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Research Article

A Comparative Study of Intrathecal Fentanyl and Intravenous Ondansetron for Prevention of Intraoperative Nausea and Vomiting During Cesarean Delivery under Spinal Anesthesia

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ABSTRACT

Context: Nausea and vomiting is very common problem encountered during cesarean section.

Aim: To compare the effects of intrathecal fentanyl and intravenous ondansetron in the prevention of intraoperative and post-operative nausea and vomiting during cesarean section under spinal anesthesia.

Methods: This is a prospective comparative study conducted in a tertiary care teaching hospital in Nepal. Patients undergoing cesarean section were divided in two groups. Group 1 received intrathecal fentanyl and group 2 received intravenous ondansetron. Incidence of nausea and vomiting, mean arterial pressure, heart rate, oxygen saturation was recorded during eight different surgical steps of cesareans section. Pain was evaluated using numeric rating scale score.

Results: Hundred and nine cases (53 in Group 1 and 56 in Group 2) undergoing cesarean section under subarachnoid block were studied. At eight specific intervals during surgery, a blinded observer questioned patients about nausea (1 nausea, 0 no nausea), observed for presence of vomiting (1 vomiting, 0 no vomiting), and recorded a pain score (0–10, 0 no pain, 10 worst unimaginable pain) using numeric rating scale score. Incidence of nausea in group 1was 16.98% in comparison to 3.57% with group 2 whereas incidence of vomiting was not significant among both groups. 49.05% vs 58.92% from group 1 and 2 respectively required intervention for hypotension and were treated with IV ephedrine. Statistically significant use of ephedrine was found during stage 6, two cases from group 1 and 10 cases from group 2 ($p<0.05$)..

Conclusion: The incidence of nausea and vomiting was lower in the ondansetron group. Incidence of nausea during 6th stage of the study was also less in ondansetron group in comparison to fentanyl group making it superior for prevention of intraoperative nausea and vomiting.

Keywords: Caesarean section; Fentanyl; Nausea; Ondansetron; Vomiting

INTROCDUTION

Intraoperative nausea and vomiting occurs in as many as 66% of cesarean deliveries performed under regional anesthesia [1,2]. This can be distressing to the patient, can make the surgery difficult to perform, and may increase the risk of aspiration of gastric contents [2]. Vomiting may also cause complications such as dehydration, electrolyte imbalance, patient dissatisfaction and economic burden. Nausea and vomiting commonly occurs during cesarean delivery performed with regional anesthesia and is frequently related to peritoneal traction and exteriorization of the uterus [2]. These problems may be accompanied by visceral pain, which occurs despite apparently adequate dermatome sensory blockade [3]. Several anti-emetics are proven to diminish this problem. 5-HT3 antagonists (ondansetron, granisetron) are effective in reducing nausea [4] whose antiemetic properties are mediated through central (vomiting center, chemoreceptor trigger zone) and peripheral (intestinal and spinal) 5-HT3 receptor blockade.

Intrathecal (IT) lipophilic opioids (fentanyl, sufentanil) increase both the duration and intensity of spinal anesthesia and decrease intraoperative nausea and vomiting [5-7]. Though it doesn't possess anti-emetic properties in their own rights, they probably reduce PONV by improving the quality of and duration of pain relief

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along with 0.5% of hyperbaric bupivacaine [8]. Thus they are used extensively as adjutants to spinal anesthesia for cesarean delivery and may provide improved intra and postoperative analgesia.

Low doses of opioids activate mu opioid receptors in the chemoreceptor trigger zone (CTZ) located in periphery with incomplete blood brain barrier, thereby stimulating vomiting however higher dose opioid may suppress vomiting by acting at receptor sites deeper in the medulla [9].

This study is carried out to compare the efficacy of intrathecal fentanyl and intravenous ondansetron for prevention of perioperative nausea and vomiting during spinal anesthesia for cesarean section and to compare the hemodynamic stability, additional requirement of analgesics, association between intraoperative nausea and vomiting with hypotension and uterus exteriorization, incidence of opioid induced pruritus and respiratory depression and effect of intrathecal fentanyl and ondansetron on fetal outcome.

