Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(4) (Part - I): 1067-1075
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6419.2

A Study to Compare the Effects of Low Dose Intrathecal Fentanyl and Low Dose Intrathecal Tramadol Combined with 0.5% Bupivacaine (Heavy) in Patients Undergoing Orthopaedic Surgeries

P. Kalyan Chakravarthy[1], Hemnath Babu Kotla[2]

[1,2]Associate Professor: Department of Anaesthesia, Great Eastern Medical School & Hospital, Ragolu, Srikakulam, Andhra Pradesh 532484, India.

Abstract

Introduction: Relief of pain during operation and postoperative period is one of the main stay of balanced anaesthesia. Bupivacaine Hydrochloride is known for long procedures due to prolonged action. The addition of opioids has been opted as a method to reach these goals. *Aims:* To compare the intra-operative effects of a single low dose of intrathecal tramadol and fentanyl with hyperbaric bupivacaine hydrochloride. *Materials and Methods:* Fifty patients posted for various elective orthopedic procedures were studied in a randomized prospective double blinded manner. Patients will be randomly divided into two following groups. Group A: SAB with addition of 25 µg fentanyl to 3 ml of 0.5% Bupivacaine. Hydrochloride (hyperbaric), Group B: SAB with addition of 25 mg tramadol to 3 ml of 0.5% Bupivacaine Hydrochloride (hyperbaric). *Results:* During Intraoperative period no significant differences in BP, heart rate and respiratory rate were noted. There was no delay in time to full motor recovery in both the groups of patients. The mean duration of analgesia did not differ in both groups. Mean duration of analgesia in Group A was 565.4 minutes and in Group B was 551 min.Time for two segment regression did not differ in both the groups. The patients showed minimal side effects, like nausea, Vomiting, shivering and pruritis in both groups which was statistically insignificant. *Conclusions:* Both intrathecal tramadol and fentanyl act synergistically to potentiate bupivacaine induced sensory spinal block. Excellent surgical anaesthesia and an extended analgesia were observed in post-operative period with minimum side effects among both the groups.

Keyword: Intrathecal tramadol; Bupivacaine; Orthopedic procedures.

How to cite this article:

P. Kalyan Chakravarthy, Hemnath Babu Kotla. A Study to Compare the Effects of Low Dose Intrathecal Fentanyl and Low Dose Intrathecal Tramadol Combined with 0.5% Bupivacaine (Heavy) in Patients Undergoing Orthopaedic Surgeries. Indian J Anesth Analg. 2019;6(4):1067-1075.

Corresponding Author: Hemnath Babu Kotla, Associate Professor, Department of Anaesthesia, Great Eastern Medical School & Hospital, Ragolu, Srikakulam District, Andhra Pradesh 532484, India

E-mail: hemnathbabu@rediffmail.com

Received on 08.04.2019, **Accepted on** 14.05.2019

Introduction

Relief of pain during operation and postoperative period is one of the main stay of balanced anaesthesia, so any experience acquired in this field should be extended to the postoperative period also. Postoperative pain relief is a growing concern for an anaesthesiologist, as an uneventful postoperative period makes surgery a comfortable proposition for surgical patients [1]. The choice between regional anaesthesia and general anaesthesia for orthopaedic procedures has been extensively debated. Many studies have found a lower incidence of morbidity and mortality in the early postoperative period, following regional anaesthesia [2]. If we can provide post-operative analgesia in a simple and inexpensive manner, it may go a long way in alleviation of pain and suffering. Spinal anaesthesia with hyperbaric.

Bupivacaine Hydrochloride is mostly used for longer procedures due to its prolonged action. But there is a need to intensify and increase duration of sensory blockade without increasing the intensity and duration of motor blockade, and thus prolong the duration of postoperative analgesia. The addition of opioids has been suggested as a method to accomplish these goals.This study is designed to quantitatively examine the effects of adding fentanyl and tramadol to Hyperbaric Bupivacaine Hydrochloride for spinal anaesthesia on duration and recovery of sensory and motor blockade.

