Arch Gynecol Obstet (2014) 290:47–52
DOI 10.1007/s00404-014-3152-5

MATERNAL-FETAL MEDICINE

The effect of gabapentin versus intrathecal fentanyl on postoperative pain and morphine consumption in cesarean delivery: a prospective, randomized, double-blind study

Abdolreza Najafi Anaraki · Kamran Mirzaei

Received: 11 December 2012 / Accepted: 9 January 2014 / Published online: 12 February 2014

Abstract
Purpose Pain after cesarean delivery is a leading cause of chronic pain and there are many attempts to reduce it without total success. Gabapentin is effective in reducing acute and chronic pain with little experience in parturient. The purpose of this study is to compare the effect of preemptive gabapentin with intrathecal fentanyl on reducing postoperative pain and morphine consumption in cesarean surgery.
Methods Seventy-eight primiparous women who scheduled for non-emergency cesarean delivery were enrolled in the study and separated into two groups. The control group received 12.5 mg of heavy bupivacaine 0.5 % plus 10 μg of fentanyl intrathecally and the case group received 300 mg of gabapentin orally 2 h before surgery and 12.5 mg of heavy bupivacaine 0.5 % intrathecally. Data collection including blood pressure, heart rate, neonate sedation, Apgar score, visual analogous scale at several hours, at first, need to analgesic postoperatively.
Results In the fentanyl group, the need for analgesic drug was earlier, total dose of morphine in 24 h and patient satisfaction was higher than the gabapentin group. The mean visual analogous scale at several hours postoperatively in the fentanyl groups was significantly higher than the gabapentin groups ($P = 0.001$).
Conclusion Preemptive use of gabapentin is a safe and effective way to reduce postoperative pain and morphine consumption in parturients after cesarean surgery.

Keywords Cesarean section · Gabapentin · Intrathecal fentanyl · Pain · Postoperative

Introduction

Although the rate of cesarean delivery is increasing but pain after delivery is a major concern and there are many attempts to reduce pain after cesarean delivery without total success [1–3]. Postoperative pain after cesarean can disturb care and breast feeding of the mother [3]. Opioid used for a long time to reduce postoperative pain but it is not without side effect especially when used intrathecally [4–6]. The four classic side effects of opioid are pruritus, nausea and vomiting, urinary retention and respiratory depression [4–6]. Most side effects are dose dependent and may be more common if opioids were used intrathecally [5, 6]. The preoperative use of gabapentin has been shown to decrease postoperative pain after many surgical procedures [7, 8]. One study in epileptic parturient showed that the rates of maternal complication, cesarean section, miscarriage, low birth weight and malformation are similar to those seen in the general population and found its use safe in pregnancy and breast feeding period [9, 10]. Chronic pain is a complication of untreatment or under treatment of acute pain [11]. Kainu et al. [11] confirmed that 6 month after cesarean delivery, some patients experience pain that affects baby care. It confirmed that gabapentin exposure during pregnancy did not lead to an increased risk for adverse maternal and fetal events [11]. The primary aim of our study was to investigate efficacy of 300 mg of oral gabapentin and 10 μg

A. Najafi Anaraki
Department of Anaesthesiology and Intensive Care Unit, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

K. Mirzaei (✉)
Department of Community Medicine, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran
e-mail: kamran.mirzaei@yahoo.com

of intrathecal fentanyl on postoperative pain. Secondary aim consists of patients' satisfaction.