METHODS AND METHODOLOGY

This is a cross sectional randomized double blinded comparative study starting from 1st June 2017 to 28th February 2018 carried out in the Department of Anesthesiology and Critical care at a tertiary care teaching hospital in Nepal. Ethical clearance was taken and approved by Institutional Review Committee (IRC) and study was carried out among 109 cases that underwent elective cesarean section of all age group. All elective term singleton pregnancy for Cesarean Section (CS) with Physical status ASA II was included. Exclusion Criteria included all patients contraindicated to regional anesthesia (SAB), Physical status ASA grade III and IV, patient with a history of motion sickness, hyperemesis gravidarum or allergy to the study medications, pregnancy induced hypertension, toxemia of pregnancy, neuromuscular diseases (e.g. myopathies and neuropathies), raised intracranial pressure, patients on anticoagulant therapy and emergency CS.

One hundred and nine patients were included in this study. Pre-anesthetic checkup was done a day before surgery and was reviewed on the day of surgery. Relevant investigations were reviewed. Informed consent was taken from all patients. Nil Per Oral (NPO) status was maintained for 8 hrs. No other premedication was allowed. On arrival to Operation Theater, baseline blood pressure, heart rate, oxygen saturation and ECG were recorded. All patients were preloaded with 10 ml/kg of Ringers lactate solution just before start of SAB. A person uninvolved in the study had prepared computer-based randomization program for each subject's group assignment. Study drugs were prepared by an anesthesiologist not involved in this study and was dispensed in unlabeled syringes.

Subjects were randomized into two groups (A and B). Using a computer-based randomization, group A (IT fentanyl) received 2 ml (10 mg) of 0.5% heavy bupivacaine followed by 0.4 ml (20 microgram) of IT fentanyl and 2 mL IV normal saline immediately after the placement of SAB.

Group B (IV ondansetron) received 2 ml (10 mg) of 0.5% heavy bupivacaine followed by 0.4 mL IT normal saline and 2 mL (4 mg) IV ondansetron immediately after SAB.

After cleaning and draping with betadine, local anesthesia was given using 2% lignocaine hydrochloride solution followed by Spinal blockade with a 25-gauge Quincke needle at L2-3 or L3-4 interspace through midline approach in sitting position. Immediately after the intrathecal injection, subjects were placed in supine position with left uterine displacement. The level of sensory, sympathetic and motor block was tested by sterile needle prick, hot and cold and movement of limbs respectively. The targeted level of sensory blockade was T4 dermatome. Heart rate, oxygen saturation and ECG measurements were monitored throughout the procedure. Noninvasive BP was monitored at every three-minute interval starting immediately after SAB till the skin closure and every five min during the post-operative period for one hour. All patients had received supplemental oxygen via face mask at 3 liters/min throughout the procedure and one-hour post-operative period.

Hypotension (decrease in MAP >20% of baseline) was treated with IV ephedrine 5 mg incremental dose with additional 250-mL boluses of RL solution. Patients who complained of pain were given 50 microgram IV fentanyl following the delivery of fetus and were excluded from the study. Vomiting in either study group was treated with 1 mg of IV granisetron as rescue drug.

Level of sensory block prior to incision was noted. Study variables were assessed by an observer blinded to treatment group assignment at eight sequential intervals during the surgical procedure for any episode of retching or vomiting as below: Stage 1: Spinal placement until skin incision, Stage 2: Skin incision until delivery of baby, Stage 3: Delivery until uterine exteriorization, Stage 4: Uterine exteriorization until replacement of uterus, Stage 5: Uterine replacement until start of fascial closure, Stage 6: Fascial closure until skin closure, Stage 7: Skin closure until arrival in recovery room and Stage 8: Post-operative observation for first four hours. Duration of surgery (SAB to the closure of uterus) was noted.

