ISSN 2515-8260 Volume 9, Issue 3, Winter 2022

INTRATHECAL HYPERBARIC BUPIVACAINE WITH VARYING DOSES OF BUPRENORPHINE AS AN ADJUVANT FOR POSTOPERATIVE ANALGESIA AFTER CAESAREAN SECTION

[1]Dr Thatipamula Nagapraveen, [2]Dr Vuppu Bhavani, [3]Dr Neela Sandeep Kumar, [4*]Dr Pakala Swathi

[1]Assistant Professor , Department of Anaesthesiology: Gandhi Medical College, Hyderabad
[2]Senior resident : Department of Anaesthesiology, Telangana Institute of Medical Sciences & Research(TIMS):Gachibowli, Hyderabad, Telangana.
[3]Assistant professor : Department of Anaesthesiology: Government Medical College : Nizamabad.
[4*]Senior resident, Department of Anaesthesiology: Mallareddy Institute of Medical Sciences, Suraram, Quthubullarpur, Hyderabad.

***Corresponding author: Dr Pakala Swathi, Email- swathir458@gmail.com**

ABSTRACT

Introduction: Postoperative analgesia after cesarean section poses unique clinical challenges to anesthesiologist. Intrathecal buprenorphine is a promising drug for postoperative analgesia.
Aims: The aim of this study was to compare the efficacy of two doses of buprenorphine (45 μg and 60 μg) as an adjuvant to hyperbaric bupivacaine for postoperative analgesia in caesarean section.
Materials and methods: This was a prospective, randomized, double-blind controlled study. Ninety ASA physical status Class II parturients posted for elective caesarean section. The computer-generated simple random sampling procedure was used to allocate the subjects into three Groups A, B, C of 30 each.
Results: Addition of buprenorphine to intrathecal bupivacaine prolonged the duration and quality of postoperative analgesia without producing any major side effect. The maximum duration of analgesia and hence decreased analgesic requirement were obtained with 60 μg buprenorphine. Addition of buprenorphine did not have any adverse outcome on the baby as assessed by Apgar score.
Conclusion: Addition of buprenorphine to hyperbaric bupivacaine provides postoperative analgesia after cesarean section without significant maternal and neonatal side effects.
Keywords: Buprenorphine, Hyperbaric bupivacaine, Postoperative analgesia.

INTRODUCTION

Pain has been a scourge for humankind and much effort has been done to understand it and thereby control it. Postoperative pain by virtue of its unique transient nature is more amenable to therapy. The rate of caesarean deliveries has increased globally over recent years. Adequate postoperative pain relief after caesarean section avoids the adverse effects of pain on various systems in the mother and facilitates early mobilization and better nursing of the baby. It is inevitable that the mode of analgesia should be safe and effective, which will not interfere with the mothers' ability to take care of her baby along with zero adverse effects to the newborn. Eisenach *et al.* found 2.5 times increased risk of persistent pain and 3.0 times increased risk of postpartum depression in women experiencing severe acute postpartum pain.

Subarachnoid block (SAB) has become the preferred anaesthetic technique for patients undergoing elective caesarean delivery.Opioids remain the mainstay among the various adjuvants to local anaesthetics (LAs) in SAB primarily by virtue of its various properties such as reducing the dose of LA, minimizing side effects, and prolonging the duration of anaesthesia.American Society of Anaesthesiologists (ASA) recommends neuraxial opioids over intermittent administration of parenteral opioids for postoperative analgesia after neuraxial anaesthesia for caesarean section.As smaller doses are used intrathecally, neonatal drug transfer is negligible compared to epidural or parenteral opioids. Although morphine is the gold standard for postoperative analgesia, its use is associated with inherent side effects such as delayed respiratory depression, nausea, vomiting, and pruritus. Moreover, developing countries face a limited supply of preservative-free preparation. [1,2]
Buprenorphine is an agonist-antagonist opioid, about thirty times more potent than morphine. It is a centrally acting lipid soluble analog of the alkaloid thebaine with both spinal and supraspinal components of analgesia.In addition, it has a ceiling effect on respiratory depression but not on analgesia.The antihyperalgesic property of buprenorphine helps in preventing central sensitization.Its high lipid solubility, high affinity for opioid receptors, and long duration of action makes buprenorphine a good choice as an adjuvant to intrathecal LA for managing moderate to severe postoperative pain. Buprenorphine is readily available as a preservative-free preparation which is compatible with the cerebrospinal fluid (CSF). Intrathecal doses (30 μg–150 μg) are much smaller than parenteral doses and are known to prolong analgesia without sensory or motor blockade. [3]Being more lipophilic than morphine, buprenorphine has low medullary bioavailability after neuraxial administration so that the occurrence of side effects is lesser, making it an attractive alternative.