Methods

This randomized double-blinded clinical trial was conducted between May 2012 and September 2012 in our educational hospitals and was approved by the ethics committee of our university and is registered at the clinicaltrials.gov database (Reference No. IRCT201202241936N8). This study was performed according to the requirements of the declaration of Helsinki. After attaining informed consent 78 full term primiparous women (ASA physical status I or II) scheduled for elective cesarean delivery under spinal anesthesia were enrolled in this study. Parturients with contraindications to neuraxial anesthesia or to any study medication, smoking, hepatitis, chronic use of gabapentin or opioid, patients with psychological problem, severe preeclampsia, parturients with known fetus abnormality and patients with diabetic mellitus were excluded. After obtaining writing informed consent, the patients were randomly divided with a computerized random number generator. Gabapentin capsule and lactose capsule in the same color were given to parturients of the gabapentin and control group by nurse staff, that is not involved in study, 2 h before surgery. Maternal demographic data including weight, age, body mass index (BMI) and gravidity was recorded. Before the spinal anesthesia was performed, the patients were placed under standard monitoring and received IV lactated Ringer's solution 8 mL/kg. Oxygen was provided during anesthesia, and the patients were covered with drapes but not actively warmed. The patients were divided equally into two groups ($n = 39$, each). The control group received intrathecal 0.5 % heavy bupivacaine 12.5 mg plus 10 μg of fentanyl (Arzneimittel Vertriebs-GmbH, Austria). The case group received 300 mg gabapentin (Gaptine 300 mg capsule; Pfizer, Goedecke GmbH, Germany) orally, 2 h before surgery and intrathecal 0.5 % heavy bupivacaine 12.5 mg. Case and control groups received spinal anesthesia in a sitting position at the L4–L5 interspace with a midline approach, using a 25-gauge needle (KIMBERLY-CLARK* Quincke Point Spinal Needle). Solutions were prepared by a second anesthesiologist so that the anesthesiologist performing the spinal block was blinded to the drug that was injected. The patients were placed in a supine position with left uterine displacement. Hypotension was defined as a decrease in systolic blood pressure to < 90 mmHg or 20 % less than baseline value. It was treated with 5–10 mg of ephedrine IV and bradycardia (heart rate < 50) was treated with intravenous atropine 0.5 mg. Nausea, sedation and pruritus were assessed on modified four-point ordinal scales (0 = absent, 1 = mild, 2 = moderate, 3 = severe) [12]. The degree of sedation was assessed in five-point scale: 1 = fully awake and oriented, 2 = drowsy, 3 = eyes closed but rousable to command, 4 = eyes closed but rousable to mild physical stimulation, 5 = eyes closed but unarousable to mild physical stimulation [13]. Sedation grades 3 and 4 were considered as deep sedation. Nausea treatment by metoclopramide 10 mg IV and pruritus was treated with slow infusion of diphenhydramine 25 mg as needed. After delivery of the neonate and clamping of umbilical cord IV syntocinon 15 U diluted in 1 L Ringer's lactate solution was infused till end of surgery. Neonatal demographic data including gestational age, birth weight, Apgar score at 1 and 5 min, neonate intensive care unit admission were recorded. An attending anesthesiologist assessed neonate Apgar score at 1 and 5 min after delivery and neonate was assessed by pediatrician attending if Apgar score was low (Apgar score lower than 7 within 5 min of the baby being born) [14]. According to our hospital practice all patients in control and case group received clindamycin 600 mg IV and diclofenac 100 mg rectally at the end of surgery. A urinary catheter was left in situ to be removed 24 h after surgery and patents transferred to recovery room till 1 h postoperatively. The pain treatment regimen was consisting of IV morphine 1 mg on demand of the patients with an interval of 5 min up to 10 mg in the first 24 h. Breakthrough pain was treated upon patient request with diclofenac 100 mg rectally and 2 mg morphine subcutaneously every 6 h. No other medication was given to patients in first day after surgery. After this time injection of morphine could be substituted with acetaminophen 1 g orally and diclofenac 100 mg rectally every 8 h on demand of the patients. Patients were assessed in recovery room and 2, 4, 6, 12, 24 h after surgery. In accordance with Dahlgren, a 100-mm visual analog scale (VAS) (0 = no pain,100 = the worst imaginable pain) was used postoperatively to assess pain on rest and after coughing [15]. Satisfaction with pain management was assessed by numerical rating scale (NRS) from 0 to 10 (0 = not satisfied, 10 = completely satisfied) [14]. Any difficulty in breast feeding of the ward was recorded.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, SPSS Inc, and Chicago, IL, USA). Descriptive statistics (e.g., mean and median) were used to assess the distribution of data for each variable. The Mann–Whitney test and Chi-square test were used to compare differences between groups. P values of 0.05 or less were considered to be significant.

Results

There were no significant differences between the groups in terms of demographic or surgical data (Table 1). The amount of bleeding, pulse rate, oxygen saturation, time of

Table 1 Maternal demographics

	Gabapentin group ($n = 38$)[a]	Fentanyl group ($n = 39$)	*P* value
Age (years)[b]	27 (4)	28 (4)	0.731
Weight (kg)[b]	78 (14)	79 (13)	0.455
BMI Score[b,c] (kg/m^2)	29 (3)	28 (3)	0.453
Gestational age (weeks)[b]	37.3 (1.3)	37.5 (1.1)	0.476
Duration of surgery (min)[b]	34 (10)	34 (9)	0.900

[a] One patient lost in the gabapentin group due to failure of the spinal block

[b] Mean (SD)

