Effectiveness of Intrathecal Morphine for Analgesia following Elective Caesarean Section

Koju RB[1,2], Gurung BS[3], Dongol Y[4]

[1]Department of Anaesthesia and Critical Care, KIST Medical College, Lalitpur, Nepal, [2]Department of Anaesthesia and Critical Care, Nagarik Community Teaching Hospital, Bhaktapur, Nepal, [3]Department of Obstetrics and Gynaecology, KIST Medical College, Lalitpur, Nepal, [4]Department of Biochemistry, KIST Medical College, Lalitpur, Nepal

Received: *January 05, 2015;* **Accepted:** *June 12, 2015*

Aims: This study evaluates the effectiveness of usage of 0.2 mg intrathecal morphine as post-operative analgesia and its effect on activity of mother after elective cesarean section.

Methods: This hospital based prospective, randomized, double-blinded and placebo controlled study was carried out at Nagarik Community Teaching Hospital, Bhaktapur between 2012 January to 2014 November after the approval was taken from the hospital authority and the written informed consent from the participating patients. Fifty women of ASA I or II physical status undergoing cesarean section under sub-arachnoid block was randomized into two groups – P group (placebo group, n = 25) and M group (Treatment group, n = 25). P Group received hyperbaric bupivacaine 2.3ml, 0.5% bupivacaine (11.5 mg) and M Group received morphine 0.2 ml (0.2 mg) plus bupivacaine 2.3ml, 0.5% (11.5 mg) intrathecally. All subjects received 8 mg ondansetron intravenously 30 minutes before surgery to prevent possible drug-induced pruritus and post-operative nausea and vomiting. 1000 mg rectal acetaminophen suppository was given at the end of the surgery. Pain, nausea and pruritus during the first 24 hours using visual analog scale were recorded by a trained nurse or attending doctor who was not involved in the study.

Results: Duration of complete analgesia and the time to request for additional analgesics was longer in M Group than in P Group. Similarly, the active movement is earlier in M Group than in P Group. There were no significant differences in adverse effects between the groups.

Conclusions: Addition of morphine 0.2 mg to heavy bupivacaine intrathecally reduced post-operative pain and analgesic requirements without any significant difference in adverse effects.

Keywords: caesarean section; intrathecal morphine; post-operative pain.

INTRODUCTION

It is a great challenge to all anaesthetics in providing optimal analgesia. The main purpose of any anaesthesiologist is to provide satisfactory pain relief with a minimal cost. Now-a-days, there are many post-operative pain controlled methods, such as patient controlled analgesia (PCA) or patient controlled epidural analgesia (PCEA), which are more expensive and may not be appropriate because of lack of knowledge among the patients. On the other hand, the sedative effects of the opioids and motor blockade due to local anaesthetics may limit the mother's ability to care for her child shortly after delivery.[1] Administration of intravenous PCA with pethedine to breast feeding mother after caesarean section may cause neonatal neurobehavioral depression.[2]

CORRESPONDENCE

Dr Ram Bhakta Koju
Department of Anaesthesia and Critical Care
KIST Medical College, Lalitpur, Nepal
Email: dr.koju@gmail.com
Phone: +977-9841113271

Sub-arachnoid block (SAB) is very popular for caesarean section because this technique is very easy and provides adequate muscle relaxation of abdominal muscles and adequate intra and post-operative analgesia.[3] Single dose of intrathecal morphine decreases post-caesarean opioid requirements and may reduce or prevent neonatal neurobehavioral depression due to maternal analgesia.[2]

The addition of intrathecal morphine to local anaesthetics provide an effective and prolonged post-operative analgesia but has been associated with incidence of pruritus.[4] Acetaminophen, when given along with opioids, potentiates the effect of opioid analgesia. Hence, small dose of intrathecal morphine combined with acetaminophen per rectally, antiemetics and medications for prutitus is clinically relevant to study post-caesarean delivery analgesia.[5-7]

In our clinical setting, we undertook a prospective, randomized, double blinded and placebo controlled study to assess the effectiveness of 0.2 mg intrathecal

injection of morphine along with 0.5%, 2.3 ml heavy bupivacaine on post-operative analgesia and activity of mother after elective caesarean section.

METHODS

This prospective, randomized, double blinded and placebo controlled study was conducted in Nagarik Community Teaching Hospital, Bhaktapur between 2012 January to 2014 November. The hospital authority approved the study protocol and written informed consent was taken from each patient. Parturients of American Society of Anesthesiologists (ASA) I or II physical status scheduled for caesarean section under spinal anaesthesia were recruited in the study. Term size was 37 completed gestation weeks with singleton or post term cases. All subjects weighed between 50-100 kgs. Parturients with history of heart disease, respiratory insufficiency, known allergy to any of the study drugs and foetal compromises for example malfunction, underweight and cardiorespiratory insufficieny were excluded from the study. Similarly, patients with any contraindication for spinal anaesthesia or those who refused to participate in the study were also excluded.