Other variables recorded included perioperative fentanyl or other analgesic use, intraoperative ephedrine usage, interval between spinal placement and first request for postoperative analgesics. APGAR score at one and five min were recorded by attending pediatrician. Numeric rating scale (NRS) with Wong-Baker faces was used to evaluate post-operative pain assessment with score of 0 as no pain and 10 with worst pain possible [10].

STATISTICAL ANALYSIS

Data were entered into a Microsoft excel spreadsheet for data management and transferred to statistical package for the social sciences version 21.0 (SPSS v 21.0) where further data management and statistical analysis were performed. A significant difference was taken as a p value of less than 0.05. Sample size was calculated with use of following formula:

$n \geq [Z\ 1\text{-}\alpha/2\ \sqrt{(r+1)p\ (1\text{-}p)} + Z\ 1\text{-}\beta\ \sqrt{rp1(1\text{-}p1) + p2(1\text{-}p2)}]2/r\ (p2\text{-}p1)$

n is the minimum number of subjects required in each group, p1 and p2 are proportions of the disease or condition expected in two independent populations. In the above equation, the denominator term p1-p2 is the minimum clinically significant difference between the two proportions.

Alpha (α)=0.005, Beta (β)=0.2, Proportion in group 1=0.25, Proportion in group 2=0.05, Ratio (group 2/group 1)=1, Minimal sample size needed for group 1=49, Minimal sample size needed for group 2=49, Minimum total sample size needed=98.

RESULTS

There were total one hundred and nine cases: 53 patients in group 1 (fentanyl group) and 56 patients in group 2 (ondansetron group). Mean age was 25.41 ± 4.861 years. Average weight was 59.78 ± 8.439 kg.

42 cases (79.24%) and 49 cases (87.5%) from group 1 and 2 respectively had mallampati score of I whereas only one cases (1.88% vs 1.78% in group 1 and 2) had mallampati score of III. All

of the patients in both groups had free temporomandibular joint movement.

Among total patients, 36.69% cases had blockade level of T4 dermatome. Majority of cases had level of blockade of T6 with incidence of 59.63% with 24 cases in group 1(45.28%) and 41 cases (73.21%) in group 2.

Average duration of the surgical procedure was found to be 41.78 ± 11.21 minutes. APGAR score at 1 minute was not a significant finding with only 0.917% having scored less than five and none had score less than five at 5 min interval among both groups.

One case from fentanyl group and eight cases (14.285%) from ondansetron group required IV pethidine for shivering ($p<0.05$) stage 4 (Figure 1).

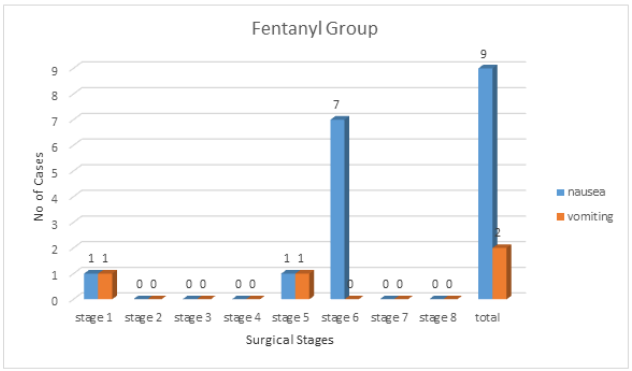

Figure 1: Prevalence of nausea and vomiting during different surgical stages among fentanyl group.

During stage 6 (fascial closure until skin closure), seven cases (13.20%) from fentanyl group had nausea in comparison to one case (1.78%) from ondansetron group ($p<0.05$) whereas none of the patient from any group had vomiting. During stage 6 (fascial closure until skin closure), seven cases (13.20%) from fentanyl group had nausea in comparison to one case (1.78%) from ondansetron group ($p<0.05$) whereas none of the patient from any group had vomiting. There was no statistically significant difference in the incidence of nausea and vomiting in the other stages of surgery (Figure 2).

