

Effect of Intravenous Dexamethasone on Postoperative Nausea-Vomiting (PONV) after Intrathecal Morphine during Caesarean Section

Ashok Jadon*, Neelam Sinha, Amit Agrawal, Priyanka Jain

Department of Anaesthesia and Pain Relief, Tata Motors Hospital, Jamshedpur

Received: March 02, 2016; Accepted: March 25, 2016; Published: April 01, 2016

***Corresponding author:** Ashok Jadon, Chief Consultant, Department of Anaesthesia and Pain Relief, Duplex 63, Vijaya Heritage Phase 6, Kadma, Jamshedpur, 831005, Jharkhand, India, Tel: 923-455-4341; E-mail: jadona@rediffmail.com

Abstract

Background: Post-operative pain relief after Caesarean section is important; it improves mobility and reduces the risk of thromboembolic complications. Neuraxial opioids are effective in postoperative pain relief but untoward effects like postoperative nausea and vomiting (PONV) prevent their regular use. Recent studies have shown that IV Dexamethasone reduces the incidence of PONV associated with intrathecal opioids when used for post Caesarean analgesia. We evaluated the efficacy of 8mg IV dexamethasone in reducing PONV in mothers receiving intrathecal morphine for post Caesarean analgesia.

Methods: Hundred mothers scheduled for LSCS under spinal anaesthesia were randomly assigned to receive either 2ml saline (Group A, n=50) or 8mg IV dexamethasone (Group B, n=50) in this prospective double-blinded study. All mothers received a standard spinal anaesthetic with 2.5 ml 0.5% heavy bupivacaine and 0.2 mg intrathecal morphine for post Caesarean analgesia. APGAR scores of the babies were noted at 1min and 5min. All the mothers were assessed postoperatively for nausea/vomiting, pain, pruritus and urinary retention in the post anaesthesia care unit (time 0 hours) and at 1, 2, 3, 4, 8, 12, 16, 20 and 24 hours. 4mg IV ondansetron was given to patients who complained of nausea or vomiting and 75mg IM diclofenac was given to any mother who complained of pain postoperatively.

Results: The incidence of nausea and vomiting scores were found to be lower in the study group when compared to the control group with 27 out of 50 subjects requiring antiemetic in the control group while only 15 out of 50 subjects requiring antiemetic in the study group ($P=0.015$). Time to request to first analgesic dose was 15 hours in the study group when compared to 13 hours in the control group ($P=0.024$). However, no difference in APGAR scores, pruritus and urinary retention was noted in both the groups ($P > 0.005$).

Conclusion: Dexamethasone reduces the incidence of postoperative nausea and vomiting associated with intrathecal morphine. Additionally, it can prolong the duration of analgesia postoperatively.

Keywords: Dexamethasone; Morphine; Neuraxial opioid; PONV; Spinal anaesthesia

Introduction

Caesarean section is a major surgical procedure with substantial post-operative pain and discomfort [1]. Optimal pain control following Caesarean delivery is essential to facilitate early mobilisation and prevent thromboembolic complications that are increased in pregnancy [2]. Besides this, mothers also need to be pain free to care for their new-born and breastfeed them effectively [3]. Conventionally, morphine has been used through neuraxial route as a safe and effective measure for post Caesarean analgesia [4]. However, despite its excellent analgesic properties, a high incidence of nausea and vomiting (30-65%) has been reported [5-7]. Persistent nausea and vomiting may result in dehydration, electrolyte imbalance and delayed discharge [7]. Persistent retching and vomiting can also cause tension on suture lines and can expose the patient to risk of pulmonary aspiration if airway reflexes are depressed from the residual effects of anaesthetic and analgesic drugs [8].

Varieties of drugs are available for the prophylaxis and treatment of post-operative nausea and vomiting (PONV). However, no drug has been proved effective and search for an ideal drug continues. Dexamethasone is an effective antiemetic agent with minimal side effects after single dose administration [9-14]. The mechanism for the antiemetic effect of dexamethasone remains unknown [15]. The proposed mechanisms include the ability of dexamethasone to deplete γ -amino butyric acid stores, reduce the blood-brain barrier's permeability to emetic toxins, inhibit brainstem enkephalin release and inhibit central prostaglandin and serotonin synthesis [15,16]. We hereby present a study performed to evaluate the efficacy of IV dexamethasone to reduce PONV in mothers receiving intrathecal morphine for post caesarean analgesia.

