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Research Article

A CLINICAL TRIAL COMPARING LEVOBUPIVACAINE, STANDARD AND LOW DOSE BUPIVACAINE FOR SUBARACHNOID BLOCK TO COMPARE THE HAEMODYNAMIC CHANGES AS WELL AS EFFECT ON EARLY AMBULATION IN PATIENTS UNDERGOING TRANS URETHRAL RESECTION OF PROSTATE

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ABSTRACT
Use of levobupivacaine as pure S(-) enantiomer of bupivacaine has progressively increased due to lower cardiotoxicity and neurotoxicity and shorter duration of motor block. The aim was to compare the efficacy of lower dose local anaesthetics used together with higher opioid dose to decrease side effects of drugs. We compared sensory, motor block levels and side effects of equal doses of low dose bupivacaine, standard dose bupivacaine and levobupivacaine with intrathecal fentanyl addition in transurethral resection of prostate operation**.** After getting approval from the Institutional Ethics Committee and obtaining written informed consent from each patient, study was conducted under the Department of Anesthesiology in IPGMER/SSKM Hospital, Kolkata from March to May 2013. Seventy five male patients of ASA physical status 1-2 scheduled to undergo elective transurethral resection of prostate were equally allocated in three groups comprising of 25 patients in each groups. Patients in Group A received intrathecal hyperbaric 0.5% bupivacaine 0.8 ml (4mg) + fentanyl 0.5ml (25µg) + 0.3ml normal saline (0.9%) i.e., a total volume of 1.6ml and those in Group B received intrathecal hyperbaric (0.5%) bupivacaine 2.7ml + fentanyl 0.5ml (25µg) i.e., a total volume of 3.2ml. Group C patients received intrathecal hyperbaric levobupivacaine(0.5%) 2.7ml + fentanyl 0.5ml (25µg) a total volume of 3.2ml.The end point of the study was complaints of pain and/or demand of first rescue analgesic. In Group A, haemodynamic parameters were stable compared to Group B and C. Haemodynamic alterations became significant around 30 min after intrathecal block and in Group C parameters were slightly better than Group B. Alteration of motor power was also less in low dose Group A. Intrathecal hyperbaricbaric levobupivacaine and fentanyl combination is a good alternative to bupivacaine and fentanyl combination in TURP as it maintains hemodynamic stability at higher sensory block levels.

Keywords: *Bupivacaine, Haemodynamic Alteration, Levobupivacaine, Spinal Anaesthesia, Transurethral Resection of Prostate*

INTRODUCTION
Spinal and epidural administration of local anaesthetics during trans urethral resection of prostate (TURP) produce analgesia, anaesthesia and motor block, depending on the volume, concentration, and doses of drug used. For the local anaesthetics selection, it is known that the agent's onset and duration of action, sensory block level to motor block level and cardiac toxicity should be considered. Hyperbaric bupivacaine(0.5%) is more commonly used for spinal anaesthesia for TURP operation. Levobupivacaine, being the S-enantiomer of bupivacaine, is less cardiotoxic and less neurotoxic in cases of accidental intravascular injection and has shorter duration of motor block than racemic bupivacaine, its use has increased progressively. There is the clinical profile of potency for motor block for the pipecolylxlidines when administered spinally: low, intermediate, and high for ropivacaine, levobupivacaine and bupivacaine respectively.
The use of low doses anaesthetics and opioids in spinal anaesthesia were reported to have advantages such as faster onset of action, better efficacy with minimum toxic effect and selective sensory block. Fentanyl can be combined with local anaesthetics for spinal anaesthesia, and when used in this way it

prolongs the duration of action and spread of sensory block as well. Fentanyl has been combined with bupivacaine for lower limb surgery and also for inguinal herniorrhaphy and caesarean section, TURP etc. We planned to compare the onset and duration of action, sensory, motor block levels and side effects of equal doses of hyperbaric bupivacaine and levobupivacaine and low dose bupivacaine with intrathecal fentanyl addition in spinal technique in TURP. Our aim was to compare the efficacy of low dose local anaesthetics use together with higher opioid dose to decrease side effects of drugs.