METHODS AND METHODOLOGY

This was a prospective, randomized, double-blind controlled study. The study was conducted at a tertiary care centre after obtaining approval from the Institution Ethics Committee and written informed consent from all patients who participated in the study. Ninety ASA physical status Class II parturients posted for elective caesarean section. The computer-generated simple random sampling procedure was used to allocate the subjects into three Groups A, B, C of 30 each.

Inclusion criteria: Age of 20 and 35 years, with height of 145–175 cm and body weight 45–85 kg were selected for this study.

Exclusion criteria:Coexisting systemic illness, emergency surgery, history of allergy to LAs or opioids, patient refusal, fetal distress, or any contraindication to SAB. Those with failed or partial block.
A thorough preoperative assessment was done on the day before surgery to exclude any systemic illness and to select patients according to the criteria. Body weight, height, and vitals were recorded. All patients were advised overnight fasting. Aspiration prophylaxis was done with oral ranitidine 150 mg on the night before surgery and in the morning along with metoclopramide 10 mg. Procedure was explained to the patient and visual analog scale (VAS) discussed. Monitors were attached and oxygen was administered with simple face mask throughout the surgery. Intravenous access was secured using an 18-gauge cannula sited in the nondominant hand. After bladder catheterization, patients were turned to lateral position. Under strict aseptic precautions, SAB was performed at L3–L4 interspace using a 25-gauge spinal needle by midline approach. After clear CSF tap, the drug was injected into the subarachnoid space.
• Group A received 1.8 ml (9 mg) of 0.5% hyperbaric bupivacaine with 45 μg buprenorphine

• Group B received 1.8 ml (9 mg) of 0.5% hyperbaric bupivacaine with 60 μg buprenorphine
• Group C (control) received 1.8 ml (9 mg) of 0.5% hyperbaric bupivacaine to which 0.2 ml of sterile normal saline was added.

Buprenorphine was taken in tuberculin syringe so as to add it precisely. The study medication was administered by an anaesthesiologist not involved in the care of patient or collection of data. The principal investigator blind to the identity of study medication, monitored and managed the patients, and collected data.

After the subarachnoid injection, patients were immediately turned to the supine position and a wedge was kept under the right buttock. Heart rate, blood pressure, and respiration were monitored every 3 min for 15 min and every 5 min thereafter. Surgery was started when the sensory level reached T4 level (assessed with pinprick) and this was taken as the time of onset of analgesia. Intraoperative fluid maintenance was done with ringers lactate. After delivery of the baby, 10 units of oxytocin was administered as an infusion in ringers lactate. Neonatal status was assessed by Apgar scores at 1 min and 5 min after delivery. Sensory level was rechecked during the procedure and peak sensory level attained was noted. The total duration of surgery was noted and the time of completion of surgery was taken as the postoperative 0 h. No other analgesics or sedatives were given intraoperatively. Postoperatively, pulse rate, blood pressure, and respiration were monitored at 1 hour, 2 hour, 6 hour, 12 hour and 24 hour intervals.

Postoperative analgesia was assessed hourly using VAS. The duration of postoperative analgesia was calculated as the time interval between the completion of surgery to the appearance of pain corresponding to VAS score of 4. Rescue analgesia was with diclofenac 75 mg IM. Patients were evaluated for efficacy of postoperative analgesia by analyzing the maximum pain score attained using VAS during the 24 h period. Pain both at rest and movement was assessed.