Methods

The ethical committee of the hospital approved the protocol and informed consent was obtained from each of the subjects. One hundred mothers of ASA physical status II, aged 19-35 years, scheduled for lower segment Caesarean section under

spinal anaesthesia were enrolled in this prospective, double blinded study. Exclusion criteria included systemic disease, contraindications to regional anaesthesia, pregnancy-induced complications like eclampsia and acute obstetric haemorrhage and mothers having compromised foetus. Any parturient requiring general anaesthesia due to failure of spinal anaesthesia was also excluded from the study.

Patients posted electively for the surgery received premedication with oral ranitidine (150 mg) on the night before and in the morning on the day of the surgery while patients undergoing emergency Caesarean received injectable ranitidine (50 mg).

All the mothers were randomly assigned to receive saline (Group A) or Dexamethasone (Group B) using a computer-generated list of random numbers. The drug for injection was prepared as a 2 ml clear solution in identical syringes. The randomization process and the identity of the study drugs were blinded from the parturients, the anaesthesiologists during surgery, and the investigators who collected the postoperative data. The study group assignments remained concealed until all the data were collected.

In the operating room, all parturients were monitored by non-invasive arterial blood pressure monitoring, electrocardiogram and peripheral pulse oximetry. Normal saline (500 ml) was given IV before surgery to maintain a stable blood pressure. All mothers received a standard spinal anaesthetic in sitting position with 2.5 ml (12.5 mg) of 0.5% heavy bupivacaine and 0.2 mg morphine (0.2 ml of 1mg/ml morphine) in L3-4 space using a 26G Quincke's needle. The parturient was placed in the supine position with 15° to 20° left uterine displacement, and supplemental oxygen was delivered through a nasal cannula at 3L/min. Group A received 2ml of normal saline IV while Group B received 2ml (8 mg) IV dexamethasone. Estimated fluid deficits and maintenance requirements were replaced with normal saline intravenously. IV ephedrine (6 mg in aliquot) was administered as needed to treat intra-operative hypotension (blood pressure <20% of the initial value). All patients received an IV infusion of 15IU oxytocin after delivery. IV ondansetron 4 mg was administered intra operatively if nausea or vomiting was not corrected with vasopressor administration or occurred unrelated to hypotension. This was considered as the primary end point for PONV. After delivery of the child, APGAR scores [17] at 1 min and 5 min were recorded in both the groups to assess foetal depression.

At the end of surgery, patients were shifted to the Post Anaesthesia Care Unit (PACU) where they were observed for one hour before being shifted to the post-operative ward. Post operatively, all patients were assessed for pain and adverse effects of morphine which included nausea and vomiting, pruritus and urinary retention. All the mothers were assessed hourly for the first four hours and then 4 hourly until the first 24 hours after the surgery. During the entire duration of the study, pulse and blood pressure were recorded at the above said intervals. Pain was assessed by a 10 point Visual Analogue Scale (VAS) [18], with 0 being no pain and 10 being the worst

imaginable pain. 75 mg IM diclofenac was given if VAS>3 or on patient demand any time during the first 24 hours. The time to first analgesic request was noted and this was considered as the end point for duration of analgesia (time duration between the end of the surgery and the request to first analgesic dose). If the patient continued to complain of pain (VAS >3) even after 45 minutes of administration of Diclofenac, an IM combination of 30 mg pentazocine and 25 mg promethazine was administered. Nausea and vomiting was assessed by a 3 point scale with 0= no nausea or vomiting, 1= nausea, 2= retching and 3= vomiting. At any point during the study, if the patient complained of nausea or vomiting, 4mg IV ondansetron was given. In case of continued nausea and vomiting, 10 mg IV metoclopramide was administered additionally. Pruritus was assessed using a nominal scale (present / absent). Urinary catheterisation was considered to be present if the mother required catheterisation (Foley's / plain catheter) anytime during the study.