Materials and Methods

This study was conducted in the Department of Anaesthesiology at GSL Medical College & Hospital over a period of 24 months from October 2015 to September 2017. Approval was obtained from the ethical committee of the institution. Fifty patients posted for various elective orthopedic procedures were studied in a randomized prospective double blinded manner at GSL General Hospital and Medical College, Rajahmundry. Patients will be randomly allocated into two following groups.

Group A: SAB with addition of 25 µg fentanyl to 3 ml of 0.5% Bupivacaine Hydrochloride (hyperbaric)

Group B: SAB with addition of 25 mg tramadol to 3ml of 0.5% Bupivacaine Hydrochloride (hyperbaric).

The selection of patients were carried out randomly, depending on the lists of operations submitted by the surgical team on the previous day. A written informed consent was obtained from all these patients.

Inclusion criteria

1. Patients between the age 20-80 years of both sexes
2. Patients belonging to ASA physical status I/II
3. Patients posted forelective lower limb surgery from orthopedics

Exclusion Criteria

1. Patients with a history of known sensitivity to the drugs used.
2. Patients with gross spinal deformity.
3. Patients with Peripheral neuropathy or having any contraindication to neuraxial block- local/Systemic infections, coagulation disorders, hypovolemia, signs of raised intra cranial tension, uncontrolled hypertension.
4. Patient refusal.
5. Patients with history of valvular heart diseases with fixed cardiac output states like mitral stenosis.

Pre-anaesthetic evaluation included general examination, systemic examination of respiratory, cardiovascular, CNS systems and examination of the spine for any diseaseor deformity, airway examination, local examination at the site proposed for lumbar puncture (LP).

Investigations carried out were Haemoglobin, Bleeding and Clotting time, Random or fasting blood sugar, Viral Markers, Blood urea, Serum Creatinine, Urine analysis for albumin, sugar and microscopy and Electrocardiogram and Chest X-ray as and when required.

Anaesthetic procedure was briefly explained to the patients and informed written consent was obtained from the patient and his/her relatives.

Premedication was standardized with medications. All patients were instructed about the visual analogue scale for pain. 0- no pain and 10- worst ever pain. All patients were given injection Ondansetron 4 mg I.V prior to SAB.

After shifting the patients to the operation theatre, intravenous access was secured with 18 G cannula. NIBP, ECG, Pulse oximeter monitors were connected & baseline pulse rate, blood pressure, ECG, respiratory rate and SPO_2 were recorded. Under strict aseptic precautions LP was

performed using 25 guage disposable Quinke type of spinal needle after local infiltration of skin using 2% Xylocaine, at L2–L3 spinal intervertebral space by midline approach. LP was performed in sitting position. Patients were made to lie supine immediately after the completion of injection. The time of injection of the drug was recorded as 0 minute. All patients were given intravenous fluids-Isotonic saline and ringers lactate for maintenance. After spinal anaesthesia all the patients were turned supine, pulse rate and blood pressure was recorded immediately and at 5,10, 15, 30, 60, 120, 180 minutes, End of surgery. Time intervals at which hypotension, bradycardia or other complications occurred were noted. Oxygen 4L/min via face mask was administered to all patients throughout the procedure. Respiratory rate was monitored.Level of sensory blockade was checked with a 23G hypodermic needle immediately after SAB and at 5, 10, 15, 30, 60, 120, 180 minutes.

Assessment of sensory blockade

Sensory blockade was assessed by pinprick and time noted for the block to reach different dermatomal level

a) Onset of sensory block – Time from the deposition of drug to the loss of pin prick Sensation
b) Duration of analgesia – Time when patient first complains of pain after the spinal block
c) Time for two segment regression – Time (counted in minutes) taken for the recovery of sensory level to two dermatomal segments below the highest level.

Level of motor blockade was also assessed by using the Bromage scale immediately after SAB and at 5, 10,15,30,60,120,180 minutes. (Bromage scale 0-full flexion of kneed and feet; 1 – just able to flex knees, full flexion of feet; 2-unable to flex knees, but some flexion of feet possible, 3-unable to move legs or feet).Onset of Motor Blockade – Time interval (counted in minutes) between injection of drug in to Subarachnoid space to Patients inability to lift the straight extended legs.