Fifty patients were randomly divided into two groups – P group (placebo group, n = 25) and M group (Treatment group, n = 25). All patients received 0.5%, 2.3 ml (11.5 mg) preservative free heavy bupivacaine. P group received 0.2 ml of normal saline and the M group received 0.2 ml (0.2 mg) morphine, for a total volume of spinal injection of 2.5 ml. The study drug and the placebo were prepared by an anesthetic nurse. She also assisted in maintaining the randomization of sample in a double-blinded fashion, using a simple lottery method. She was oriented of the study procedure but neither involved in the study nor in the patient care. Therefore, both the patients and the anaesthesiologists performing the spinal anaesthesia and collecting the post-operative data were blinded as to the study drugs.

Following fluid preload of 1000 ml crystalloid solution, spinal anaesthesia was performed using a 25 gauze Whitacre or Quincke needle with the patient in left lateral or sitting position, at the level of L3-L4 or L4-L5. 8 mg ondansetron intravenous was given to all patients in both the groups 30 minutes before SAB. ECG, NIBP, SpO_2 and heart rate were continuously monitored. 1000 mg rectal acetaminophen suppository was given at the end of the surgery to both of the groups. A visual analog scale (VAS) was used to assess post-operative pain with anchor point at 0 mm and 100 mm marked scale (0 = No pain and 100 mm = worst pain).

The surgery was started when the sensory block reached the level of T4, as detected by the loss of cold sensation. The end point of this study was 24 hours post-operative period. Post-operative care was provided as per the institutional monitoring protocol. Our post-operative ward is well equipped with monitors, 24-hours on duty doctors, experienced nurses and bed-side availability of naloxone. Staffs were instructed to be aware of the study patients who may become drowsy due to intrathecal morphine, monitor SpO_2, respiratory rate, send ABG if needed and report to anesthesiologist. Attending doctors or nurses– who were blinded observers – were involved in the patient care and data collection in the format provided.

From the study of Terajima et al.,[8] we used the standard deviations of pain at rest during 24 hours to detect the difference of 18 units in average pain score between two groups, with 80% power and at 5% level of significance. The minimum sample size calculated was 24 in each group.

Statistical analysis was performed using chi square test and data were presented in mean with standard deviation and the percentage. P-value less than 0.05 was considered to be significant.

RESULTS

All the enrolled patients participated until the completion of the study. Demographic characteristics, as shown in table 1,

Table 1. Demographic Characteristics of the Patients *(Mean ± SD)*

Variables	Study Group Placebo (P); n=25	Treatment (M); n=25	p-value
Age (years)	25.2 ± 3.27	24.2 ± 3.56	0.859
Height(Cm)	157.4 ± 4.77	155 ± 4.12	0.895
Weight(Kg)	69.2 ± 9.96	70 ± 8.56	0.845

were similar in both groups. The new born characteristics in both the groups were also similar and the APGAR Score in 1 minute and 5 minutes

were similar and within normal limits, which was shown in Table 2.

Table 2. New Born Baby Characteristics *(Mean ± SD).*

Variables	Study Group: Placebo (P); n=25	Treatment (M); n=25	p-value
Weight (gms)	3100 ± 300	3110 ± 250	0.857
APGAR score			
1 minute	8.7 ± 0.6	8.7 ± 0.6	0.999
5 minute	9.0 ± 0.5	9.1 ± 0.5	0.857

Table 3 illustrates the VAS pain score within 24 hours in the two groups at two different situations; namely, at rest and during movement. At rest, M Group (30 ± 10 mm) have significantly lower pain score than P Group (70 ± 20 mm). During movement as well, the pain score between the two groups are statistically significantly – 60 ± 20 mm in M group whereas 80 ± 10 mm in P group.

Table 3. Maximum Pain Score within 24 hours Post-operation scored in VAS *(Mean ± SD).*

Variables	Study Group: Placebo (P); n=25	Treatment (M); n=25	p-value
At rest (in mm)	70 ± 20	30 ± 10	<0.0001
During Movement (in mm)	80 ± 10	60 ± 20	<0.0001

The duration of complete analgesia and time of first request for additional analgesia were longer in M group than in P group with p-value less than 0.0001 (statistically significant), as shown in table 4.

Table 4. Time of Request of Additional Analgesia *(Mean ± SD).*

Variables	Study Group: Placebo (P); n=25	Treatment (M); n=25	p-value
Time of first additional analgesia request (in hours)	5.0 ± 2	24.0 ± 0	<0.0001

In M group request for first additional analgesia was after 24 ± 0 hours whereas in P Group it was 5 ± 2 hours. 90% of the patients requested for analgesia within 24 hours in P group whereas no patient had requested for additional analgesia in M group (table 5). The opioid used in cases of additional analgesia was tramadol injection.