[c] Body mass index

Table 2 Maternal hemodynamic data

	Gabapentin group ($n = 38$)	Fentanyl group ($n = 39$)	*P* value
SBP[a] (mmHg)[d]			
Pre-induction	116.13 (10.72)	111.00 (9.63)	0.439
During cesarean section	114.58 (13.21)	109.54 (18.41)	0.172
In recovery room	101.77 (13.02)	104.42 (10.70)	0.333
DBP[b] (mmHg)[d]			
Pre-induction	64.50 (13.85)	65.38 (12.10)	0.766
During cesarean section	71.23 (13.91)	75.42 (10.73)	0.145
In recovery room	62.13 (12.80)	57.38 (13.37)	0.116
PR[c] (/min)[d]			
Pre-induction	94.33 (16.79)	88.30 (17.36)	0.125
During cesarean section	86.92 (12.35)	85.13 (12.46)	0.528
In recovery room	87.50 (16.22)	86.74 (15.57)	0.835
O_2 saturation[d]	98.76 (1.07)	98.85 (0.93)	0.718
Vomiting (%)	4 (10.26)	5 (12.82)	0.937
Shivering (%)	9 (23.08)	7 (17.95)	0.808
Pruritus (%)	0 (0.0)	0 (0.0)	1.000
Apgar[e]			
Min 1	10 (7–10)	10 (7–10)	0.404
Min 5	10 (9–10)	10 (9–10)	0.979
Onset of 1st analgesic (h)[d]	4.59 (1.63)	2.65 (0.92)	0.000
Total dosage of analgesic (mg)[d]	7.18 (3.26)	12.62 (5.16)	0.000
Mother sedation (%)			0.012
Score: 1	32 (84.2)	39 (100.0)	
Score: 2	6 (15.8)	0 (0.0)	
Patient satisfaction[e]	7 (4–10)	5 (1–9)	0.0001

[a] Systolic blood pressure

[b] Diastolic blood pressure

[c] Pulse rate

[d] Mean (SD)

[e] Median (range)

surgery, neonatal Apgar in minutes 1 and 5, shivering and vomiting were equal in two groups of participants after each time interval (Table 1).

We lost one patient in the gabapentin group due to failure of the spinal block. There was no need for rescue doses of fentanyl during the surgery in either group. There were no signs of bradycardia or respiratory depression in either of the groups. None of the patients suffered from postspinal headache or other neurologic complications. No sign of respiratory depression was seen in neonate in the gabapentin and fentanyl group.

The need for analgesic drug in the fentanyl group was earlier than the gabapentin group and total dose of morphine in 24 h was higher in the fentanyl group (Table 2).

The median (range) of maternal sedation score in gabapentin was higher than fentanyl groups [0.00(0–1) and 0.00(0–0), respectively] ($P = 0.012$).

The mean (95 % confidence interval) VAS scores were 24 mm (13–30) and 38 mm (24–56) in the gabapentin and fentanyl groups, respectively ($P = 0.001$) (Fig. 1).

Patient satisfaction was higher in the gabapentin group relative to the fentanyl group (Table 2).

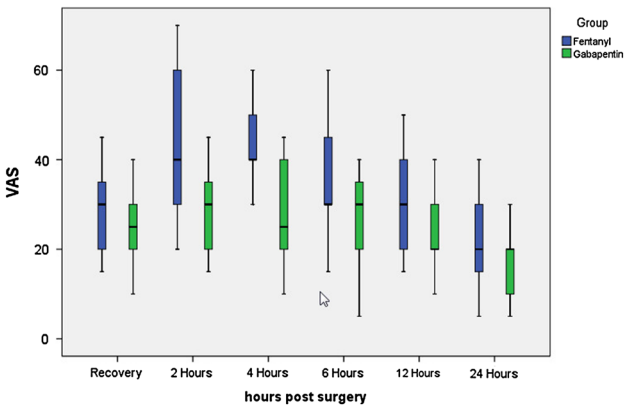

Fig. 1 Visual analog scale (VAS) scores at several hours post-surgery

Discussion

The results of our study suggest that a 300 mg single dose of gabapentin given orally 2 h before cesarean delivery can improve significantly pain scores in the first 48 h postpartum, reduce onset of first need and total dose of morphine consumption to relieve postpartum pain and increase patient satisfaction without any hemodynamic change in comparison to routine use of intrathecal opioid.