The following side effects due to intrathecal administration of fentanyl were noted down during the perioperative and postoperative period. Nausea, vomiting, pruritis, shivering, desaturation or hypoxaemia ($SpO_2 < 90\%$), respiratory depression (RR < 10), hypotension, sedation. Hypotension was defined as decrease in systolic blood pressure more than 30% of base line and was treated with Inj. Ephedrine 6 mg increments IV. Inj. Atropine was given when heart rate decreases greater than 20% of base line.

Duration of post-operative analgesia

The duration was calculated from the time when the block was given. The patients were followed up for 24 hours after surgery. They were asked to point out the intensity of their pain on the linear visual pain scale. VAS score along with heart rate and blood pressure was recorded in the recovery room (3 hours after SAB), evening of surgery (6 hours after SAB) and on the first post-operative day (24 hours after SAB).

During the post-operative period the injections of analgesics or opioids were avoided until demanded by the patients due to pain. The time at which supplementation given was noted down along with drug and dosage. This point corresponded to poor analgesia on the scale. Total dose of analgesics administered to the patients in 24 hours was noted. Pain assessment was conducted by a single observer. The time taken for complete motor and sensory recovery was noted. The duration of motor blockade was taken from the time of injection of the drug to the time when the patient was able to move his ankle.

Statistical methods

The data were analyzed as follows. First, the descriptive statistics were computed. These included the range, mean and standard deviation (SD) for quantitative variables, and category frequency counts for qualitative variables.

The independent sample (Student's) t test was employed to compare the means of two independent groups. Alpha for significance for all inferences was set at $p < 0.05$. All tests of hypotheses, wherever applicable, were two-tailed.

Results

Table 1: Age and gender distribution in study

		Group A	Group B
Age	Range	20-70	20-65
	Mean	42.88	39
	S.D	16.89	12.71
Sex	Male	15	14
	Female	10	11

The two groups did not differ significantly in age and gender (Table 1).

Table 2: Baseline heart rate

		Group A	Group B	Significance
Base line Heart Rate	Range	71-114	66-109	T=1.47
	Mean	88.4	83.8	Df=48
	S.D	12.44	9.43	p=0.14
Baseline systolic blood pressure	Range	110-150	105-160	T=0.82
	Mean	126.64	123.6	Df=48
	S.D	12.78	13.33	p=0.41
Baseline diastolic blood pressure	Range	55-105	70-104	T=0.16
	Mean	81.16	81.60	Df=48
	S.D	10.29	9.08	p=0.87

Baseline heart rate, systolic blood pressure, and diastolic bloodpressure are not significant in both groups and comparable with each other (Table 2).

Even though there was significant difference in heart rate over time among both the groups but there was no significant difference in the pattern of decrease in heart rate between the Groups (Fig. 1).

Even though there was significant difference in systolic blood pressure over time among both the groups but there was no significant difference in the pattern of decrease in heart rate between the Groups except in first five minute reading which showed a significant fall in blood pressure in Group B. (Fig. 2).

Even though there was significant difference in diastolic blood pressure over time in both groups but there was no significant difference in the pattern of decrease in diastolic blood pressure between Groups. (Fig. 3).

