A Blinded Study Using Celecoxib for Prevention of Morphine Induced Pruritus in Patients Undergoing Cesarean Section

Saghar Samimi; M.D.[1], Fatemeh Davari Tanha; M.D.[2], Masume Malekian; M.D.[2]

1 Anesthesiology department of women's hospital, Tehran University of medical sciences, Tehran, Iran
2 OBS & GYN department of women's hospital, Tehran University of medical sciences, Tehran, Iran

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Abstract

Objective: we aimed to evaluate the efficacy of celecoxib in reducing Intrathecal morphine-induced pruritus in parturient undergoing cesarean section delivery under spinal anesthesia.

Materials and methods: In a randomized double-blind placebo controlled study 126 women undergoing elective cesarean section under spinal anesthesia (0.5% bupivacaine 12mg plus 0.2 mg preservative-free morphine)were randomly allocated to receive celecoxib 400 mg or placebo, 2 hours prior to surgery. Severity of pruritus and pain score and frequency of opioid's side effects were recorded.

Results: patients receiving celecoxib had significantly lower pruritus incidence and severity at 30 min,2,4 and 8 hours (40% versus 82%), but not at 12 and 24 hours postoperatively. Also there was a reduction in pain score but it was not significant (1.5±0.5 versus 1.9±0.65).Analgesic requirement was similar between two groups.

Conclusion: Oral administration of celecoxib significantly reduced Intrathecal morphine-induced pruritus in parturient undergoing cesarean section under spinal anesthesia. There was no significant difference in pain scores and analgesic requirement.

Keywords: Pruritus, celecoxib, cesarean, morphin

Introduction

Spinal anesthesia using local anesthetics and opioid is a common and effective way to provide anesthesia and postoperative analgesia during and after cesarean section; morphine is commonly employed for this reason (1,2). However, when Intrathecal opioid are administered, pruritus occurs as an unwanted and troublesome side effect .Pruritus is an unpleasant and uncomfortable sensation which provokes an urge to scratch, particularly on the cheek,nose,eyelids, neck and upper thorax. The phenomenon is even more common in pregnancy with a reported as high as 80% (3,4).

Correspondence:
Dr. Fatemeh Davari, OBS& GYN department, Women's hospital, North Villa St., Karimkhan zand Ave., Tehran, IRAN
telefax: + 98- 21- 88313955
E–mail: fatedavari@yahoo.com

The mechanisms of neuraxial opioid-induced pruritus remain unclear.Postulated mechanisms include the presence of "itch center "in the central nervous system, medullary dorsal horn activation and antagonism of inhibitory transmitters. Modulation of the serotonergic pathway and involvement of prostaglandins may also be important in the etiology of neuraxial opioid-induced pruritus (5,6). It has been suggested that prostaglandins (PGE1 and PGE2) are involved in the etiology of pruritus. They enhance c-fiber transmission to the central nervous system, also release histamine and potentiate pruritus induced by histamine. The concurrent use of non-steroidal anti-inflammatory drugs (NSAIDS) has been reported to reduce the incidence of pruritus by inhibiting cyclooxygenases and decrease the formation of prostaglandins (7).

They also reduce analgesic consumption postoperatively but have undesirable side effects. Celecoxib, a cyclooxygenase 2 (COX2) isoenzyme specific inhibitor, due to its selectivity causes fewer side effects that make it an alternative option (8,9). The principal objective of our study was to evaluate efficacy of oral celecoxib for preventing of Intrathecal morphine-induced pruritus in parturient undergoing cesarean section under spinal anesthesia.

Materials and methods

The protocol was approved by ethics and clinical studies committee of Tehran University of Medical Sciences and informed consent was obtained from all patients who were in the study. This was a prospective double blind, randomized placebo controlled study, involving 126 full term women of ASA class I ,aged 18-40 years,weighting 55-75 kg, scheduled for elective cesarean section under spinal anesthesia. The exclusion criteria were: patient refusing to give informed consent and contraindication for or refusal of spinal anesthesia, patients with NSAIDs allergy or history of peptic ulcer, gastrointestinal bleeding or gastritis, severe cardiovascular respiratory and renal disease and treatment with opioid or NSAIDs within 48 hours of surgery. All patients were given a verbal explanation of scoring used for assessment of severity of pruritus and pain before surgery. Participants were randomly allocated equally to one of placebo or celecoxib groups, using a computer-generated list.