Every hour, patients were monitored for the appearance of sedation and respiratory depression. Respiratory depression was taken as respiratory rate <10/min. Sedation was assessed using sedation scoring system; 0: none (awake and alert), 1: mild (drowsy but easy to arouse), 2: moderate (frequently drowsy but still fully arousable), 3: severe (difficult to arouse). The highest score attained was noted.

Other side effects such as postoperative nausea and vomiting (PONV) and pruritus were watched for. As bladder was catheterized, urinary retention was not looked into. Patients who had nausea or vomiting were treated with ondansetron 4 mg intravenous. Pruritus was treated with pheniramine maleate.

The data collected were entered into a master chart and necessary statistical tables were constructed. The statistical constants such as arithmetic mean, standard deviation, and percentage were computed to get valid inference about the data for comparison. Unpaired *t*-test and Chi-square test were used to test the significance of difference between the groups. Peak sensory levels, maximum pain score, and side effects were analyzed using Chi-square test and the rest using unpaired *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1: Distribution by Mean Age of the study groups

AGE (in years)	Group A	Group B	Group C	P value
Mean	24.17	25.77	24.70	.265, NS
Standard deviation	2.842	4.840	3.573	
Height				
Mean	156.93	157.06	157.20	0.941, NS
Standard deviation	3.51	2.40	2.88	

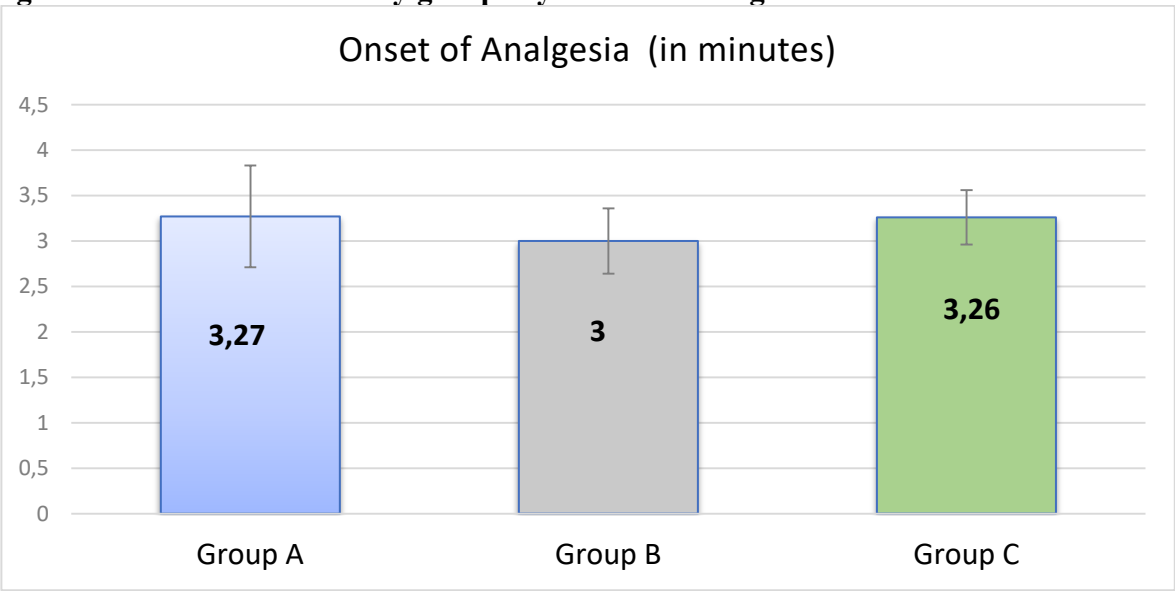
Weight				
Mean	67.57	67.67	64.63	0.054, NS
Standard deviation	5.09	5.77	5.41	

In the present study, the three groups were allocated such that there was no significant statistical difference between the groups with respect to mean age, height and weight of the participants ($p > 0.05$).

Table-2: Distribution of study groups by Onset of Analgesia.

Onset of Analgesia	Group A	Group B	P value
Group A Vs Group B			
Mean	3.27	3.00	0.030, S
Standard deviation	0.56	0.36	
Group A Vs Group C			
Mean	3.27	3.26	0.010, S
Standard deviation	0.56	0.30	
Group B Vs Group C			
Mean	3.00	3.26	0.003, S
Standard deviation	0.36	0.30	

Figure-1: Distribution of study groups by Onset of Analgesia



In the present study, a statistically significant difference was seen between the Mean Duration of Onset of Anaesthesia of three groups.