Statistical Analysis

Sample size was predetermined by using a power analysis based on the assumptions that (a) the total incidence of nausea and vomiting in the saline group would be 50%, [11] (b) a 40% reduction in the total incidence of nausea and vomiting (from 50% to 30%) in the treatment group would be of clinical relevance and (c) $\alpha=0.05$, $\beta=0.2$. [14] The analysis showed that 40 parturients per group would be sufficient to detect the antiemetic effect of dexamethasone [14]. Considering an attrition of 20% (8 parturients per group), the number of subjects were rounded to 50 per group. To examine differences among the groups with respect to parametric variables t-test was used to detect the intergroup differences. The Kruskal-Wallis test was used to determine differences among the groups with respect to nonparametric variables. Categorical variables were analysed by using 2 × 2P tests or Fisher's exact tests, as appropriate, for inter group differences. P value < 0.05 was considered statistically significant. MedCalc® Software Version 16.2 was used for statistical analysis.

Results

All the enrolled parturients completed the study. All the patients were hemodynamically stable during the entire study as assessed by the intra operative and post-operative pulse and B.P monitoring and no significant difference was found between the two groups. At all points during the study, nausea and vomiting scores were found to be significantly higher in the control group as compared to the study group Table 2. However statistical significance was noted only between 4 to 8 hours (P <0.05). Twenty-seven out of 50 mothers in the control group and 15 out of 50 mothers in the study group required antiemetics to relieve nausea and vomiting (P=0.015). Mean VAS scores in both the groups was found to be <5 during the entire duration of the study Table 3. The mean of time to first analgesic request in the study group was 15 hours as compared to 13 hours in the control group. 20 out of 50 (40%) mothers developed pruritus in the control group while 19 of 50 (38%) mothers developed pruritus in the study group (P=0.838). There was no difference

Table 1: Demographic and Intra-operative Characteristics.

	Group A (n=50)	Group B (n=50)	P
Age (years)	23 ± 5	24 ± 4	0.272
Weight (kg)	82 ± 13	78 ± 16	0.173
Height (cm)	163 ± 7	162 ± 6	0.444
Gestational age (weeks)	38 ± 2	38 ± 2	1.00
Parity (nulliparous/multiparous)	24 / 26	23 / 27	1.00
Duration of surgery (min)	58 ± 11	60 ± 12	0.387
Duration of anaesthesia (min)	68 ± 11	70 ± 10	0.343
Total ephedrine administered (mg)	8 ± 2	8 ± 1	1.00
Total IV fluids administered (ml)	1460 ± 210	1420 ± 190	0.320

Table 2: Post-operative Nausea and Vomiting (PONV).

Mean N/V score	Group A (n=50)	Group B (n=50)	P
1	0.9	0.78	0.584
2	1.02	0.88	0.515
3	0.9	0.59	0.110
4	0.98	0.5	0.035*
8	0.76	0.2	0.006*
12	0.64	0.06	0.000*
16	0.52	0.3	0.174
20	0.5	0.32	0.266
24	0.4	0.24	0.271
Number of mothers requiring antiemetics	27	15	0.015*

*p<0.05

Table 3: Post-operative Pain Score & First request to Analgesic.

Mean VAS score	Group A (n=50)	Group B (n=50)	P
1	1	1	0.237
2	1	1	0.318
3	1	1	1.00
4	2	2	0.437
8	3	3	0.53
12	3	3	0.371
16	3	4	0.005
20	4	4	0.495
24	3	3	0.357
Mean of time to first analgesic request(hrs)	13	15	0.024*

p<0.05

in the incidence of urinary retention between the two groups (P=0.433). Similarly no difference in APGAR scores was found between the two groups Table 4.

Discussion

The results of our study indicate that a single dose of IV dexamethasone is an effective antiemetic in patients receiving intrathecal morphine as part of a neuraxial anaesthetic technique for LSCS. However, a lag period of 4 hours was noted before the effect of dexamethasone was seen. Another finding noted in the study was that the antiemetic effect of dexamethasone was

short-lived (4 hours). In addition, dexamethasone also produced a small prolongation in the time request to first analgesic dose. Dexamethasone, however did not reduce the incidence of neuraxial morphine induced pruritus, urinary retention or foetal depression when compared with the saline group.

Intrathecal opioids have proved to be reliable in relieving post-operative pain. However, associated PONV remains a major challenge occurring in as many as 30% of the patients [6]. Dahl et al. [19] reported that the number needed to harm for PON and POV in patients receiving intrathecal morphine for caesarean

Table 4: Pruritus, Urinary Retention and APGAR Score.