Fig. 1: Heart rate at different intervals of time

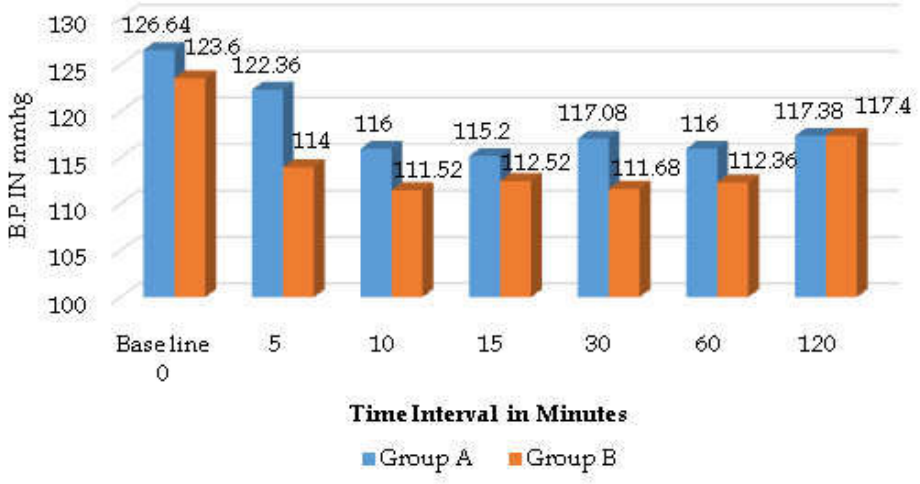

Fig. 2: Systolic blood pressure at different intervals of time

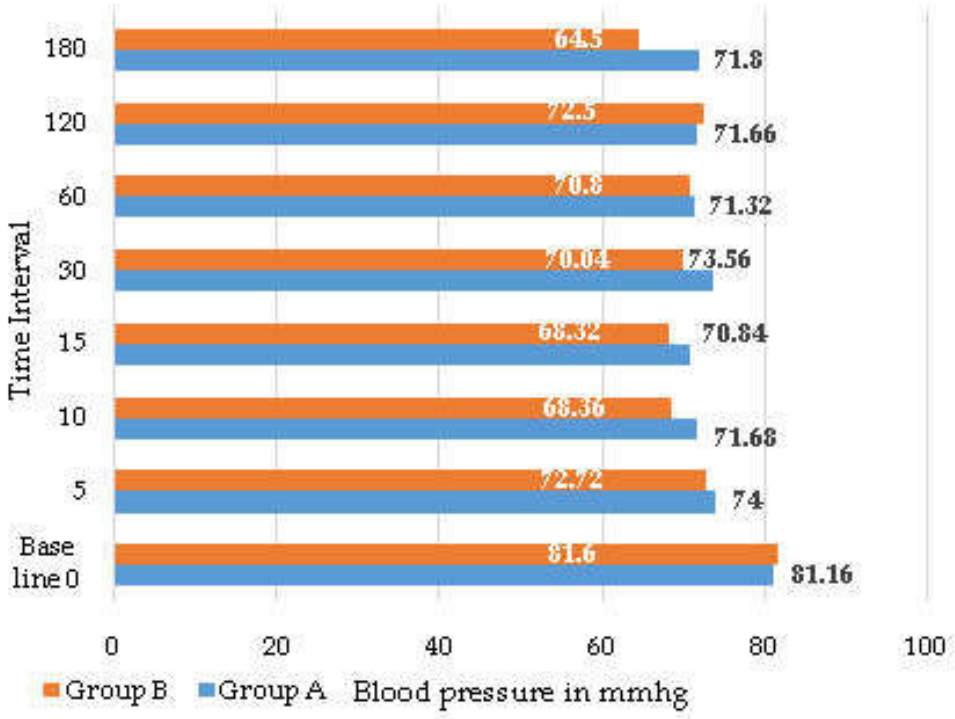

Fig. 3: Diastolic blood pressure at different time intervals

Table 3: Visual analogue scale at different time intervals post operatively.

Visual analogue scale	Group A Mean (SD)	Group B Mean (SD)
0	0 (0)	0.12 (0.43)
6 hours	0.4 (0.64)	0.64 (0.85)
24 hours	1.88 (1.2)	1.68 (1.35)

Visual analogue scale 6 hours post operatively was significantly more likely to be greater than 0 in Group B as compared to Group A.Visual analogue scale 24 hours post operatively was significantly greater than 1 in both the groups (Table 3).

Table 4: Time of first request of analgesic and dose

Variable		Group A	Group B	Significance
Time of first request for analgesic	Mean	565.4	551	T=0.38
	SD	150.4	112.64	P=0.70
Dose	Mean	108.6	100.2	T=1.10
	SD	29.5	23.8	P=0.27

There was no significant difference with respect to time of first request for analgesic between the two groups. There was no significant difference in total analgesic dose required between both the groups (Table 4).