Table-3: Distribution of study groups by Peak Sensory Level attained

Peak Sensory Level attained	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)
T2	4 (13.3%)	6 (20%)	2 (6.7%)
T4	19 (63.3%)	20 (66.7%)	21 (70%)
T6	7 (23.3%)	4 (13.3%)	7 (23.3%)
TOTAL	30 (100%)	30 (100%)	30 (100%)
Chi square = 3.100, df = 4, p = 0.541, NS			
Group A versus group B			p = 0.536, NS

Group A versus Group C	p = 0.681, NS
Group B versus Group C	p = 0.241, NS

In the present study, in majority, 63.3%, 66.7% and 70% of the cases of Group A, B and C, the Peak sensory level attained was at the level of T4 and the difference was found to be statistically not significant.

Figure-2: Distribution of study groups by Peak Sensory Level attained

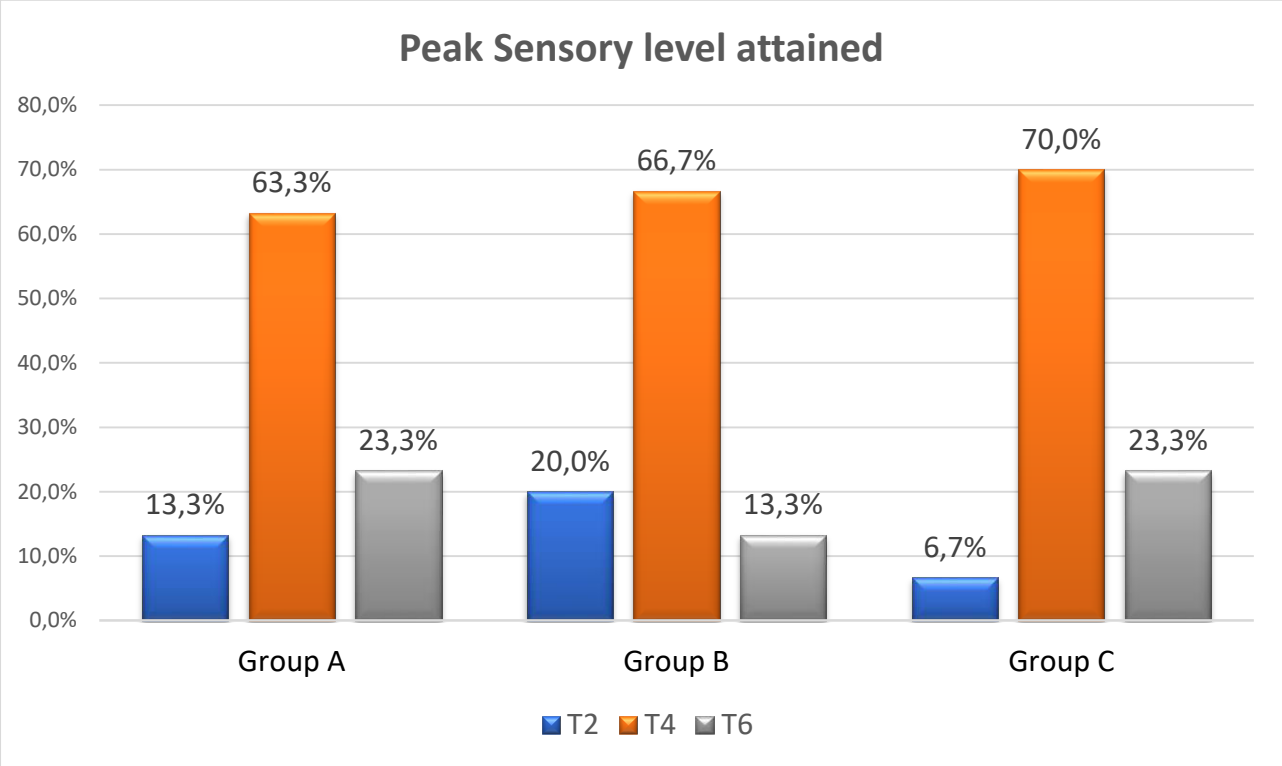


Table-4: Distribution of study groups by Duration of Surgery.