Unfortunately there are no clinical trails that compare the effect of intrathecal opioid and gabapentin on postoperative pain and there is only a few clinical trails on the effect of pre-emptive gabapentin on postoperative pain in parturient. Moore et al. [16] studied forty-six women undergoing cesarean delivery to receive preoperative gabapentin 600 mg, or placebo. Spinal anesthesia was achieved with 0.75 % hyperbaric bupivacaine 12 mg, fentanyl 10 μg and morphine 100 μg. Postoperative analgesia was initiated with intraoperative ketorolac and acetaminophen, and continued with postoperative diclofenac, acetaminophen and morphine. They assessed patients at 6, 12, 24 and 48 h after spinal anesthesia for pain at rest and on movement using a VAS, satisfaction, opioid consumption and side effects. They also assessed neonatal interventions, Apgar scores, umbilical artery blood gases and breastfeeding difficulties. Chronic pain was assessed 3 months after delivery. Maternal and umbilical vein gabapentin plasma concentrations were measured in a subgroup of patients. They resulted that pain scores on movement at 24 h were 21 mm in the gabapentin and 41 mm in the placebo group ($P = 0.001$) and maternal satisfaction was higher in the gabapentin group. There found no difference in opioid consumption between two groups. Severe maternal sedation was more common in the gabapentin group. There was no difference in neonatal Apgar scores, interventions or umbilical artery pH. The incidence of pain at 3 months was similar in both groups. They concluded that preoperative gabapentin 600 mg in the setting of multimodal analgesia reduces post-cesarean delivery pain and increases maternal satisfaction in comparison with placebo. There is some deference between our study and study of Moore and colleague. We did not inject intrathecal morphine because synergism effects of intrathecal morphine with gabapentin in CNS can enhance analgesia [8] and it could change our results. Sedation can influence perception of pain and is dependent to the dose of gabapentin; to avoid effect of sedation on pain score we used 300 mg of gabapentin. All the findings of this study confirm us. In present study we tried to avoid synergism effect on gabapentin on sedation score in case group by decreasing dose of gabapentin.

Ajori et al. [17] investigated effects of pre-emptive use of gabapentin on postoperative pain, nausea and vomiting and meperidine consumption in patients after hysterectomy by a double-blind randomized clinical trial. 140 patients were randomly assigned to one of two groups according to the method of treatment, gabapentin or placebo. Pain was assessed on a visual analogue scale (VAS) at 1, 4, 8, 12 and 24 h at rest. Patients in the gabapentin group had significantly lower VAS scores at all time intervals than those in the placebo group. The total meperidine consumed in the gabapentin group was significantly less than in the placebo group. Postoperative nausea and vomiting (PONV) and antiemetic drug consumption were significantly decreased in gabapentin group. They concluded that pre-emptive use of gabapentin 600 mg orally, significantly decreases postoperative pain and PONV, and also rescues analgesic and antiemetic drug requirements in patients who undergo abdominal hysterectomy. Some findings of this study confirm us (pain score and opioid consumption) and others (incidence of postoperative nausea and vomiting and antiemetic drug consumption) are against us.

Rorarius et al. [7] tested effect of gabapentin on prevention of acute nociceptive and inflammatory pain in animals and volunteers, especially when given before trauma. They gave 1,200 mg of gabapentin or 15 mg of oxazepam (active placebo) 2.5 h prior to induction of anesthesia to patients undergoing elective vaginal hysterectomy in an active placebo-controlled, double-blind, randomized study. Gabapentin reduced the need for additional postoperative pain treatment (PCA boluses of 50 μg of fentanyl) by 40 % during the first 20 postoperative hours. They concluded that visual analogous pain score (VAS) during the first 2 h postoperative at rest and activation were significantly higher in the active placebo group compared to the gabapentin-treated patients. In addition, pretreatment with gabapentin reduced the degree of postoperative nausea and incidence of vomiting/retching possibly either due to the diminished need for postoperative pain treatment with opioids or because of an antiemetic effect of gabapentin itself. The findings of this study explain and confirm lower pain score at rest and

coughing and reduce analgesic consumption in gabapentin group in our study, but incidence of vomiting/retching did not differ between case and control in our study.

Dirks et al. [18] investigated 70 patients undergoing radical mastectomy to determine effect of gabapentin on morphine consumption and postoperative pain in a randomized, double-blind study. All patients in case group received a single dose of oral gabapentin (1,200 mg) and control group received placebo 1 h before surgery. Patients received patient-controlled analgesia with morphine at doses of 2.5 mg with a lock-out time of 10 min for 4 h postoperatively. Pain was assessed on a VAS at rest and during movement, and side effects were assessed on a four-point verbal scale 2 and 4 h postoperatively. They found gabapentin reduced total morphine consumption ($P < 0.0001$). Pain during movement was reduced from 41 to 22 mm at 2 h postoperatively ($P < 0.0001$) and from 31 to 9 mm at 4 h postoperatively ($P = 0.018$). No significant differences between groups were observed with regard to pain at rest or side effects. They concluded that a single dose of 1,200 mg oral gabapentin resulted in a substantial reduction in postoperative morphine consumption and movement-related pain after radical mastectomy, without significant side effects. All finding of this study confirm us, except pain at rest.