All patients were fasted over night. The patients in the celecoxib group received 400 mg of celecoxib orally and the patients in the placebo group received equal numbers of identical-looking capsules in which the active gradients had been removed and replaced by glucose powder,1 hour prior to surgery. After arrival in the operating room and intravenous access,15 ml/kg of ringer solution was infused before the initiation of the spinal anesthesia. Spinal anesthesia was performed in the sitting position with a 26 gauge whitacare needle, using a midline approach at L3-L4 orL4-L5 interspaces.

Once free CSF had been recognized the anesthetic solution was injected over 15 seconds. All patients received 12mg of 0.5% bupivacaine and 0.2 mg preservative-free morphine mixed in the same syringe. After Intrathecal injection, the patients were turned in supine position with left uterine displacement .Surgery was started when a sensory level up to T5 dermatome was obtained, for intraoperative sedation each patient received an iv injection of midazolam 0.05mg/kg before spinal anesthesia and after that each time that it was needed. Monitoring included intermittent non-invasive blood pressure monitoring, continuous electrocardiography and pulse oximetry. Ephedrine 0.1mg/kg was given if required, to keep systolic blood pressure greater than 95 mmHg. The surgical technique was uniform for all patients. The anesthetists were blinded to the study drugs. The nurse who prepared and administered the study drug was not involved in patient care.

After ending of surgerypatients were monitored in the post anesthetic care unit (PACU) with vital signs recorded every 5 min. The patients were asked by an investigator who was blinded to details of the study, about the presence location and severity of pruritus. The severity of pruritus was defined as no pruritus, mild pruritus, moderate pruritus and severe pruritus that needed rescue treatment .The primary outcome measure of study was the incidence of pruritus during 24 h follow-up period. Secondary outcome measures included onset time of pruritus ,duration and location of pruritus, also the pain score with using visual analogue scale (VAS) .assessments were recorded at 30 min,2 ,4 ,8 ,12 and 24 hours after administration of Intrathecal morphine .

The patients were discharged back to the ward when stable(hemodynamic and respiratory stability, sensory block no higher than T10).Postoperative pain was treated with two paracetamol tablets when the patient asked for an analgesic medication or her VAS were $\geq$ 5, chlorpheniramin 4 mg orally was administered as rescue pruritus relief. Sample size was determined prospectively .A power analysis showed that 60per treatment group would be adequate to provide an 80% power and a β value of 0.2 and a statistical significance of 0.05 for detection of a 50% difference in the incidence of pruritus. Statistical tests were performed using SPSS 12 for windows. Results are reported as absolute value, means or number. Continuous variables were analyzed using Student's T test. Nominal parametric data were analyzed using the fisher exact test or Mann-Whitney test. A P value <0.05 was considered statistically significant.

Results

All 126 patients completed the study. There were no significant differences between the two groups with

Table 1: Patients' demographic characteristics

Demographic characteristic	Placebo group	Celecoxib group	P value
Age (yr) (Mean± SD)	27.79±5.34	25.34±5.39	P>0.05
Weight (kg) (Mean± SD)	65.13±10.21	66.32±10.50	P>0.05
Height (cm) (Mean± SD)	156.42±6.22	159.21±5.36	P>0.05
Duration of surgery (min) (Mean± SD)	71.65±11.37	70.02±10.53	P>0.05
Incidence of hypotension	22%	25%	P>0.05
Ephedrine usage (Mean± SD)	1.0±5.4	1.2±4.8	P>0.05
Pain score (Mean± SD)	1.9±0.5	1.2±4.8	P>0.05

P value< 0.05 shows significance

regard to patient's age, height, weight and duration of surgery (Table 1). The maximal height of sensory block was similar in both groups (T6 – T10 derma toms). The frequency of hypotension did not differ between two groups (22 %in placebo group versus 25% in celecoxib group) and any difference in the use of ephedrine (placebo group 1.0±5.4 and celecoxib group 1.2± 4.8). No significant opioid related side effects were reported In the placebo group number of patients that developed pruritus in first 24 hours post operation was significantly larger than the corresponding proportion in the celecoxib group (52 (82.5%) versus , 25(40%)) , P<0.05% (Table 2).