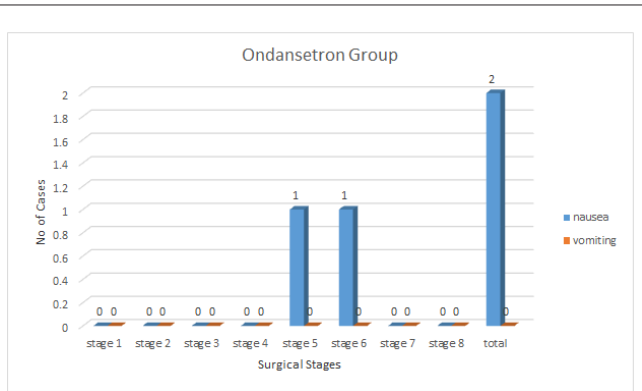

Figure 2: Prevalence of nausea and vomiting during different surgical stages among ondansetron group.

Two cases (3.77%) from fentanyl group and 10 cases (17.85%) from ondansetron group required IV Ephedrine during stage 6 ($p<0.05$).

Among total patients, mean NRS score in fentanyl group was 1.87 ± 2.067, 2.3 ± 1.102, 2.57 ± 0.91 and 2.75 ± 0.939 during 1st, 2nd ,3rd and 4th post-operative hour respectively whereas mean NRS score in ondansetron group was 3 ± 1.673, 2.64 ± 1.242, 2.84 ± 0.96 and 2.98 ± 1.286 during 1st, 2nd ,3rd and 4th post-operative hour respectively (Table 1).

Table 1: NRS score postoperatively.

NRS Score	Fentanyl Group ($\bar{x}$±SD)	Ondem Group ($\bar{x}$±SD)
1st Post op Hr	1.87± 2.067	3±1.673
2nd Post op Hr	2.3± 1.102	2.64±1.242
3rd Post op Hr	2.57 ± 0.91	2.84±0.96
4th Post op Hr	2.75±0.939	2.98±1.286

DISCUSSION

Nausea and vomiting are recognized side effects during caesarean section under spinal anesthesia. Intra-operative incidence may be related to sudden hypotension, use of intravenous opioids, surgical procedures related such as peritoneal traction and exteriorization of the uterus, use of uterotonic agents such as oxytocin and visceral pain due to inadequate level of blockade under spinal anesthesia. It remains controversial whether exteriorization of the uterus increases the risk of nausea and vomiting [11].

In our study there was no any statistical significance regarding demographic variables such as age, weight, gender, mallampati score, temporomandibular joint movement, ASA physical status score, level of sensory blockade and duration of the surgical procedure.

Non pharmacological method such as supplemental oxygen for hypoxia, intravenous fluids for hypotension or dehydration and acupuncture or acupressure has varying success.

The best pharmacologic agents are 5-HT 3 antagonists and dopamine antagonists. Ondansetron has been demonstrated to be an effective and well-tolerated drug with better safety profile which acts by blocking 5-HT 3 receptors on vagal afferent terminals and located centrally in the area postrema [12].

In study done by Griffiths et al 5-HT 3 antagonists were more effective than placebo at reducing intraoperative and postoperative nausea and vomiting [13]. During entire period of 24 hours after recovery from general anesthesia, incidence of nausea and vomiting was 29% and 26% in ondansetron group [12]. Similar to this study, our study also showed efficacy of intravenous ondansetron for prevention of nausea and vomiting. Total incidence of nausea was 16.98 % vs 3.57% and vomiting 3.77% vs 0 respectively in group 1(fentanyl) and group 2 (ondansetron). Incidence of nausea during 6th stage of the study was less in ondansetron group in comparison to fentanyl group (0 vs 13.20% respectively) making it superior for prevention of intraoperative nausea and vomiting.

