing the patient's ability to maintain poikilothermia.[74] Intrathecal morphine has been reported to further contribute to hypothermia, but the mechanism in this setting is not completely understood.[75] Several case reports have described persistent hypothermia after spinal anesthesia with intrathecal morphine. Symptoms usually include nausea, diaphoresis and, sometimes, feeling hot. The duration of hypothermia in those case reports varied widely from a short period of two hours to as long as 22 h and treatment was successful in most cases using IV naloxone 0.04 mg or IV lorazepam 0.5–1 mg.[17,75–78] In a randomized controlled trial of 60 parturients undergoing cesarean delivery under spinal anesthesia, Hui et al. reported a greater decrease in mean (SD) tympanic membrane temperature in those randomized to receive 150 μg intrathecal morphine with bupivacaine [1.11 (0.61)°C] compared to those who received intrathecal bupivacaine with added saline [0.76 (0.39)°C, P=0.01].[79] The time to the nadir of temperature was also significantly longer (59.5 (17.6) min vs. 50.4 (15.9) min respectively, P=0.047).

Hess et al. described a two-part study to determine the incidence of hypothermia, defined as a sublingual temperature <35.8°C, in women undergoing cesarean delivery under spinal anesthesia with intrathecal morphine.[78] Part one of the study was a case series, in which the authors collected information about women who developed hypothermia and the associated symptoms of feeling warm or diaphoretic in the recovery room after cesarean delivery, under spinal anesthesia and over a six-month period. During this time period they identified 14 out of 193 (7%) elective cases who received intrathecal morphine and developed symptomatic hypothermia, defined as a subjective warm or cold sensation, shivering or diaphoresis. Treatment for hypothermia was either conservative (consisting of warmed blankets, heat lamps or a forced-air warmer) or medical (consisting of lorazepam 0.5–1 mg IV) at the individual clinician's discretion. All 14 women reported feeling diaphoretic and hot. The mean (range) preoperative temperature was 36.7°C (36.4–37.0°C), and the mean postoperative temperature was 34.9°C (34.0–35.3°C). Four of the 14 patients were treated conservatively and remained hypothermic for hours, with a gradual temperature increase over 4–6 h postoperatively. The other 10 patients were treated with lorazepam and eight had an immediate cessation of symptoms and a return to normothermic temperatures within 90 min. The other two patients had a delayed return to normothermia but improvement in their symptoms. Based on the results of the case series, the investigators performed an observational study to determine the incidence of symptomatic hypothermia, defined as a sublingual temperature <35.8°C with associated symptoms of diaphoresis or feeling hot. One hundred consecutive parturients who delivered by elective cesarean section under spinal anesthesia with 250 μg intrathecal morphine were observed.[78] Hypothermia occurred in 32% but 80% of these patients (26 of 32) reported no symptoms. Symptomatic hypothermia was, therefore, observed in only 6% of cases. The temperature decline of these six symptomatic hypothermic patients was greater than that of the 26 asymptomatic patients with hypothermia (2.6°C vs. 1.6°C, P=0.04). The temperature of the asymptomatic patients returned to normal within 30 min of regression of spinal anesthesia, whereas in symptomatic patients the temperature remained below 35.8°C for several hours (range 120–360 min). Animal studies have highlighted the role that stress seems to play in hypothermia as pretreatment with diazepam prevented morphine-induced hypothermia in rats while flumazenil potentiated the hypothermic action of morphine.[80] The fact that lorazepam reversed symptomatic hypothermia in 80% of the parturients in this study is of interest and warrants further study.

In summary, treatment of intrathecal morphine-associated postoperative hypothermia warrants more investigation. Case reports and observational studies have demonstrated treatment success with naloxone and benzodiazepines when routine warming methods (blankets, warmed IV fluids, forced-air body-surface warming) have failed. A standard approach is not defined in the literature and as the mechanism of hypothermia is not well understood, morphine-induced hypothermia is often a diagnosis of exclusion after other treatments have failed. Further studies may help to elucidate its mechanism and the impact on maternal well-being.

Conclusions

Neuraxial morphine is considered a gold standard for post-cesarean delivery analgesia. Multiple studies have demonstrated that the overall safety profile in this patient population is quite high. Although side effects occur, they are typically mild and self-limiting. The more common side effects such as pruritus, nausea

and vomiting seem to be dose-related, so the minimum effective dose should be used. The most serious complication associated with neuraxial opioid use is respiratory depression, which has a very low incidence of <1% in the obstetric patient population. Obtaining a thorough history and physical examination to identify at-risk patients, employing appropriate monitoring after its administration, coupled with careful dose selection, can further reduce the risk of this rare life-threatening side effect. Hypothermia is multifactorial but it appears that intrathecal morphine can contribute to its occurrence in some cases. Further studies are needed to understand the mechanisms involved and to better elucidate its impact on maternal and fetal outcomes.

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