

## ORIGINAL ARTICLE

# INTRATHECAL SUFENTANIL ALONG WITH BUPIVACAINE PROLONGS POSTOPERATIVE ANALGESIA AS COMPARED TO FENTANYL WITH BUPIVACAINE: A RANDOMIZED TRIAL

Birva N Khara<sup>1</sup>, Krutika B Rupera<sup>1</sup>

**Authors' Affiliation:** <sup>1</sup>Assistant Professor, Anesthesiology, Pramukhswami Medical College, Karamsad  
**Correspondence:** Dr. Birva N. Khara, Email: birvakothari@gmail.com

## ABSTRACT

**Objectives:** We designed a prospective, randomized, single blind study to compare the postoperative analgesic efficacy and common adverse effects of fentanyl and sufentanil along with hyperbaric bupivacaine by intrathecal route.

**Methodology:** Sixty patients undergoing lower abdominal, gynecological, plastic surgery and orthopedic surgery were randomly divided in two groups. Group I (n=30) received 2.5 ml bupivacaine heavy (0.5%) and 0.5 ml (25 micrograms) fentanyl where as group II (n=30) received 2.5 ml bupivacaine heavy (0.5%) and 0.2 ml (6 micrograms) sufentanil with 0.3 ml normal saline intrathecally. Intraoperative and postoperative vitals, onset of spinal anesthesia and duration of sensory and motor blockade and occurrence of any side effects were assessed at specific time intervals. Analgesic efficacy in terms of duration of analgesia postoperatively was assessed by using the Pain Intensity Score (PIS) for 24 hours.

**Results:** Mean duration of pain free period in group I was 145+/-84.08 minutes (mean+/-SD) as compared to 266.5+/-114.5 minutes (mean+/-SD) in group II which was highly significant. Cardiovascular and respiratory stability was maintained with no significant incidence of side effects in either group.

**Conclusion:** We conclude that intrathecal fentanyl(25 microgram) and sufentanil (6 microgram) with bupivacaine heavy prolong postoperative analgesia without respiratory depression or other serious adverse effects. This prolonged analgesia is more marked with sufentanil than fentanyl.

**Key words:** Spinal anesthesia, fentanyl, sufentanil, postoperative pain, postoperative analgesia

## INTRODUCTION

Any pain is accompanied by anxiety and the urge to eliminate or terminate the feeling. Adequate postoperative pain control is necessary to prevent adverse consequences of surgical insult. Spinal anaesthesia has the advantages of a simple technique, rapid onset of action, and reliability in producing uniform sensory and motor blockade. Its major limitation is the duration of action and lack of long lasting postoperative analgesia. Administration of a combination of a low dose opioid to the local anaesthetic agent intrathecally can overcome this limitation<sup>1, 2</sup>. A single small dose of intrathecal opioid may relieve postoperative pain of lower abdominal or orthopedic surgery. Lipophilic opioids like fentanyl and sufentanil when used in combination with hyperbaric bupivacaine intrathecally provide substantial pain relief. Sufentanil is a newer and potent analgesic, about five to ten times more potent than fentanyl<sup>3</sup>. Sufentanil, when given by intrathecal route for postoperative pain control showed comparable analgesia<sup>4</sup>. We conducted the study to compare the postoperative analgesic efficacy and common side effects of fentanyl and sufentanil along with hyperbaric bupivacaine by intrathecal route.

## MATERIALS AND METHODS

After obtaining approval from the Institutional Ethical Committee, sixty patients undergoing lower abdominal, gynecological and orthopedic surgery under spinal anesthesia were randomly divided in two groups by a computer generated randomization program. All the patients belonged to ASA grade I or II. All of them were explained in detail about the study and informed written consent was obtained from all of them. Patients were premedicated with injection glycopyrrolate 4 micrograms/kg intramuscular and injection promethazine 0.5 mg/kg intramuscular 45 minutes before surgery. Recording of vital data was done 15 minutes before and after premedication and just before administration of spinal anesthesia. Intravenous preloading was done with Ringer's lactate as a bolus of 6-8 ml/kg given over 15 minutes before anesthesia. Subarachnoid puncture was performed at L3-L4 interspace with 25G spinal needle with patient in sitting position under strict aseptic and antiseptic precautions. After clear and free flow of CSF, fentanyl 25 micrograms (0.5 ml) plus bupivacaine heavy (0.5%) 2.5 ml was given in group I and sufentanil 6 micrograms (0.2 ml with 0.3 ml normal saline) plus bupivacaine heavy (0.5%) 2.5 ml was given in group II after

CSF aspiration. Patients were placed in supine position immediately after spinal injection.