Opioid induced nausea and vomiting (OINV) may be due to multiple opioid effects, including (I) enhanced vestibular sensitivity (II) direct effects on the chemoreceptor trigger zone and (III) delayed gastric emptying [14]. CTZ contains a great concentration of 5HT 3-receptors and dopaminergic receptors and endogenous opioid appears to be involved in the mechanisms of opioid induced vomiting, likely via stimulating mu opioid receptors and delta opioid receptor in the chemoreceptor trigger zone of the vomiting center [15]. If the interaction between opioid agonists and opioid receptors in the chemoreceptor trigger zone for a particular opioid is relatively long compared with its peripheral actions, tolerance to the emetic actions of opioids could occur earlier or may be more intense [16].

Spinal administration of fentanyl, a lipophilic drug, may potentiate spinal anesthesia and be associated with a decreased incidence of

side effects with less frequent incidence of intraoperative side effects such as severe hypotension, nausea, and vomiting [17]. Fentanyl 25 g which is highly lipophilic do not remain free in the cerebrospinal fluid long enough when administered in the subarachnoid space at the lumbar level to reach CTZ in sufficient concentration to induce vomiting [18]. However, it sufficiently augments local anesthesia mediated block to decrease nociceptive stimulation which occurs during maneuvers like peritoneal traction and thus reduces nausea and vomiting [18].

Intrathecal fentanyl has been in use during spinal anesthesia as an adjunct as it provides hemodynamic stability with better analgesic effect in both intra and post-operative period. Our result showed lesser incidence of nausea with ondansetron group than fentanyl group whereas only two cases (3.77%) from fentanyl group had vomiting in comparison to none with use of ondansetron.

In a study done by Dahl et al., intraoperative nausea and vomiting/retching were reduced in the IT fentanyl group as compared with the control group [19]. Duman A et al. compared efficacy of intrathecal fentanyl 20 μg and morphine 200 μg as additive to hyperbaric bupivacaine and concluded that intrathecal opioids effectively decreased the incidence of PONV compared to placebo [20]. Pallab R et al. compared efficacy of midazolam (2 mg) and fentanyl (12.5 μg) as additive to intrathecal bupivacaine in prevention of PONV and reported incidence of nausea-vomiting to be 25% with fentanyl use [21].

In study done by David et al., patients in the plain bupivacaine group complained of nausea more frequently than patients in the mini dose bupivacaine-fentanyl group (69% vs 31% respectively) [22]. Manullang TR et al., showed decreases incidence of perioperative nausea with IT fentanyl compared with IV ondansetron; the median difference in number of episodes of nausea was 1 (P=0.03) [8] whereas our study showed that incidence of nausea in group 1 (fentanyl) was 16.98% vs 3.57 % of group 2 (ondansetron) respectively. Seven cases from group 1 and only one case from group 2 complained of nausea during stage 6, showing statistically significant data of more incidence of nausea among group 1 rather than group 2 ($p<0.05$). Incidence of vomiting was not significant among both groups.

Lussos et al. believed that PONV after delivery is related to the surgical manipulation of the uterus, abdominal viscera and peritoneum, even in the presence of adequate sensory-motor blockade [2]. In our study, no such relation was found as most number of incidence of nausea was present during stage 6 (fascia closure to skin closure) rather than during uterus exteriorization (stage 3) or during replacement of the uterus (stage 4). Siddiqui et al. advised for in situ repair of uterus as exteriorization of uterus for repair was associated with in increased incidence of nausea and vomiting and tachycardia (18% compared to 38%; p=.04) [23] whereas no such correlation was found regarding incidence of nausea and vomiting during stage 3 and 4 though use of IT fentanyl or IV ondansetron might have obscured the result.

In a study done by Hunt et al., addition of fentanyl 6.25-50 microgram to 10.5 microgram (on average) hyperbaric 0.75% bupivacaine for spinal anesthesia reduced the intraoperative need for supplemental IV analgesics from 67% to 0% during cesarean section [24]. Similarly in Manullang et al. study, IT fentanyl group required less supplementary intraoperative analgesia [8]. In our study total three cases fentanyl group and 15 cases from ondansetron group required additional analgesia intra operatively with maximum requirement seen during stage 5. Six cases (10.71%) from ondansetron group and none from fentanyl group required additional analgesia ($p<0.05$) showing addition of fentanyl reduced intraoperative need for supplemental IV analgesics as in earlier studies.