Short et al. [19] studied effects of 300 or 600 mg oral gabapentin, or placebo on postoperative pain after delivery. One hundred thirty-two women were randomized in this study. Pain assessments at rest and on movement (VAS 0–100 mm) were recorded at 6, 12, 24 and 48 h after surgical incision. Pain on movement at 24 h, patient satisfaction with analgesia, supplemental opioid consumption, lactation difficulties, neonatal outcomes, maternal sedation and other adverse effects were recorded. Result showed no obvious difference between groups. They concluded that a single preoperative dose of gabapentin (300 and 600 mg) did not improve post-cesarean analgesia compared to placebo in the context of a multimodal analgesic regimen and a larger study is required. The findings of this study are against us.

We had one limitation in our study. It wasn't possible for us to measure maternal and umbilical gabapentin level to find best time of its administration and appropriate dose of gabapentin with less effect on neonate and most effect on pain perception in parturient. The best way to explain the finding of this study is to check correlation between blood gabapentin levels with parturient pain scores and neonate status.

Conclusion

Pre-emptive use of gabapentin is a safe way to reduce postoperative pain and morphine consumption in parturient after cesarean surgery and can be a substitute for intrathecal opioid especially in patients who are sensitive to side effect of opioids.

Conflict of interest Not declared.

References

1. Eltzschig HK, Lieberman ES, Camann WR (2003) Regional anesthesia and analgesia for labor and delivery. N Engl J Med 23(348):319–332
2. Halpern SH, Walsh VL (2001) Multimodal therapy for postcesarean delivery pain. Reg Anesth Pain Med 26:298–300
3. Miovech SM, Knapp H, Borucki L, Roncoli M, Arnold L, Brooten D (1994) Major concerns of women after cesarean delivery. J Obstet Gynecol Neonatal Nurs 23:53–59
4. Fukushima S, Takenami T, Yagishita S, Nara Y, Hoka S, Okamoto H (2011) Neurotoxicity of intrathecally administered fentanyl in a rat spinal model. Pain Med 12:717–725. doi:10.1111/j.1526-4637.2011.01084.x
5. Etches R, Sandler A, Daley M (1989) Respiratory depression and spinal opioids. Can J Anaesth 36:165–185
6. Chaney M (1995) Side effects of intrathecal and epidural opioids. Can J Anaesth 42:891–903
7. Rorarius MG, Mennander S, Suominen P, Rintala S, Puura A, Pirhonen R, Salmelin R, Haanpää M, Kujansuu E, Yli-Hankala A (2004) Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. Pain 110:175–181
8. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G (2000) Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Anesth Analg 91:185–191
9. Montouris G (2003) Gabapentin exposure in human pregnancy: results from the gabapentin pregnancy registry. Epilepsy Behav 4:310–317
10. Ohman I, Vitols S, Tomson T (2005) Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? Epilepsia 46:1621–1624
11. Kainu JP, Sarvela J, Tiippana E, Halmesmäki E, Korttila KT (2010) Persistent pain after caesarean section and vaginal birth: a cohort study. Int J Obstet Anesth 19:4–9. doi:10.1016/j.ijoa.2009.03.013
12. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond agitation–sedation scale. Am J Respir Crit Care Med 15(166):1338–1344
13. Wilson E, David A, MacKenzie N, Grant IS (1990) Sedation during spinal anaesthesia: comparison of propofol and midazolam. Br J Anaesth 64:48–52
14. Christensen M, Thomson V, Letson GW (2008) Evaluating the reach of universal newborn hearing screening in Colorado. Am J Prev Med 35(6):594–597. doi:10.1016/j.amepre.2008.09.007
15. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H (1997) Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg 85:1288–1293
16. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JCA (2011) Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesth Analg 112:167–173. doi:10.1213/ANE.0b013e3181fdf5ee
17. Ajori L, Nazari L, Mazloomfard MM, Amiri Z (2012) Effects of gabapentin on postoperative pain, nausea and vomiting after abdominal hysterectomy: a double blind randomized clinical trial. Arch Gynecol Obstet 285:677–682. doi:10.1007/s00404-011-2023-6

18. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB (2002) A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 97:560–564

19. Short J, Downey K, Bernstein P, Shah V, Carvalho JC (2012) A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: a randomized, double-blind, placebo-controlled dose-finding trial. Anesth Analg 115:1336–1342. doi:10.1213/ANE.0b013e31826ac3b9