Table 5. Use of Additional Analgesia to manage the Post-caesarean Pain.

Variables	Study Group: Placebo (P); n=25	Treatment (M); n=25	p-value
Analgesic requested within 24 hrs	90%	0%	<0.0001
Total tramadol dose (mg/pt) at 24 hours	50 ± 25mg	0 ± 0.0	<0.0001

Regarding the adverse effects, the incidence of pruritus was same (5%) in both the groups and was cured without any medication. Similarly, the incidence of nausea was also same (3%) in both the groups and was treated by injection metoclopramide intravenous, if needed (table 6).

Table 6. Adverse Effects observed in the Patients under SAB.

Variables	Study Group: Placebo (P); n=25	Treatment (M); n=25
Pruritus	5%	5%
Antipruritic use	0%	0%
Nausea	3%	3%

The significant decrease in the incidence of pruritus and nausea might be due to prophylactic administration of ondansetron. There was no question of retention of urine because all patients were catheterized with foley's catheter.

DISCUSSION

Morphine, an opioid, is an alkaloid constituent of opium. It is dried latex obtained as natural product in opium poppy (Papaver Somniferum). Morphine is an archetypal opioid which, in clinical medicine, is still considered as a gold standard of analgesic therapy used to relief intense pain. It elicits analgesia by stimulating the opioid receptors, a G protein coupled receptor (GPCR) highly expressed in the CNS.[9] Morphine-6 beta-glucronide is a major metabolite of morphine with potent analgesic effect and is 5 fold

more effective at the level of the spinal cord than supra-spinally.[10]

This study shows that additional intrathecal morphine 0.2 mg with 0.5% heavy bupivacaine for elective caesarean section is highly effective in reducing post-operative pain and analgesic requirement. These findings are very much similar to other studies.[8,11] Intrathecal morphine provides very effective analgesia after caesarean delivery even when administered in very small doses (25-200mcg).[12] Intrathecal morphine when combined with other analgesia such as ketorolac and other NSAIDs for post-caesarean pain management are found to be very effective.[6,13] NSAIDs and intrathecal morphine seems to act synergistically.[4,5,13] Similarly, acetaminophen is well known to potentiate opioid analgesia.[7] Multi classes of analgesic administration simultaneously to the same patient produces competitive, additive or synergistic effects resulting into powerful analgesic effects and also decreases side effects due to the use of minimal doses in such scenario.[8]

SAB induced prior to surgical incision attenuates peripheral and central sensitization.[14] On the other hand, pain is also induced by uterine contraction due to involvement of several chemical nociceptive pathways,[15] which is mediated by prostaglandin cascade.[16] This theory postulates the effectiveness of intrathecal morphine and NSAIDs combination therapy for post-caesarean pain management but it may concern post-operative platelet dysfunction. So, this study explores the effectiveness of intrathecal morphine and the rectal acetaminophen suppository. Small dose of intrathecal morphine if used along with other analgesia provide adequate pain relief after caesarean delivery without respiratory depression or compromising mothers ability in caring her new born baby.[8] Early mobilization also decreases complications such as deep vein thrombosis (DVT).[17]

Pruritus and nausea are common and troublesome side effects of neuraxial opioid administration after caesarean section. Intravenous droperidol,[18] ondansetron[19] and dexamethasone[20] all are found to be effective to decrease nausea and pruritus after caesarean delivery. Activation of opioid receptor and 5-HT3 receptors in the dorsal part of spinal cord and the nucleus of the spinal tract of the trigeminal nerve in the medulla by neuraxial opioid administration or by circulating oestrogen in the parturients result into neuraxial opioid-induced pruritus.[21] In this study, the incidence of puritus and nausea are similar in both the groups because of prophylactic administration of 8 mg ondansetron 30 minutes before surgery. Intrathecal morphine is safe for new born baby as the APGAR score in 1 minute and 5 minutes are similar and within normal limits in both the groups because of very minimal systemic absorption of intrathecal morphine. The onset of intrathecal morphine is 30-60 minutes,[22] so baby can be delivered before the occurrence of effect of intrathecal morphine.

This study suggests that intrathecal morphine in very small dose 0.2 mg has an effective role in post-caesarean delivery pain management. The results of this study are in good agreement with the work of Rosaeg et al[23] who have shown that intrathecal morphine is effective as part of multimodal pain management after caesarean delivery.

CONCLUSIONS

Very small doses of intrathecal morphine added to bupivacaine for spinal anaesthesia for caesarean delivery provides effective analgesia to mothers at rest and during activity such as breast feeding, locomotive activities in the ward etc, up to 24 hours and reduced intravenous opioid requirements. Similarly, it also does not pose the adverse effects to the newborn since it has lesser and delayed systemic absorption.

DISCLOSURE

The authors report no conflicts of interest in this work.

No violation of human rights and safety.

Funding: Nil

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