The rostral dermatome level of sensory anesthesia to pin prick was determined and motor block was assessed using Modified Bromage Scale<sup>5</sup> (0 = No paralysis 1 = Inability to raise extended leg, 33% blockade, 2 = Inability to flex knee, 66% blockade and 3 = Inability to flex the ankle or complete motor block). Sedation score was also calculated from Chernik Sedation Scale<sup>6</sup> (0=awake, 1=sleeping comfortably, easily arousable, 2=Deep sleep but arousable, 3=deep sleep but not arousable). Temperature, pulse, blood pressure (BP), respiratory rate, oxygen saturation (SpO<sub>2</sub>) and ECG were monitored and measured immediately after spinal anesthesia, 15 minutes after spinal blockade and then at 15 minute interval till completion of surgery. After surgery, patients were shifted to recovery unit and pulse, BP, respiratory rate and SpO<sub>2</sub> were recorded at every 15 minutes for first two hours and then at 3, 6, 9, 12 and 24 hours.

The level of sensory and motor block during the post-operative period was assessed every 15 minutes until sensory block reached L5 dermatome and the Bromage Scale reached grade 0 for residual anesthesia effect. Each patient was carefully questioned about pain relief and it was assessed in graded form as pain intensity score (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain). Patients were observed for adverse effects like nausea, vomiting, bradycardia, tachycardia, hypotension, respiratory depression (respiratory rate<8/minute) and drowsiness. They were carefully questioned regarding duration of pain free period, type and severity of pain, if occurred. Postoperative complete analgesia was defined as the time from the intrathecal injection to the first perception of pain i.e.PIS>0. Postoperative analgesia was provided by intramuscular diclofenac sodium 75 mg if required.

Sample size of 60 patients with 30 patients in each group was determined with power of study of 80%. The data were analyzed statistically using chi-square test and demographic data were analyzed using analysis of variance. The data were expressed as mean +/- SD. Standard tests of significance were applied to determine the p value. P value of <0.05 was considered significant and <0.001 as highly significant. Pulse rate, BP, onset of spinal anesthesia, duration of sensory and motor block-

ade and duration of pain free period were compared among the two groups.

**RESULTS**

There were no significant differences between the two groups with respect to demographic characteristics like age, sex and weight [Table 1].

**Table 1 – Comparative data of age, weight and sex of both groups**

	Group I (n=30)	Group II (n=30)
Total Patients	30	30
Age range	16-60	16-60
Mean age (years)+/-SD	28.1+/-9.48	32.34+/-11.5
Mean weight (kg)+/-SD	48.83+/-5.83	52.6+/-6.7
Sex		
Male	18 (60%)	16 (53.3%)
Female	12 (40%)	14 (46.7%)

P value for age : 0.1246; P value for weight: 0.0236; P value for sex: 0.60

P value for age and weight has been calculated by using ‘unpaired t test’ and P value for sex by ‘chi square’ test.

**Table 2- Hemodynamic parameters at two hours post operatively**

	Group I	Group II
Mean pulse rate (per minute)±SD at 2 hours post operatively	128.8±7	82.33±4.55
Mean arterial pressure (mm Hg)±SD at 2 hours post operatively	93.48±4.4	86.31±6.2
P value for mean pulse rate and mean arterial pressure	P<0.0001 (Highly significant)	

Onset of spinal anesthesia and duration of sensory and motor blockade did not show significant difference. But duration of analgesia was significantly prolonged in Group II.

It was observed that the duration of pain free period in group I was 145+/-84.08 (mean+/-SD) minutes and in group II it was 266.5+/-114.5 minutes (mean +/-SD). This was statistically significant (P<0.001) in favour of sufentanil group. [Table-3]

**Table 3-Onset of spinal anesthesia, duration of sensory blockade, motor blockade and painfree period following intrathecal fentanyl vs sufentanil with bupivacaine**

Variable	Group I (n=30)		Group II (n=30)		T value	P value
	Min-Max	Mean±SD	Min-Max	Mean±SD		
Onset of spinal anesthesia(min)	2-15	6.13±3.31	2-7	4.93±1.50	1.8	0.075*
Duration of Sensory Blockade(min)	105-200	155.5±26.24	140-250	168±24.5	1.9	0.06*
Duration of Motor Blockade(min)	90-180	131.17±27.17	110-185	141.3±15.8	1.73	0.08*
Duration of pain free period(min)		145±84.08		266.5±114.5	6.69	<0.0001#

