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Case Report

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Strategy for Postoperative Nausea and Vomiting After Cesarean Section: A Literature Review

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Introduction

Postoperative nausea and vomiting (PONV) as a common side effect caused unpleasant experience after cesarean section. We searched literatures in the past five years from PubMed and summarized how to prevent PONV.

Keywords: Cesarean Section; Opioid Induced Nausea and Vomiting; Postoperative Nausea and Vomiting

Introduction

Post operative nausea and vomiting (PONV) as a common side effect occurs 20-30% in all patients and 70%-80% in high risk patients [1,2]. PONV is an unpleasant experience usually associated with poor satisfaction. The risk factors of PONV is commonly including female sex, nonsmoking, younger age and preoperative opioid use etc [2,3]. Cesarean Section (CS) as a way for childbirth, is popular worldwide. Liu et al. reported the CS rate by analyzing 160,278,075 live cesarean births had increased from 28.8% in 2008 and to 36.7% in 2018 in China [3]. The World Health Organization (WHO) reported that CS rate was up to 25.7% worldwide, higher above 40% in Latin America [4,5]. In the USA, the prevalence rate of CS was also raised from 5.5% in 1970 to 32.2% in 2014 [6,7]. CS estimated to take account of 7% of all surgical procedures worldwide [8]. Different from the vaginal delivery, the patients with CS suffer stronger pain postoperatively. Traditionally, as first-line analgesia, more opioids are consumed after CS. Evidences showed the consumption of opioids in the United States increased fourfold from 1999 to 2015 [9]. The reason of PONV after CS has not been defined. It mostly focused on hypotension, opioid consumption, Peritoneal Cavity Saline Irrigation (PCSI) intraoperatively and

so on. Hypotension which occurs commonly in cesarean section under spinal anesthesia, is associated with high incidence of nausea and vomiting intraoperative and early postoperative. The treatment of hypotension mostly focuses on fluid resuscitation and vasopressor administration [10,11]. Keeping the maternal blood pressure decreased no more than 20% of baseline should reduce the incidence of nausea and vomiting intraoperative and early postoperative [12]. However, which vasopressor and how to administrate is better for preventing nausea and vomiting intraoperative and early postoperative still undefined.

The mechanisms of Opioid Induced Nausea and Vomiting (OINV) are still not clear, even so, the multiple mechanisms of peripheral and central components had been mentioned [13]. For example, it had been postulated that morphine and synthetic opioids increase vestibular sensitivity, perhaps by opioids activating μ opioid receptors on the vestibular epithelium [14]. The vestibular apparatus provided direct input into the vomiting center by the Histamine H1 and Cholinergic (AChM) pathways [15]. In addition, the opioids direct effected on the brainstem chemoreceptor trigger zone of the vomiting center by stimulating μ - and δ -opioid receptors [16] as well as 5-HT₃ [17] in that area. Moreover, the opioids can also induce gastrointestinal dysfunctions via vagal afferent fibers [18,19] such as gastrointestinal motility [20] bowel distention and cramping [21,22]. These inputs project to the nucleus of the solitary

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tract, which potentially had output pathways to local brainstem areas to produce the vomiting reflex and projections to the mid- and forebrain for the perception of nausea [23].

The PCSI increased the incidence of postoperative nausea ($P<0.001$) and vomiting ($P=0.008$). At the same time, the postoperative use of antiemetic was also higher in PCSI group [24]. There was some difference that another meta-analysis which focus on PCSI indicated that the PCSI increased the incidence of postoperative nausea. However, the incidence of postoperative vomiting seemed have no statistical difference (RR=1.65, 95% CI 0.74-3.67) [25]. Tramadol, as a routine analgesia for pain release after cesarean section, commonly causes the side effective of nausea and vomiting. However, the recent study presented Tramadol was not associated with increasing incidence of PONV compared with Sufentanil. ($P=0.14$) [26]. Recent result of researches showed that Neostigmine as an adjuvant administrated intrathecally (IT) can prolonged the sensory and motor blockade [27,28]. Unfortunately, IT neostigmine increased incidence of PONV [29,30].