	Group A (n=50)	Group B (n=50)	P
Incidence of urinary retention (%)	40	35	0.838
Incidence of urinary retention (%)			
No retention	38	34	
Foley's Catheter	30	22	0.43
Plain Catheter	32	44	
APGAR Score			
1 min	8	8	0.904
5 min	9	9	0.235

delivery under spinal anaesthesia was 6.3 and 10.1, respectively.

Dexamethasone has a well-established role as a prophylactic antiemetic with minimal adverse effects after single dose administration [9-14]. The mechanism for the antiemetic effect of dexamethasone remains unknown [15]. The proposed mechanisms include the ability of dexamethasone to deplete γ -amino butyric acid stores, reduce the blood-brain barrier's permeability to emetic toxins, inhibit brainstem enkephalin release and inhibit central prostaglandin and serotonin synthesis [15, 16]. Its long duration of action makes it an ideal drug for prophylaxis in patients receiving long-acting neuraxial opioids [14]. Published consensus guidelines for the management of PONV recommend doses of 4 to 5 mg for antiemetic prophylaxis [20].

Some factors which may interfere with the interpretation of the study result, such as consumptions of ephedrine and IV fluids were also evaluated in our study [21, 22]. We found that the intra operative consumptions of ephedrine and IV fluid were similar among both the groups. Therefore, differences in the occurrence of nausea and vomiting among the groups can be attributed to the study drug.

Another finding noted in our study was that the time request to first analgesic dose was longer in the dexamethasone group as compared to the saline group. This highlights the probable analgesic efficacy of dexamethasone. The administration of a single dose of dexamethasone has been associated with a reduction in tissue inflammatory mediators including bradykinin, prostaglandins and other nociception-promoting neuro peptides which may contribute to its analgesic properties [23]. Dexamethasone has been shown to significantly reduce postoperative peritoneal inflammation and abdominal pain after colectomy [23].

Pruritus is a common adverse effect of neuraxial morphine but currently there seem to be no consistently effective therapies [24].

In present study both the groups showed similar incidence of pruritus indicating that dexamethasone had no antipruritic effect. Mechanism of intrathecal opioid-induced pruritus is complex and pathogenesis is still not clear. Many treatments have been tried, but to date, the data are conflicting and only limited studies have

confirmed their efficacy. MOR antagonists, mixed opioid receptor agonist-antagonists, serotonin 5-HT₃ receptor antagonists, and D₂ receptor antagonists have been demonstrated most consistent in terms of attenuating opioid-induced pruritus. A recent update has discussed these issues in detail [25]. No difference in urinary retention was noted between the two groups possibly due to no antagonistic effect of dexamethasone on opioid receptors which is an important contributing reason in urinary retention.

A dreadful complication associated with the use of intrathecal morphine is foetal depression. No significant difference in the APGAR score (1 min and 5 min) was noted in both the groups. This probably indicates that a dose as low as 0.2 mg of intrathecal morphine had no significant effect on neonatal outcomes [26].

Limitations of the study

Since pain & PONV are a subjective phenomenon associated with a wide variability of responses among the individuals, it is difficult to standardize the variables. What may be tolerable for one person may be intolerable for another person. Under these circumstances, it is difficult to assess and grade pain & PONV in the same manner, which may lead to a lot of unwanted bias in this study. Urinary retention, which is a known complication of neuraxial opioids could not be assessed, many patients who had previous LSCS were catheterized preoperatively with Foley's catheter.

Conclusion

Therefore, it was concluded that, use of 8 mg IV dexamethasone decreases the incidence of PONV in patients receiving intrathecal morphine (0.2 mg) for LSCS & it also enhances the duration of analgesia postoperatively.

So intrathecal morphine is a good option for postoperative analgesia in pts undergoing LSCS & the PONV associated with its use can be decreased by use of IV Dexamethasone.