Table 5: Motor recovery and 2 segment regression of sensory level

Variable		Group A	Group B	Significance
Time to full motor recovery	Mean	230	226.8	T=0.38
	SD	28.9	29.5	P=0.70
Time to 2 segment regression of sensory level	Mean	94	97.4	T=0.595
	SD	23.0	16.9	P=0.55
Motor Sensory recovery	Mean	245	241.4	T=0.42
	SD	27.48	32.53	P=0.67

There was no significant difference with respect to time to full motor recovery, time to 2 segment regression of sensory level and time for complete motor sensory recoverybetween both the groups (Table 5).

Table 6: Side effects in both the groups

Side Effects	Group A	Group B
Nausea	Nil	Nil
Vomiting	Nil	Nil
Pruritis	2	2
Shivering	2	0
Desaturation or hypoxaemia (SpO2 < 90%)	Nil	Nil
Sedation	Nil	Nil

Sedation score was recorded every 10 minutes first hour and every 30 minutes next till end of

surgery (Table 6).

0 = wide awake, 1 = Sleeping comfortably, responding to verbal commands

2 = Deep sleep but arousable, 3 = Deep sleep, not arousable.

Discussion

Effective pain control is mandatory for optimal care of patients in the pre and postoperative period. With advancements in the knowledge of pain pathophysiology development of more effective techniques even then patients continue to experience considerable pain after surgery. To become a successful method of analgesia it should be available to large number of patients, and it must be suitable for use in a general surgical ward with simple routine monitoring of nurse. Most commonly drugs used for spinal subarchnoid block are lignocaine and bupivacaine. One disadvantage with spinal anesthesia using local anesthetics is that analgesia ends with the regression of the block, which means that there is an early post-operative need of analgesia post-operative pain, apart from causing discomfort.

In modern era, the use of intrathecal narcoticsis increasing even there is risk for respiratory depression. Tramadol, in contrast, is a centrally acting analgesic that has minimal respiratory depressant effects, by virtue of its 6000 fold decreased affinity for μ receptors compared to morphine. Thought it would be appropriate to study the effects of intrathecally administered tramadol and compare it with a commonly used intrathecally administered opioid like fentanyl.

Fentanyl has rapid onset and shorter duration of action following intrathecal administrations. It prolongs the duration of bupivacaine induced sensory blockade. This suggests a potential synergism between fentanyl and bupivacaine as reported in an animal study by Wang *et al.* [3]. and Gielen MJM *et al.* [4] in 1993 reported that fentanyl is one of the safest opioids. The principal advantage of intrathecal opioids over systemic is that the former produces 'segmental analgesia' resulting in localised nociception without motor, sensory, autonomic or systemic side effects. In order to reduce the side effect profile the use of 'low dose' intrathecal opioids have been advocated, but it is a relative concept.

The main reason for selecting orthopaedic patients was, most of the procedure can be done under regional anaesthesia like spinal anaesthesia. Oue prospective study was conducted to compare intrathecal bupivacaine with low dose tramadol and bupivacaine with low dose fentanyl in orthopaedic lower limb surgeries.

Patient characteristics across the groups

The patients studied across the group which is not significant in respect to age or sex. In group A the range of age was 20-70 years and in group B was 20-65 years which is almost similar. There were 15 male patients and 10 female patients in group A and 14 male patients and 11 female patients which is almost similar in present study. Base line heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were also similar in both the groups with standard deviations of 12.44 (HR), 12.78 (SBP), 10.29 (DBP) for group A and 9.43 (HR), 13.33 (SBP), 9.08 (DBP) for group B respectively.

Changes in the perioperative cardiovascular parameters

In the present study, the incidence of hypotension was equal in both groups but in first five minutes there was significant hypotension in group B with a 'p' value of 0.023, indicating 98% confidence levels. But this effect has to be studied further weather the hypotension is due to bupivacaine alone or contemplating with tramadol.Hypotension was corrected by giving iv fluids and administration of injection mephentermine 6mg iv in incremental doses.