\*Not significant; #Highly significant

## DISCUSSION

Pain is an unpleasant sensory emotional experience associated with actual or potential tissue damage. Postoperative pain is due to direct trauma to the tissue caused by surgery but it may be aggravated by associated reflex muscle spasm or visceral distension. The first application of neuraxial opioid can be traced to 1901 when a Japanese surgeon used 10 mg of morphine intrathecally with local anesthesia cocaine in two cancer patients<sup>7</sup>. Opioids administered neuraxially for postoperative pain provided substantial pain relief. A single small dose of intrathecal opioid may relieve postoperative pain of lower abdominal and orthopedic surgeries. Sufentanil is a newer and potent analgesic opioid of anilidopiperidinederivative like fentanyl, but more potent than latter. Thomas G used sufentanilin intrathecally for early postoperative management in orthopedic surgeries. In 1973, opioid receptors were demonstrated to be present in brain and nervous tissues<sup>8</sup>. After intrathecal administration, the disposition of opioids is complex and multicompartamental. Simultaneously, intrathecal opioids travel cephalad within CSF, enter the spinal cord where they bind with specific opioid receptors within the dorsal horn and traverse the dura mater to enter the epidural space where they bind to epidural fat. Both fentanyl and sufentanil exert their analgesic effects via  $\mu$  receptors. Sufentanil is a superior ligand for  $\mu$  opiate receptors<sup>9</sup>. Activation of  $\mu$  receptors causes presynaptic modulation and release of excitatory neurotransmitters. Analgesic effect of sufentanil may be partly attributable to stimulation of serotonin receptors resulting in an anti-nociceptive effect.

In 1987, R Donadoni et al<sup>10</sup> studied about intrathecal-sufentanil as a supplement to subarachnoid anesthesia with lignocaine. In a double blind comparative trial, 40 urologic patients were randomly divided into two groups and received 5% lignocaine 1.5 ml with either 1.5 ml sufentanil (5 micrograms/kg) or physiological saline 1.5 ml. The only clear benefit of adding low dose sufentanil to lignocaine was significantly longer period of postoperative analgesia. In our study, we added low dose sufentanil to bupivacaine heavy and given intrathecally in a variety of surgeries and observed prolonged duration of analgesia (266+/-114.5 minutes). In 1995, DC Campbell<sup>11</sup> designed a prospective, randomized, double blind study to evaluate the efficacy of combination of intrathecalsufentanil with a low dose of local anesthetic in an attempt to prolong analgesia during labor in 52 patients. In that study, group A received 2.5 mg bupivacaine, group B received 10 micrograms of sufentanil and group C received 2.5 mg bupivacaine with 10 micrograms of sufentanil. It was concluded that addition of 10 micrograms of sufentanil to bupivacaine intrathecally prolonged labor analgesia significantly. The types of surgeries selected in our study were general surgery and gynecological lower abdominal surgeries and orthopedic and plastic lower limb surgeries. The dose of sufentanil selected in our study was 6 microgram lower than that used in the previous study. We observed that even with this dose a reasonably pro-

longed duration of analgesia was obtained. In 1997, Dahlgren G<sup>12</sup> compared the effects of intrathecalsufentanil 2.5 and 5 micrograms, fentanyl 10 micrograms and placebo when administered with hyperbaric bupivacaine 0.5%, 12.5 mg for Caesarian Section in 80 healthy, full term parturients. In conclusion, small doses of fentanyl or sufentanil added to bupivacaine for spinal anesthesia for CS increased the duration of analgesia in early postoperative period when compared to placebo. Roxane Fournier et al<sup>13</sup> designed a study to compare postoperative analgesic effects of sufentanil and fentanyl added to 2 ml normal saline given postoperatively intrathecally after elective total hip replacement surgery continuous spinal anesthesia in geriatric patients as soon as they had a pain score more than 3. They concluded that both the opioids provided satisfactory analgesia. In our study we administered the drugs fentanyl and sufentanilin intrathecally along with bupivacaine heavy preoperatively. This contributed to analgesia in the post operative period also. Wang YC et al<sup>14</sup> in 2006 studied the clinical efficacy of intrathecal low dose of sufentanil 15 micrograms and 7.5 micrograms with bupivacaine TURP patients and they concluded that spinal anesthesia with low dose sufentanil with bupivacaine possesses relatively steady hemodynamics.