References

1. Farragher RA, Laffey JG. Postoperative pain management following Caesarean section. In: Shorten G, Carr D, Harmon D, et al. eds. Postoperative pain management: an evidence-based guide to practice. 1st ed. Philadelphia, PA: Saunders Elsevier, 2006;225-228.
2. Ismail S. What is new in post-operative analgesia after Caesarean

- sections? *Anaesth, Pain and Intensive Care* 2012; 16(2):123-126.
3. McDonnell J, Curley G, Carney J, Benton A, Costello J, Maharaj C et al. The analgesic efficacy of transversus abdominis plane block after Cesarean delivery: A randomized controlled trial. *Obstetric Anesthesiology*. 2008;106(1):186-191. doi: 10.1213/01.ane.0000290294.64090.f3.
 4. Sujata N., Hanjoo VM. Pain control after Cesarean birth – What are the options? *Journal of General Practice*. 2014; 02:164. doi: 10.4172/2329-9126.1000164.
 5. Kotelko DM, Rottman RL, Wright WC, Stone JJ, Yamashiro AY, Rosenblatt RM. Transdermal scopolamine decreases nausea and vomiting following Cesarean section in patients receiving epidural morphine. *Anesthesiology* 1989;71(5): 675–678.
 6. Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anaesth* 1995;42(10): 891-903.
 7. Andrews PLR. Physiology of nausea & vomiting. *Br J Anaesth*. 1992;69(1): 24-32. doi:10.1093/bja/69.supplement_1.2S.
 8. Vance JP, Neill RS, Norris W. The Incidence and aetiology of post operative nausea and vomiting in a plastic surgery unit. *Br J Plast Surg* 1973;26(4):336-339 doi:10.1016/S0007-1226(73)90035-0.
 9. Wang J-J, Ho S-T, Lee S-C, Liu Y-C, Liu Y-H, Liao Y-C. The prophylactic effect of dexamethasone on post-operative nausea and vomiting in women undergoing thyroidectomy: a comparison of droperidol with saline. *Anesth Analg* 1999;89(1):200-203.
 10. Tzeng JI Wang JJ, Ho ST, Tang CS, Liu YC, Lee SC. Dexamethasone for the prophylaxis of nausea and vomiting after epidural morphine for post Caesarean analgesia: a comparison of droperidol with saline. *Br J Anaesth* 2000; 85(6):865-868.
 11. Splinter WM, Robert DJ. Prophylaxis for vomiting by children after tonsillectomy: dexamethasone versus perphenazine. *Anaesth Analg* 1997;85(3):534-537.
 12. Wang JJ, Ho ST, Liu YH et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. *Br J Anaesth* 1999;83(5):772-775.
 13. Fujii Y, Tanaka H, Toyooka H. The effects of dexmethasone on antiemetics in female patients undergoing gynaecologic surgery. *Anaesth Analg* 1997;85(4):913-917.
 14. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systemic review. *Anaesth Analg* 2000; 90(1):186-194.
 15. Glare PA, Dunwoodie D, Clark K, Ward A, Yates P, Ryan S, Hardy JR. Treatment of nausea and vomiting in terminally ill cancer patients. *Drugs* 2008; 68(18):2575–2590. doi:10.2165/0003495-200868180-00004.
 16. Jordan K, Schmoll HJ, Aapro MS. Comparative activity of antiemetic drugs. *Crit Rev Oncol Hematol* 2007;61(2):162–175.
 17. Manganaro R, Mami C, Gemelli M. The validity of the Apgar scores in the assessment of asphyxia at birth. *Eur J Obstet Gynecol Reprod Biol*. 1994;54(2):99–102.
 18. Ismail S, Shahzad K, Shafiq F. Observational study to assess the effectiveness of postoperative pain management of patients undergoing elective cesarean section. *Journal of Anaesthesiology, Clinical Pharmacology*. 2012;28(1):36-40. doi:10.4103/0970-9185.92432.
 19. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche 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. *Anesthesiology* 1999;91(6): 1919–1927.
 20. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2007;105(6):1615–1628.
 21. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992;77(1):162–184.
 22. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg* 1994;78(1):7–16.
 23. Zargar-Shoshtari K, Sammour T, Kahokehr A, Connolly AB, Hill AG. Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy. *Br J Surg* 2009;96(11):1253–1261. doi: 10.1002/bjs.6744.
 24. George RB, Allen TK, Habib AS. Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing caesarean delivery with intrathecal morphine: a systematic review and meta-analysis. *Anesth Analg* 2009;109(1):174–182. doi:10.1213/ane.0b013e3181a45a6b.
 25. Kumar K, Singh SI. Neuraxial opioid-induced pruritus: An update. *J Anaesthesiol Clin Pharmacol* 2013;29(3):303-307. doi:10.4103/0970-9185.117045.
 26. Abouleish E, Rawal N et al. Combined intrathecal morphine and bupivacaine for caesarean section. *Anaesth Analg* 1988; 67(4):370-374.