Materials and Methods

Publication searching was conducting using PubMed with “PONV”, “Cesarean Section” from 2015 to early 2020, concluded the opioids in different ways causing PONV and medications to prevent PONV.

Result

Total seventy-five articles have been recruited in this review.

Opioids in different ways

Neuraxial opioids: Neuraxial opioid was usually recommended in clinical in recent years because of it providing sufficient analgesia postoperative. However, the most common complications are PONV and pruritus [31,32]. One review indicated that the relationship between neuraxial opioids and PONV depended on vascular uptake and dose-related [33,34] compared 0.1mg Morphine and 0.2mg Morphine administrated intrathecally (IT). The incidence of nausea (42% vs. 15%; $P=0.0005$) and vomiting (20% vs. 8%; $P=0.007$) were higher in those who was given 0.2mg compared with 0.1mg. Similarly, another meta-analysis also pointed out the incidence of PONV was lower in low dose IT Morphine (50-100mcg) group than in high dose IT Morphine (100-250mcg) group (OR, 0.44 [95% CI, 0.27-0.73]; $P=0.002$) [35,36], there was no statistical difference between 0.1mg IT Morphine group and Transversus Abdominis Plane (TAP) block group ($P=0.907$). Another retrospective study supported that although the incidence of pruritus was high in IT Morphine (0.1mg) group, there was no statistical difference for the incidence of PONV in IT Morphine (0.1mg) group compared with local anesthetic infusion in epidural catheter ($P=0.64$) [37]. Hydromorphone as a long-act analgesia alternative to Morphine was currently [38] compared with different dose in epidural among all groups (0, 0.2mg, 0.4mg, 0.6mg). There was no statistical different among all groups ($P<0.05$). Fentanyl as a short-act opioid was administrated intrathecally in cesarean section. The result of one randomized controlled study showed that there was no significant difference between IT 25mcg Fentanyl and placebo group ($P=0.67$). The reason of this result was undefined, it was probably because of lower intravenous pethidine postoperative consumption in Patient Control Anesthesia (PCA)

in Fentanyl group (92.1 ± 41.1 vs. 158.3 ± 76.4 , $P=0.002$) [39]. Sometimes, to pursue prolonged anesthesia intraoperatively and analgesia postoperatively, anesthesiologists would administrate long-act opioid plus short-act opioid intrathecally [40]. Compared IT 0.1mg Morphine to IT 0.1mg Morphine plus 25mcg Fentanyl, the incidence of PONV was significant higher in group Morphine plus Fentanyl ($P=0.01$).

Oral opioids: Compared to intravenous (IV) opioids, oral opioid is an alternative choose to control the pain postoperatively [41]. In stead of giving IV PCA, oral oxycodone reduced the incidence of nausea at 4hour postoperative ($P=0.001$) and vomiting at 8hour postoperative ($P=0.010$).

Opioids administration in TAP block: Very limited evidence illustrated the effective of PONV prevention on opioids in TAP block [42]. As compared 0.25% bupivacaine plus 50mcg fentanyl and 0.25% bupivacaine administration in TAP block, the result showed that there was no significant difference in the incidence of PONV.