Duration of Surgery (in minutes)	Group A	Group B	P value
Group A Vs Group B			
Mean	49.17	47.87	0.137, NS
Standard deviation	4.08	2.38	
Group A Vs Group C			
Mean	49.17	47.43	0.103, NS
Standard deviation	4.08	4.06	
Group B Vs Group C			
Mean	47.87	47.43	0.610, NS
Standard deviation	2.38	4.06	

In the present study, a statistically significant difference was not seen between the Mean Duration of surgery between the three groups.

Figure-3: Distribution of study groups by Duration of Surgery.

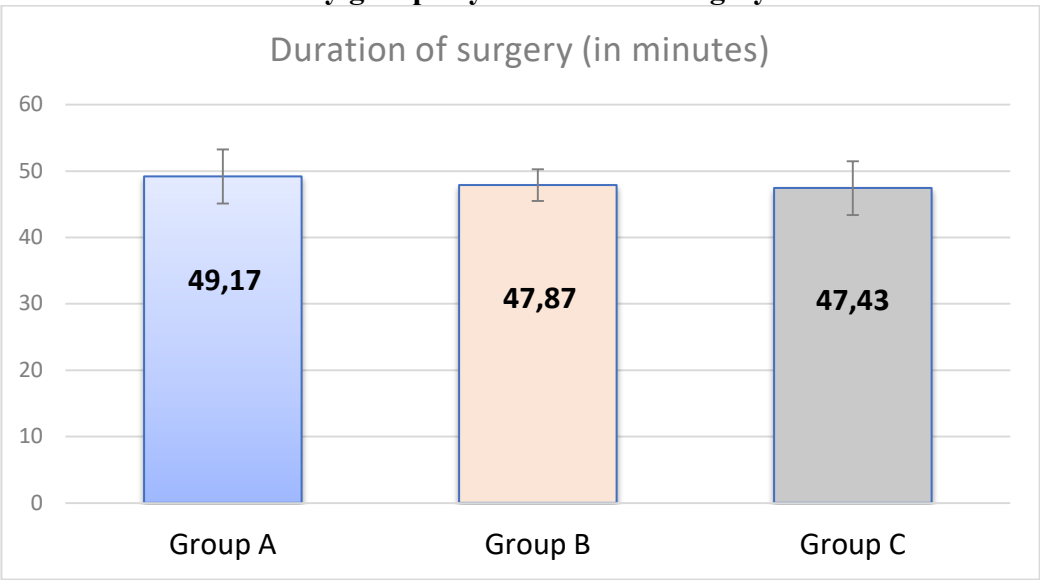
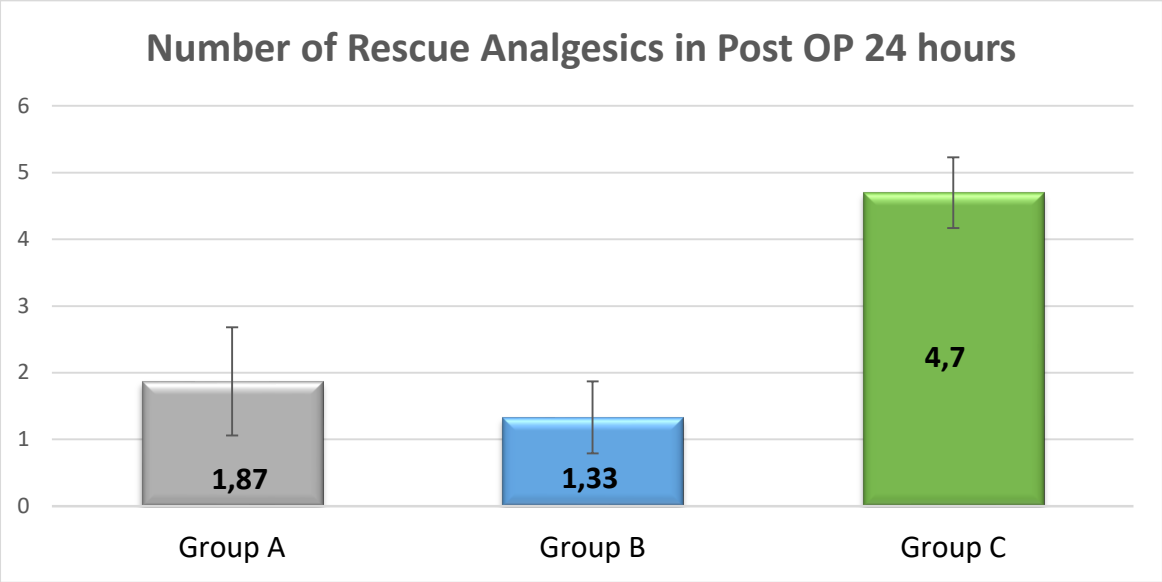