Wong C *et al.* [5] in their experimental work found that the decrease in sympathetic efferent activity after spinal anesthesia is does related to bupivacaine and not to the intrathecal opioid which was added. In the present study, the significant fall in blood pressure is probably the effect of 3 ml of bupivacaine rather than the low dose of the intrathecal opioid. Heart rate, systolic blood pressure and diastolic blood pressure in the both groups did not vary significantly. Jagtap S *et al.* [6] concluded Intrathecal RF provided satisfactory anaesthesia with haemodynamic stability for major lower limb orthopaedic surgery. It provided similar sensory but shorter duration of motor block compared to BF which is a desirable feature for early ambulation, voiding and physiotherapy. This concludes that fentanyl adds prolonged analgesic duration when added with local anaesthetics, and this supports current study. Li Z *et al.* [7] conducted a four group study which included Group A –Bupivacaine with Fentanyl (gBF), Group B–Bupivacaine with Clonidine (gBC),

Group C – Bupivacaine with Dexmedetomidine (gBD), Group D – Bupivacaine (gb), which were administered intrathecally. This study found that onset of blockade was significantly faster in group gBD and group gBC, than group with fentanyl. But group gBD, gBC had more sedation than group with fentanyl, suggesting that fentanyl causes less sedation than other medication. They concluded that addition of dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine provided adequate anesthesia and postoperative analgesia compared to fentanyl adjuvant without causing any significant side effects.

Alsheshmi J. A *et al.* [8] in 2003 found that intrathecal tramadol did not influence the intra operative hemodynamic parameters. Idowu OA, Sanusi AA, Eyelade [9] concluded that 25 microg of fentanyl to bupivacaine intrathecally for elective Caesarean section increases the duration of complete and effective analgesia thereby reducing the need for early postoperative use of analgesics, supporting the present study.

In study done by Yaddanapudi C.N. *et al.* [10] in 2000 with epidurally administered tramadol. Reuben S.S. *et al.* [3] studied different dosages from 0 to 50 mcg of fentanyl and observed that not a single patient had respiratory depression.

Changes in the onset and duration of sensory and motor blockade:

The total mean duration of analgesia in group A was 565.4 minutes and in group B 551 minutes. This was significantly longer duration compared with bupivacaine alone. The two groups did not differ significantly in total analgesic dose requirement. Binay Kumar *et al.* [11] conducted a study on 80 patients undergoing orthopedic surgeries. This study concluded that both 25-µg fentanyl and 25-µg butorphanol given intrathecally with 12.5 mg of hyperbaric bupivacaine provide effective and safe anesthesia for lower limb surgeries with minor side effects.

Neeta S, Upadya M, Gosain A, Manissery JJ [12] conducted a study concluding that Fentanyl with bupivacaine produced prolonged analgesia and delayed two-segment regression and demonstrated reduced incidence of complications as compared with intrathecal sufentanil. As the quality of analgesia was complete and comparable, fentanyl emerges as a better option for analgesia and it is much economical too when compared to sufentanil. Thus inferring that opioids provide prolonged analgesia when used along with local anaesthtetics which strongly supports the current study.

Visual analogue scale 6 hours post operatively was significantly more likely to be greater than 0 in Group B as compared to Group A. Visual analogue scale 24 hours post operatively was significantly greater than 1 in both the groups.

Afolayan JM *et al.* [13] Conducted a study on 186 patients undergoing emergency open appendicectomy under spinal anaesthtesia. showed that intrathecal tramadol (25 mg) can safely replace intrathecal fentanyl (25 µg) in the management of visceral pain and discomfort during subarachnoid block for appendicectomy.

Brijesh Jain *et al.* [14] in 2000 found that intrathecal tramadol 25 mg added to bupivacaine provided a mean duration of post-operative pain relief of about eight hours, which is similar to our finding. Frikha N *et al.* [15] concluded that 2.5 micrograms of intrathecal sufentanil combined with 2.5 mg bupivacaine provides rapid-onset and profound analgesia during the first stage of labor without adverse maternal or fetal effects. 25 mg intrathecal tramadol with 2.5 mg bupivacaine had longer-lasting analgesia. The major side effect was vomiting.