PONV Prevention

Antiemetic: The guideline for postoperative care by Enhanced Recovery After Surgery (ERAS) society pointed out that the antiemetic agents were effective for PONV prevention [11]. Ondansetron which is antiemetic, non-sedative and no anti-analgesic effect is an antagonist to 5-HT₃ receptor, would be an attractive treatment strategy for PONV. One study demonstrated that the incidence of PONV decreased 48 percent when Ondansetron administration compared with normal saline after cesarean section [42-44]. By comparing different dose of Ondansetron on the incidence of PONV, it was found that either 8mg or 4mg was effective compared with placebo. However, there was no statistical difference between 8mg and 4mg. Palonosetron, as the first of “second-generation” 5-HT₃ receptor antagonists, was studied to superior to Ramosetron in preventing PONV [45]. Currently, some researches transferred to multi-mode antiemetic for PONV prevention [46] by designing a retrospective study including 369 patients which compared intraoperative intravenous Dexamethasone 4mg and placebo in the incidence of PONV after CD, all patients were under spinal or combined spinal and epidural anesthesia. All patients received IV Ondansetron 4mg before wound closure. The result indicated that the incidence of PONV was 34.0% in Dexamethasone group vs. 27.5% in placebo group ($P=0.20$). The incidence of anti-emetic treatment was 26.7% in Dexamethasone group vs. 22.5% in placebo group ($P=0.35\%$). Similarly, [47] it was found there was no statistical difference between Dexamethasone plus Palonosetron and Palonosetron alone in the incidence of PONV. Another prospective study also indicated there was no advantage for Dexamethasone 8mg plus Ondansetron 4mg compared with either Dexamethasone 8mg alone or Ondansetron 4mg alone in the incidence of PONV ($P>0.05$) [48].

Propofol: One study compared Propofol 0.5mg/kg, Metoclopramide 10mg and placebo IV administration 10-15 minutes before wound closure in cesarean section. All patients were under spinal anesthesia with 7.5-10mg bupivacaine plus 0.2mg morphine. The result indicated Propofol and Metoclopramide groups both significantly reduced the incidence of PONV and reduced the rescue

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antiemetic administration[49, 50], it also indicated the Propofol plasma concentration of 1000 ng/ml administered after clamping of the umbilical cord reduced the incidence of nausea postoperative. However, the incidence of vomiting postoperative had no significant difference.

α -Receptor Agonist: One systematic analysis which recruited 201 reports and 12 clinical trials was designed to prove the effective of Clonidine administered intrathecally in cesarean section. The result demonstrated Clonidine added intrathecally prolonged the duration of sensory block and did not increase the incidence of PONV [51]. Another study also presented IT Clonidine 75mcg reduced the IT Morphine dose and the incidence of postoperative nausea related with IT Morphine[52]. Dexmedetomidine, as a high selectivity α_2 receptor agonist, was increasingly researched in clinical in recent years[53]. Compared PCA with 100mcg Sufentanil alone, PCA with 300 mcg Dexmedetomidine plus 100 mcg Sufentanil reduced significantly the incidence of PONV($P=0.005$). A meta-analysis identified six randomized controlled trials which indicated Dexmedetomidine reduced the incidence of PONV and shivering ($RR: 0.26$; 95% CI: 0.11 to 0.60; $I^2(2) = 0\%$)[54]. Over the past decade, researches on intrathecal Dexmedetomidine were increased in clinical[55-57]. YH Bi et al. [58] By adding 3mcg or 5mcg Dexmedetomidine with Bupivacaine intrathecally, they demonstrated Dexmedetomidine prolonged the motor and sensory block. However, the incidence of PONV was no significant difference($P=1.000$) [59] although intrathecal Dexmedetomidine prevented shivering, it had no statistical difference for the incidence of PONV ($RR=1.34$; 95% CI [0.82, 2.18]; $P=0.24$).

Lidocaine intravenous: Lidocaine intravenous administration was performed effective for postoperative pain release in some surgeries such as thoracic surgery, bariatric surgery, laparoscopic cholecystectomy etc [60-62]. However, limited evidence showed its effective in Obstetrics. It is also undefined that administered 1.5mg/kg Lidocaine for induction with cesarean section patients under general anesthesia could reduce the incidence of PONV in spite of opioids consumption decreased [63]. They found the Morphine consumption was significant low in Lidocaine group compared with placebo (0 vs 3.8mg, $P<0.001$). Nevertheless, the incidence of PONV was no significant difference (14.3% vs 10.0%, $P=0.496$) [64] if added 50ml 2% Lidocaine plus 30mg Morphine combined 47ml saline into total 100ml PCA pump. Compared with 30mg Morphine plus 97ml saline into total 100ml PCA pump, the lidocaine group did not reduce the incidence of PONV.