Table-5: Distribution of study groups by number of rescue Analgesics in Post OP 24 hours. Group A Vs Group B

Number of rescue analgesics	Group A	Group B	P value
Group A Vs Group B			
Mean	1.87	1.33	0.003, S
Standard deviation	0.81	0.54	
Group A Vs Group C			
Mean	1.87	4.70	0.0001, S
Standard deviation	0.81	0.53	
Group B Vs Group C			
Mean	1.33	4.70	0.0001, S
Standard deviation	0.54	0.53	

Figure-3: Distribution of study groups by number of rescue Analgesics in Post OP 24 hours.



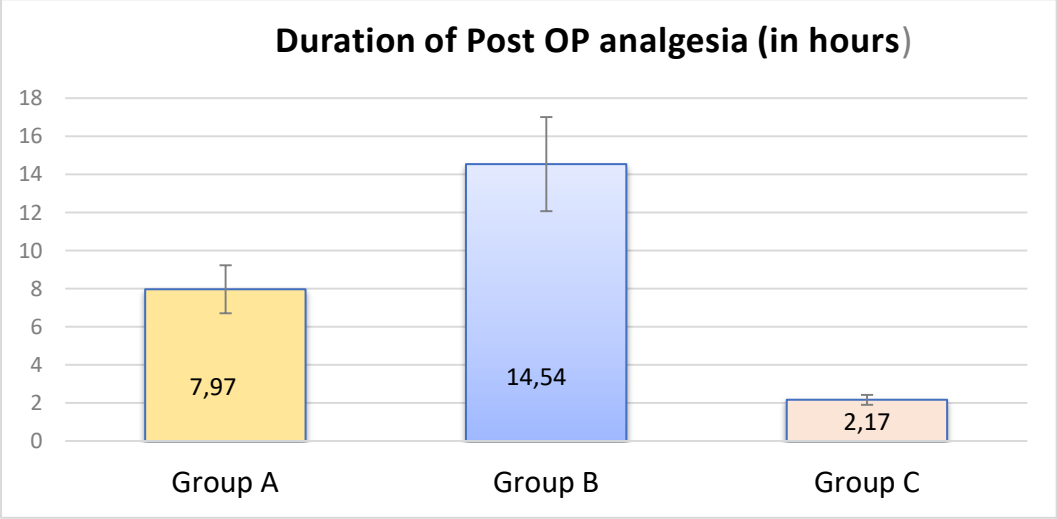
In the present study, a statistically significant difference was seen between the Mean number of rescue analgesics in post op 24 hours between the three groups.

Table -6: Distribution of study groups by duration of Post OP Analgesia.

Duration of Post OP Analgesia (in hours)	Group A	Group B	P value
Group A Vs Group B			
Mean	7.97	14.54	0.0001, S
Standard deviation	1.26	2.47	
Group A Vs Group C			
Mean	7.97	2.17	0.0001, S
Standard deviation	1.26	0.26	
Group B Vs Group C			
Mean	14.54	2.17	0.0001, S
Standard deviation	2.47	0.26	

In the present study, a statistically significant difference was seen between the Mean duration of Post OP Analgesia (in hours) between the three groups.

Figure-4: Distribution of study groups by duration of Post OP Analgesia.