The same analysis also demonstrated a significantly lower overall severity of pruritus in celecoxib group than the placebo group, (P< 0.05%. In the placebo group the number of patients that required rescue antipruritic treatment in the first 24 hours was significantly larger than that in celecoxib group(33(52%) versus ,14(22%)), P<0.05%.There was no difference among the groups with respect to time to onset of pruritus (celecoxib (128±50), placebo(136±42)) ,P>0.05% .75% of patients who developed pruritus in the study time experienced it at more than a site. There was no difference among the groups with respect to sites of pruritus: the most common site was face (70%) and then, neck (65%), chest (63%),back(39%) and abdomen and extremities (29%). The pain score was lower in celecoxib group but that was not significantly. Analgesic requirement was similar between two groups. (Table 1,2).

Discussion

Intrathecal morphine is an attractive option for anesthetic practice, providing successful analgesia and is commonly used for pain relief in patients. undergoing cesarean section delivery. However, a wide variety of clinically relevant side effects have been reported. One of the most common side effects is pruritus Itch is by definition a sensation that provokes the desire to scratch and it is bothersome to the patients and sometimes may be more unpleasant than pain itself for the patient[10]. Reported incidence in parturient is high and different, varies between 60% to 100% (11).

This increased incidence may be due to an interaction of estrogen with opioid receptors. The treatment of Intrathecal opioid-induced pruritus remains a challenge. Many pharmacological therapies including antihistamines, 5-HT-receptor antagonists, opioid antagonists, propofol, NSAIDs and droperidol have been studied (12,13). It has been suggested that prostaglandin (PGE1 and PGE2) release may be associated with neuraxial opioid- induced pruritus (14,15).

Table 2: Characteristics of pruritus in two groups

	Placebo group	Celecoxib group	P value
Incidence of pruritus n (%)	52(82.5)	25(40)	<0.05
Time to onset of pruritus Mean± SD	128±50	136±42	<0.05
Pain score (n)			
0	11	38	<0.05
1	22	15	
2	30	10	
Rescue antipruritic n (%)	52 (82.5)	25 (40)	<0.05

P value <0.05 shows significanc

Colbert and colleagues assumed that the antipruritic effects of NSAIDs in patients following Intrathecal and epidural opioid may have been largely due to their analgesic effect. They showed rectal administration of diclofenac significantly reduces the incidence and severity of postoperative pruritus and also significantly reduces pain and analgesic requirement (16).

NSAIDs have the advantage of improving postoperative pain control in cesarean section delivery. Hence, the combination of NSAIDs and subarachnoid morphine may provide better quality analgesia in the post operation period than Intrathecal morphine alone. These drugs inhibit COX-1 isoenzyme that plays an important role in many homeostatic mechanisms thus NSAIDs have undesirable side effects. The recent developments of drugs that can specifically inhibit the cyclooxygenase 2 isoenzyme have become an attractive alternative (17,18). Lee and colleagues studied the effect of celecoxib on Intrathecal morphine-induced pruritus in patients undergoing cesarean section, but their study failed to demonstrate any significant antipruritic or analgesic effects of celecoxib in a single dose of 200 mg (administered after delivery of baby) within the first 24 hours postoperatively. Lee suggested that cause of the failure was inadequate dosing of celecoxib and timing of administration and possible altered pharmacokinetic (19).

Recart and colleagues showed that a 400 mg dose provided more effective in post operation analgesia (20). Our study with using of 400 mg celecoxib orally 1 hour before surgery showed effectiveness of celecoxib in decreasing incidence of Intrathecal morphine-induced pruritus. We suggested, timing of administration was important because the time of peak effect of celecoxib with regard to its latency in parturient was almost correlated with initiation of Intrathecal morphine-induced pruritus. But our study did not show significant difference in pain score between two groups.

Conclusion

400 mg celecoxib administered 1 hour prior to cesarean section was more effective than placebo for the prevention of Intrathecal morphine-induced pruritus in parturient undergoing cesarean section under spinal anesthesia. Therefore, celecoxib may be an alternative treatment for this side effect. The pain score was lower in celecoxib group but that was not significant, maybe it needs to administration of a larger dose of celecoxib.

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