Inanoglu K, Ozcengiz D, Gunes Y, Unlugenc H, Isik G. [16] aimed to compare the effects of ropivacaine (R) alone and ropivacaine plus tramadol (RT) administered epidurally for postoperative analgesia in children. The duration of analgesia was significantly longer in group RT than in group R (298.6 ± 28 and 867.9 ± 106.8 min in group I and II, respectively) ($p < 0.05$). CHEOPS scores were significantly lower in group RT at 30 min, 45 min, and 3 h postoperatively than in group R ($p < 0.05$). Turker G *et al.* [17] study revealed that the quality of analgesia achieved with repeated doses of lumbar epidural tramadol after muscle-sparing thoracotomy is comparable to that achieved with repeated doses of lumbar epidural morphine. Compared with morphine, lumbar epidural tramadol results in less sedation and a less-pronounced decrease in oxygenation.

Mean Time for full motor recovery in the current study was 230 minutes in group A, and 226 minutes in group B, Mean Time for 2 segment regression of sensory level in group A was 94 minutes and in group B was 97.4 minutes which shows there was no significant difference between the two groups. Mean time for complete motor sensory recovery in groupA 245 minutes and in group B was 241.4 minutes which showed no significant difference between the groups.Gauchan S, Thapa C, Prasai A, Pyakurel K, Joshi I, Tulachan J. [18] conducted a study on parturients undergoing

caesarean section electively and this study found that duration of sensory block was prolonged in fentanyl group ($p < 0.05$). Duration of complete analgesia (97 ± 8.23 minutes vs 153 ± 7 minutes; p value = 0.00) and effective analgesia (134 ± 5.6 minutes vs 164 ± 9; p value = 0.00) were also found to be prolonged in fentanyl group. There was not much difference in the occurrence of side effects in both the groups. Addition of fentanyl to intrathecal bupivacaine for cesarean section increases the duration of postoperative analgesia without increasing maternal or neonatal side effects. This strongly supports the current study saying that less side effects with addition of fentanyl despite of prolonged analgesic effect.

Roussel JR, Heindel L. [19] conducted a study on fifty patients. This study found no differences in onset and duration of sensory or motor block. This study concluded that fentanyl does not enhance the onset and duration of sensory or motor block produced by 12 mg of intrathecal bupivacaine. Fentanyl, however, prolongs postoperative analgesia and increases the risk of pruritis. Yaddanapudi LN *et al.* [10] study shows that epidural tramadol can provide adequate postoperative analgesia comparable to that of epidural morphine in patients undergoing laminectomy.

In present study there are minimal side effects. In group A 3 patients developed pruritis, two patients developed shivering. In group B 2 patients developed vomiting, 3 patients developed pruritis, 1 patient developed shivering. Bruce-Ben David *et al.* [20] found significant pruritis with of intrathecal opioids. The prophylactic use of ondansetron in both groups would explain the incidence of minimal pruritis and nausea in our study.

Conclusion

Addition intrathecal tramadol or fentanyl to bupivacaine hemodynamic changes, post-operative analgesia, and sensory blockade without prolonging motor recovery showed no significance in groups. Addition of both opioids produced minimal intraoperative and postoperative side effects.