In our study, we studied 30 patients for the effect of intrathecal fentanyl with bupivacaine in group I and sufentanil with bupivacaine in group II. We observed that there was no significant change in mean arterial pressure in both groups at different time intervals. There was no difference in onset of spinal anesthesia and duration of sensory and motor blockade in both the groups. Intra operatively and for one hour post operatively, the mean pulse rate was comparable in both the groups. But at 2 hour post operatively the mean pulse rate in group I was 128.8+/-7 per minute as against 82.33+/-4.55 per minute in group II. Similarly mean arterial blood pressure was comparable in both the groups intra operatively and in the 1<sup>st</sup> hour post operatively. But in the 2<sup>nd</sup> hour it was 93.48+/-4 mm Hg in group I whereas it was 86.31+/-6.2 mm Hg in group II. These differences in mean pulse rate and mean arterial blood pressure in both the groups at 2<sup>nd</sup> hour postoperatively were statistically significant. This difference could be attributed to the occurrence of pain at 2 hours post operatively in the fentanyl group patients and not in the sufentanil group. In our present study it was found that there was no difference in the onset of spinal anesthesia when either fentanyl or sufentanil was added to bupivacaine intrathecally. Mean duration of sensory and motor block were also comparable in both the groups with no statistical significance. Postoperative pain was less in sufentanil group as compared to fentanyl group and pain relief was significantly greater in sufentanil group (266.5+/-114.5 minutes) as compared to fentanyl group (145+/-84.08 minutes). Both groups were comparable for adverse effects. Comparing the occurrence of side effects in both the groups, two patients of group I had hypotension as against one patient in Group II. No other complications were observed in any group.

## CONCLUSION

We conclude that addition of sufentanil provides enhancement and increased duration of analgesia in post-operative period as compared to fentanyl when used intrathecally with bupivacaine heavy in surgeries performed under spinal anesthesia.

## REFERENCES

1. Torda TA, Hann P, Mills G, Leon De et al. Comparison of extra-dural fentanyl, bupivacaine and two fentanyl-bupivacaine mixtures for pain relief after abdominal surgery. *Br. J. Anaesth* 1995;74:35-40
2. Tan Ping-Heng, Chia Yuan-Yi, Lo Yuan, Liu Kang, Yang Lin-Chang et al. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. *Canadian Journal of Anesthesia* 2001; 48:551-56.
3. Rosow CE. Sufentanil Citrate: A new opioid analgesic for use in anesthesia. *Pharmacotherapy*, 1984; 4:11-18
4. Thomas G. Standl et al. Subarachnoid sufentanil for early post operative pain management in orthopaedic patients. *Anaesthesiology* 2001, 94:230-238
5. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *ActaAnesthesiaScand* 1965; 16:55-69
6. Chernik DA, Gilling D, Laine H et al. Validity and reliability of the observers assessment of alertness/sedation score. Study with intravenous midazolam. *J Clin Psychol Pharmacology* 1990; 10:244-257
7. Matsuki A. Nothing new under the sun – A Japanese pioneer in the clinical use of intrathecal morphine. *Anesthesiology* 1983; 58:289-290
8. Synder SH. Receptors, neurotransmitters and drug responses. *N Engl J Med* 1979; 300:465-472
9. Leysen JE, Gommeren W. In vitro binding properties of sufentanil, a superior ligand for M opiate receptor. *Archives Internationales de Pharmacodynamie et de Therapie* 1991;260:287-289
10. Donadoni R, Vermeulen H, Noorduyn H, Rolly G. Intrathecal sufentanil as a supplement to subarachnoid anesthesia with lignocaine *Br. J. Anaesth* 1987 59 (12):1523-1527
11. Campbell DC. Efficacy of combination of intrathecal sufentanil with a low dose of local anesthetic agent for prolonging analgesia in parturients. *Anaesthesia and Analgesia* 1995; 81:1102-1110
12. Dahlgren G. Effects of intrathecal sufentanil, fentanyl and placebo with bupivacaine for elective caesarean section. *Anaesthesia and Analgesia* 1997; 85:1288-1293
13. Roxane Fournier et al. A comparison of intrathecal analgesia with fentanyl or sufentanil after total hip replacement. *Anaesthesia and Analgesia* 2000; 90:918-922
14. Wang YC, Guo QL, et al. Spinal anesthesia with low dose sufentanil-bupivacaine in transurethral resection of the prostate. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2006; 31(6): 925-8