ISSN 2515-8260 Volume 9, Issue 3, Winter 2022

DISCUSSION

Pain relief is the most gratifying service that can be offered to any patient. Postoperative analgesia after cesarean section poses unique clinical challenges to anesthesiologist as it should allow early ambulation of the mother to prevent thromboembolic episodes and ensure bonding with the baby. It should have no undesirable effects on the mother or newborn. SAB with LA alone provides limited postoperative analgesia. Opioid adjuvants can subjugate this limitation. Buprenorphine is a highly potent and lipophilic agonist-antagonist opioid with long duration of action which makes it an excellent choice for postoperative analgesia.High lipid solubility and high-molecular weight limit rostral spread of buprenorphine reducing the incidence of adverse effects compared to morphine. Different doses of buprenorphine ranging from 30 μg to 150 μg have been used as adjuvant to LA in SAB.No ideal dose has been described that can produce postoperative analgesia with minimum side effects.

This study was done mainly to assess efficacy of two doses of intrathecal buprenorphine for postoperative pain relief in cesarean section and involved 90 patients divided into three groups of 30 each. The groups were comparable with respect to demographic characteristics.

The mean duration of postoperative analgesia was 6.9 h for 45 μg group and 14.94 h for 60 μg group. There was significantly prolonged analgesia in both study groups when compared to control group. The mean duration of analgesia was highly significant in 60 μg group compared to both the other groups. A similar study was conducted by Dixit, in cesarean section with 60 patients in two groups. In the control group, he used 1.7 ml of 0.5% hyperbaric bupivacaine and in the study group, bupivacaine with 60 μg buprenorphine.The 60 μg buprenorphine group had a mean duration of analgesia of 8.2 h. In the study by Capogna *et al*.[4], patients who received 45 μg buprenorphine had a mean duration of analgesia of 7.1 h.Fifty percent patients had analgesia at 6 h which declined to 16% at 20 h in the study conducted by Ipe *et al*. using150 μg buprenorphine.Results in the present study are comparable with the above studies. This shows that addition of buprenorphine to intrathecal bupivacaine produces prolonged duration of analgesia which is dose-dependent. This is due to its great affinity for mu receptors and its slow dissociation from the receptors.

Rescue analgesic requirement was less in 45 μg group and 60 μg group compared to control group, which was statistically significant. In the control group, analgesic requirement was more than twice that in 60 μg group. Mean number of rescue analgesic doses required were 1.43, 1.03, and 2.2 for 45 μg, 60 μg, and control groups, respectively. An increase in dose of buprenorphine from 45 μg to 60 μg significantly reduced the rescue analgesic requirement. Singh *et al*. also found a significantly lower requirement of rescue analgesic with addition of 60 μg buprenorphine to intrathecal ropivacaine.

Patients were evaluated for efficacy of postoperative analgesia by analyzing the maximum pain score attained using VAS during the 24 h period. Maximum pain scores were significantly lower in buprenorphine groups compared to control group. Eighty percent of patients in control group had VAS scores >4. Lowest VAS score of two was seen only in 60 μg group. Quality of analgesia as assessed by VAS score was significantly better with an increase in dose of buprenorphine.

Among the groups, 60 μg group alone had a statistically significant rapid onset of block. The rapid onset may be due to its high lipid solubility and high affinity for opioid receptors. In the study by Dixit et al[5] onset of analgesia in the study group was also faster than control.The peak sensory level of block was comparable among the three groups. This may be because the same dose of bupivacaine (9 mg) was used in all three groups and also the volume of drug administered was almost same. Samal *et al*[6]. reported elevated sensory levels with the addition of 150 μg buprenorphine intrathecally.

Of all the side effects evaluated, sedation was the most common one seen in the study groups. Although the incidence of sedation was significant in the 60 μg group, all patients were easily

arousable (sedation score 1). Mild sedative effect which is desirable in the perioperative period was also noted by Dixit in his study.Incidence of PONV was more with 60 μg buprenorphine, which was statistically significant when compared with control group. There was no significant difference in the incidence of side effects when comparing 45 μg and 60 μg buprenorphine groups. Capogna *et al*.[4] also noted PONV in 36% patients receiving 30 μg buprenorphine and in 46% patients receiving 45 μg of buprenorphine in contrast to lower incidence in our study.Higher incidence reported may be explained by the elderly population involved. Ipe *et al*.[7] reported a lower incidence of 20% in cesarean patients even with 150 μg buprenorphine.