Vasopressor: Phenylephrine which is the first-line vasopressor to treat hypotension intraoperatively is associated with the complication of bradycardia[65,66] demonstrated the incidence of postoperative vomiting at 2 hours was lower in Phenylephrine infusion at 50 mcg/min than Phenylephrine bolus at 100mcg (11% vs 25%; $RR, 0.44$; 95% CI, 0.21 to 0.90; $P=0.02$). Ephedrine was also an alternative vasopressor to treat hypotension especially in patients with bradycardia in the cesarean section. The rate of infusion probably influences the incidence of PONV[67] compared 80 patients in the two different groups by 6mg Ephedrine bolus and infusion during 20s when hypotension occurred. The result indicated the incidence of PONV was 35% in bolus group while 0 in the infusion during 20s group ($P<0.01$).

Others: One meta-analysis indicated that chewing gum three times one day reduced the incidence of PONV ($RR 0.33$, 95%CI 0.12 to 0.87) [68]. Pentazocine, an opioid receptor mixed agonist-antagonist, was indicated effective for pruritus prevention. Nonetheless, it seemed no effective on PONV prevention [69]. Nalbuphine, same class as pentazocine, was also prove effective on prevention of pruritus but PONV [70]. Pregabalin, a drug structurally related to the inhibitory neurotransmitter γ -aminobutyric acid (GABA), was used to reduce postoperative pain in cesarean section postoperatively. The results presented that the total Morphine consumption was lower in 300mg Pregabalin group ($P<0.009$) and the incidence of PONV was also lower in 300mg Pregabalin group ($P<0.05$) [71]. Nonsteroidal anti-inflammatory agents (NSAIDs) postoperative administration reduced the opioid consumption. However, there were no significant difference of nausea($P=0.48$) and vomiting($P=0.17\%$) postoperatively compared with patients group of free non-steroidal anti-inflammatory drug (NSAID) [30]. Low dose Ketamine intravenous also was proved to reduce postoperative pain [72] compared intravenous Ketamine at 0.25mg/kg administration five minutes after infant delivery with normal saline. The incidence of vomiting (18.8% vs 35.0%, $P=0.020$) in 24h operative was significant low in experiment group and the incidence of nausea (32.5% vs 31.2%, $P=0.865$) was no significant difference. Glycopyrrolate, as a long-act β_2 receptor agonist, usually used to reduce the salivation in patients under anesthesia. The recent study presented 0.2mg Glycopyrrolate has same effective compared with Ondansetron 4mg in preventing PONV after cesarean section[73]. Wound infiltration with local anesthetic reduced the total opioid consumption. However, the incidence of PONV had no significant decreased [74]. Compared with sufentanil, midazolam added as an adjuvant with Bupivacaine intrathecally reduced the incidence of nausea postoperative ($P=0.02$). However, no significant difference in vomiting postoperative reported[75].

Discussion

As a common complication after CS, the incidence of PONV should be drew more attentions. Low dose of IT Morphine (0.1mg) is effective for analgesia postoperative and not associates with high incidence of PONV. Oral opioid is prior to intravenous administration because of low incidence of PONV. The nausea and vomiting in the early postoperative were possibly caused by hypotension. Correct administration of phenylephrine and ephedrine are both effective. Seemly infusion is better than bolus. Current researches manifest single antiemetic is as same effective as multi-mode antiemetic administration. It is needing more evidence for which antiemetic is best in preventing PONV. Propofol and Glycopyrrolate are probably effective for preventing PONV. Lidocaine, Dexamethasone, opioid receptor agonist-antagonist, Ketamine, NSAIDs and Midazolam all reduced the total opioid consumption. Nevertheless, the incidence of PONV seems not decreased.

Conclusion

PONV is an unpleasant experience after surgery and the mechanism is still incomplete defined. Recently, as the conception of Enhanced Recovery After Surgery (ERAS) mentioned, how to reduce the incidence of PONV should be paid more attention.

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