References

1. Vaswani RK, Raiger LK, Purohit R, Bajaj P. The effect of intrathecal midazolam on postoperative pain relief in orthopedic surgery. Hospital Today. 2002;7(4):150-53.
2. Valentine N, Lomoholt B, Jeusen JS, Hejgarrd N, Kreiner S. Spinal or general anesthesia for surgery of the fractured hip? Br J Anaesth. 1986;58:284-91.
3. Wang CY. Respiratory depression after extradural fentanyl (Letter). Br J Anaesth. 1992;69:544.
4. Gielen MJM. Spinal anesthesia. Current opinion in Anaesthesiology. 1993;6:803-7.
5. Benzon HT, Wong HY, Belavic AM, Goodman I, Mitchell D, Lefheit T, Locicero J. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. Anesth Analg 1993;76:316-22.
6. Jagtap S, Chhabra A, Dawoodi S, Jain A. Comparison of intrathecal ropivacaine-fentanyl and bupivacaine-fentanyl for major lower limb orthopaedic surgery: A randomised double-blind study. Indian J Anaesth. 2014;58:442-6.
7. Li Z, Tian M, Zhang CY, Li AZ, Huang AJ, Shi CX, Xin DQ, Qi J, Li KZ. A randomized controlled trial to evaluate the effectiveness of intrathecal bupivacaine combined with different adjuvants (fentanyl, clonidine and dexmedetomidine) in caesarean section. Drug Res. 2014;65:581–86.
8. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after trans urethral resection of prostate. British Journal of Anaesthesia. 2003 Oct;91(4):536-40.
9. Idowu OA, Sanusi AA, Eyelade OR. Effects of intrathecally administered fentanyl on duration of analgesia in patients undergoing spinal anesthesia for elective caesarean section. Afr J Med Med Sci. 2011;40:213–9.
10. Yaddanapudi LN, Wig J, Singh B, Tewari MK. Comparison of efficacy and side effects of epidural tramadol and morphine in patients undergoing laminectomy : a repeated dose study. Neurol India 2000;48:398-400s.
11. Kumar B, Williams A, Liddle D, Verghese M. Comparison of intrathecal bupivacaine-fentanyl and bupivacaine-butorphanol mixtures for lower limb orthopedic procedures. Anesth Essays Res. 2011;5(2):190–95. doi:10.4103/0259-1162.94775.
12. Neeta S, Upadya M, Gosain A, Manissery JJ. A prospective randomized controlled study comparing intrathecal bupivacaine combined with fentanyl and sufentanil in abdominal and lower limb surgeries. Anesth Essays Res. 2015 May-Aug;9(2):149-54.
13. Afolayan J M, Olajumoke T O, Amadasun F E, Edomwonyi NP. Intrathecal tramadol versus intrathecal fentanyl for visceral pain control during bupivacaine subarachnoid block for open appendicectomy. Niger J Clin Pract 2014;17:324-30.
14. Brijesh Jain, V.K. Sarasawat. Efficacy of intrathecal Tramadol for post operative pain relief in cases of L.S. C.S, and major gynaecological surgeries – a

clinical evaluation. Indian Journal Anesthesia. 2001; 45(4):282.

15. Frikha N, Ellachtar M, Mebazaa MS, Ben Ammar MS. Combined spinal-epiduralanalgesia in labor--comparison of sufentanil vs tramadol. Middle East J Anaesthesiol. 2007 Feb;19(1):87-96. PubMed PMID: 17511185.
16. Inanoglu K, Ozcengiz D, Gunes Y, Unlugenc H, Isik G. Epidural ropivacaine versus ropivacaine plus tramadol in postoperative analgesia in children undergoing major abdominal surgery: a comparison. J Anesth. 2010 Oct;24(5):700-4.
17. Turker G, Goren S, Bayram S, Sahin S, Korfali G. Comparison of lumbar epiduraltramadol and lumbar epidural morphine for pain relief after thoracotomy: a repeated-dose study. J Cardiothorac Vasc Anesth. 2005 Aug;19(4):468-74.
18. Gauchan S, Thapa C, Prasai A, Pyakurel K, Joshi I, Tulachan J. Effects of intrathecal fentanyl as an adjunct to hyperbaric bupivacaine in spinal anesthesia for elective caesarean section. Nepal Med Coll J. 2014 Sep;16(1):5-8.
19. Roussel JR, Heindel L. Effects of intrathecal fentanyl on duration of bupivacaine spinal blockade for outpatient knee arthroscopy. AANA J. 1999 Aug;67(4):337-43.
20. Nieuwenhuij SD, Bruce J, Drummond GB, *et al.* Influence of oral tramadol on the dynamic ventilatory response to CO_2 in healthy volunteers. Br.J.Anaesth. 2001;87:860-865.