Both groups had received equal amount of bupivacaine and none cases had level of block >T4, 96.33% had level of blockade >T6 with 36.69% having block height of T4.

Hypotension occurring after spinal anesthesia was treated with IV fluids followed by IV ephedrine bolus of 6 mg if there was fall of MAP of >20% from baseline. Manullang et al. showed that IT fentanyl group needed less ephedrine for treatment of intraoperative hypotension [8]. Our study also showed similar result with 26 cases from group 1 (fentanyl) and 33 cases from group 2(ondansetron) requiring ephedrine for treatment of intraoperative hypotension (49.05% vs 58.92% respectively). Statistically significant use of ephedrine was found during stage 6, two cases from group 1 and 10 from group 2 ($p<0.05$). Thus, indicating IT fentanyl group had better hemodynamic parameter than IV ondansetron, with lesser use of ephedrine.

One case from group 1(fentanyl) and 10 cases from group 2 (ondansetron) had intra operative shivering (1.88% vs 17.85% respectively) for which pethidine 20 mg IV bolus was given. During stage 4 there was statistically significant use of pethidine as eight cases from group 2 requiring intervention for shivering (1.88% vs 14.28% respectively) with $p<0.05$ showing decrease incidence of shivering and use of pethidine with intrathecal fentanyl.

Pruritus is another common side effect of IT opioid occurring with larger doses. Manullang TR et al. study had no patients requiring treatment for pruritus [8]. Similar to the above study no patient from both groups requested or received treatment for pruritus. No patient in either group experienced clinically significant sedation or had oxygen saturations lower than 94% indicating less incidence of respiratory depression with the use of IT fentanyl.

APGAR score was not a significant finding. Umbilical cord blood gas analysis and neonatal neurobehavioral scores may be more sensitive measure for neonatal assessment.

In study by Palmer et al., 15 microgram fentanyl added to hyperbaric bupivacaine for subarachnoid anesthesia for cesarean section provided increased duration of analgesia of approximately 30 minutes [6]. Manullang et al. study showed IT fentanyl group had a lower cumulative perioperative pain score than iv ondansetron group [8] and required less supplementary intraoperative analgesia. In our study, mean NRS score for group 1(fentanyl) was 1.87, 2.30, 2.57, 2.75 during 1st, 2nd, 3rd and 4th post-operative hour respectively in comparison to mean score of 3, 2.64, 2.84, 2.98 during 1st, 2nd, 3rd and 4th post-operative hour respectively in ondansetron group indicating better analgesic action with use of intrathecal fentanyl leading to reduced use of analgesics post operatively similar to the above mentioned study.

SUMMARY AND CONCLUSION

Incidence of nausea during 6th stage of the study was less in ondansetron group in comparison to fentanyl group (0 vs 13.20% respectively) making it superior for prevention of intraoperative nausea and vomiting.

In our study total incidence of nausea and vomiting among the two groups were nine and two (16.98 % vs 3.57%) and two and none cases (3.77% vs 0) respectively in group 1(fentanyl) and group 2 (ondansetron) respectively.

However, due to adequate intra operative and post-operative

analgesia, less requirement of ephedrine for hypotension, pethidine for shivering and insignificant incidence of vomiting makes intrathecal fentanyl an attractive option and could be used routinely with further studies.