None of our patients developed respiratory depression. In the study by Ipe *et al*.[7] in cesarean section, respiratory depression was not observed even with 150 μg intrathecal buprenorphine.Being more lipophilic than morphine, rostral spread of intrathecal buprenorphine and therefore the risk of respiratory depression is much less.Addition of 60 μg buprenorphine produced increased incidence of minor side effects when compared to control group; however, addition of 45 μg buprenorphine did not produce significant increase in side effects compared to control group. Pruritus, though more likely in obstetric patients receiving neuraxial opioids, was observed only in one patient in the study group.

Apgar score of all babies delivered was within normal limits. None of them required any resuscitative measures. Neonatal outcome was shown to be good in several similar studies.[8,9] This shows that buprenorphine can be safely used intrathecally for cesarean section without any adverse outcome on the baby. Our study has resulted in addition of 60 μg buprenorphine to hyperbaric bupivacaine in every scheduled cesarean section in ASA physical status Class II patients under SAB in our institution. [10]

LIMITATIONS OF THE STUDY

In this study, we chose a maximum dose of 60 μg of buprenorphine though higher doses might have resulted in further prolongation of analgesia. However, higher doses have been reported to cause more adverse effects which were undesirable in this particular study population. We also did not study the effect of adding buprenorphine on hemodynamic variables and characteristics of motor block during intraoperative period. This is accountable as we preferred to concentrate on postoperative analgesia. Neonatal effects were assessed using Apgar score though umbilical cord blood gas analysis would have been less subjective.

CONCLUSION

We have demonstrated that addition of buprenorphine to hyperbaric bupivacaine provides postoperative analgesia after cesarean section without significant maternal and neonatal side effects. Increasing the dose of buprenorphine from 45 μg to 60 μg produced significantly prolonged duration of analgesia without increase in the incidence of adverse effects. Hence, addition of 60 μg buprenorphine to intrathecal bupivacaine is a safe, easy, and effective method of postoperative analgesia after cesarean section.

REFERENCES

1. Eisenach JC, Pan PH, Smiley R, Lavand'homme P, Landau R, Houle TT. Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. Pain 2008;140:87-94.
2. Tsen LC. Anesthesia for cesarean delivery. In: Chestnut DH, Polley LS, Tsen LC, Wong CA, editors. Chestnut's Obstetric Anesthesia: Principles and Practice. 4th ed. Philadelphia: Elsevier; 2009. p. 521-73.
3. Khan FA, Hamdani GA. Comparison of intrathecal fentanyl and buprenorphine in urological surgery. J Pak Med Assoc 2006;56:277-81.

4. Capogna G, Celleno D, Tagariello V, Loffreda-Mancinelli C. Intrathecal buprenorphine for postoperative analgesia in the elderly patient. Anaesthesia 1988;43:128-30.
5. Dixit S. Post operative analgesia after caesarean section: An experience with intrathecal buprenorphine. Indian J Anaesth 2007;51:515.
6. Samal S, Rani P, Chandrasekar LJ, Jena SK, Mail ID. Intrathecal buprenorphine or intrathecal dexmedetomidine for postoperative analgesia: A comparative study. Health 2014;2:9-14.
7. Ipe S, Korula S, Varma S, George GM, Abraham SP, Koshy LR. A comparative study of intrathecal and epidural buprenorphine using combined spinal-epidural technique for caesarean section. Indian J Anaesth 2010;54:205-9.
8. Raffa RB, Haidery M, Huang HM, Kalladeen K, Lockstein DE, Ono H, et al. The clinical analgesic efficacy of buprenorphine. *J Clin Pharm Ther.* 2014;39:577–83.
9. American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Practice guidelines for obstetric anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology 2007;106:843-63.
10. Vadivelu N, Anwar M. Buprenorphine in postoperative pain management. Anesthesiol Clin 2010;28:601-9.