REFERENCES

1. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiol. 1992;76(6):906-916.
2. Lussos SA, Bader AM, Thornhill ML, Datta S. The antiemetic efficacy and safety of prophylactic metoclopramide for elective cesarean delivery during spinal anesthesia. Reg Anesth. 1992;17(3):126-130.
3. Alahuhta S, Kangas-Saarela T, Hollmén AI, Edström HH. Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. Acta Anaesthesiol Scand. 1990;34(2):95-98.
4. Pan PH, Moore CH. Intraoperative antiemetic efficacy of prophylactic ondansetron versus droperidol for cesarean section patients under epidural anesthesia. Anesth Analg. 1996;83(5):982-986.
5. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg. 1997;85(6):1288-1293.
6. Palmer CM, Voulgaropoulos D, Alves D. Subarachnoid fentanyl augments lidocaine spinal anesthesia for cesarean delivery. Reg Anesth. 1995;20(5):389-394.
7. Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? Br J Anaesth. 1997;78(3):311-313.
8. Manullang TR, Viscomi CM, Pace NL. Intrathecal fentanyl is superior to intravenous ondansetron for the prevention of perioperative nausea during cesarean delivery with spinal anesthesia. Anesth Analg. 2000;90(5):1162-1166.
9. Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. Ann Palliat Med. 2012;1(2):121-129.
10. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al. Assessment of pain. Br J Anaesth. 2008;101(1):17-24.
11. Ishiyama T, Yamaguchi T, Kashimoto S, Kumazawa T. Effects of epidural fentanyl and intravenous flurbiprofen for visceral pain during cesarean section under spinal anesthesia. J Anesth. 2001;15(2):69-73.
12. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new, selective, 5-HT3 receptor antagonist. Anesth Analg. 1991;72(6):751-755.
13. Griffiths JD, Gyte GM, Paranjothy S, Brown HC, Broughton HK, Thomas J. Interventions for preventing nausea and vomiting in women undergoing regional anaesthesia for caesarean section. Cochrane Database Syst Rev. 2012;9(9):Cd007579.
14. Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. Ann Palliat Med. 2012;1(2):121-129.
15. Jongkamonwiwat N, Phansuwan-Pujito P, Sarapoke P, Chetsawang B, Casalotti SO, Forge A, et al. The presence of opioid receptors in rat inner ear. Hear Res. 2003;181(1-2):85-93.
16. Herndon CM, Jackson KC, Hallin PA. Management of opioid-induced gastrointestinal effects in patients receiving palliative care. Pharmacother. 2002;22(2):240-250.
17. Siddik-Sayyid SM, Aouad MT, Jalbout MI, Zalaket MI, Berzina CE, Baraka AS. Intrathecal versus intravenous fentanyl for supplementation of subarachnoid block during cesarean delivery. Anesth Analg. 2002;95(1):209-213.
18. Seyedhejazie M, Madarek E. The effect of small dose bupivacaine-fentanyl in spinal anesthesia on hemodynamic nausea and vomiting in cesarean section. Pk J Med Sci. 2007;23(7):747-750.
19. Jørgen DB, Inge JS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia : A qualitative and quantitative systematic review of randomized controlled trials. Anesthesiol: J Ame Soci Anesthesiol. 1999;91(6):1919.
20. Apiliogullari S, Gök F, Canpolat A, Soysal S, Toy H. Comparison of prophylactic dimenhydrinate and metoclopramide for Prevention of nausea-vomiting caused by intrathecal opioids in parturients undergoing caesarean delivery. Region Anesth Pain Med. 2008;33(Suppl 1):e131.
21. Rudra P, Rudra A. Comparison of intrathecal fentanyl and midazolam for prevention of nausea–Vomiting during caesarean delivery under spinal anaesthesia. In J Anaesth. 2004;48(6):461-464.
22. Ben-David B, Miller G, Gavriel R, Gurevitch A. Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. Reg Anesth Pain Med. 2000;25(3):235-239.
23. Siddiqui M, Goldszmidt E, Fallah S, Kingdom J, Windrim R, Carvalho JC. Complications of exteriorized compared with in situ uterine repair at cesarean delivery under spinal anesthesia: a randomized controlled trial. Obstet Gynecol. 2007;110(3):570-575.
24. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiol. 1989;71(4):535-540.