MATERIALS AND METHODS

This prospective double-blinded randomized study was performed in March to May 2013. The study was approved by institutional ethics committee and patients provided written consent. The study was conducted in Urology OT, IPGMER/SSKM Hospital, Kolkata. Total 75 male patients of ASA Physical Status 1-2 suffering from benign prostatic hypertrophy posted for trans-urethral resection of prostate were included in the study. Patients refusing subarachnoid block or having any contraindication to subarachnoid block such as infection at the site of injection, autonomic dysfunction, coagulopathy, neurological disorders, stenotic heart diseases, spinal deformity were excluded from the study. Patients receiving β-blocker, patients with known allergy to study drugs, patients on anti-platelet drugs or anticoagulants were not included in the study. The injection with the drug was prepared by the study coordinator according to software which was carefully designed to prevent duplicate injections. The injectors were numbered and given to the staff who did not know the content. Also, patients did not know which agent they were given. All patients were evaluated initially by medical history and a complete physical examination was done. The patients did not receive any pre-medication and were kept fasting from midnight on the day before surgery.

Before spinal anaesthesia, the patients received sodium chloride 0.9% (300 ml) solution over 20 min. Patients in Group A received intrathecal hyperbaric 0.5% bupivacaine 0.8 ml (4mg) + fentanyl 0.5ml (25µg) + 0.3ml normal saline (0.9%) i.e., a total volume of 1.6ml. Group B patients received intrathecal hyperbaric 0.5% bupivacaine 2.7ml + fentanyl 0.5ml (25µg) i.e., a total volume of 3.2ml as standard text book method and those in Group C received intrathecal hyperbaric 0.5% levobupivacaine 2.7ml + fentanyl 0.5ml (25µg) making a total volume of 3.2ml.

Spinal puncture was performed at L3–4 or L4–5 inter-vertebral space with a 25G Quincke's spinal needle with the patient in a seated position. After observing free flow of clear cerebrospinal fluid (CSF), the drug mixture was administered over 10–15 seconds with cephalic orientation of the spinal needle bevel. The i.v. infusion was minimally maintained during the surgical procedure to avoid fluid overloading associated with absorption of the irrigation fluid.

Adverse effects such as hypotension, bradycardia, nausea or vomiting, pruritus, shivering, and respiratory depression were recorded during the operation and recovery. Data regarding the preoperative ultrasound-estimated prostate volume was collected, and systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were monitored continuously and was recorded every 5 min until the end of surgery. Hypotension was defined by a decrease in SBP of <90 mm Hg or <75% from the baseline value, and bradycardia was defined as heart rate <45 beats/ min. Degree of motor block was assessed by the Modified Bromage Score (MBS) at regular intervals. Analgesia was assessed by VAS pain score. Rescue analgesia was administered postoperatively when VAS score > 4 or when patient requested for analgesia, with diclofenac sodium 1 mg/kg body weight intramuscularly. Time from institution of successful subarachnoid block to request for first rescue analgesia was recorded.

The most frequently used measure of motor block is the Modified Bromage scale. In this scale The intensity of motor block is assessed by the patient's ability to move their lower extremities (0=Free movement of legs and feet; 1=Just able to flex knees with free movement of feet; 2=Unable to flex knees, but with with free movement of feet; 3=Unable to move the legs or feet. Onset of motor block was recorded as when Bromage scale score was "1" after administration of local anaesthetics, motor block duration was recorded as time to complete termination of motor block, maximum motor block level was also recorded.

RESULTS AND DISCUSSION

Results

Total of seventy five patients were included in the study. However, in two patients, due to insufficient regional anaesthesia, additional local anaesthetics were given and patient was excluded from the study as the doses were changed. No significant differences were detected among the groups with respect to age, weight, height and duration of surgery [Table 1].

Table 1: Demographical data of study population

Variables	Group A Mean±SD	Group B Mean±SD	Group C Mean±SD	*P* value
Age (years)	62.22±6.89	63.76±5.59	64.16±7.15	0.541
Height (cm)	163.92±3.58	162.96±3.95	162.48±3.90	0.402
Weight (kg)	61.84±4.69	60.84±4.60	63.88±4.48	0.306
Prostate Wt (grams)	39.48 ± 7.15	40.28±6.02	47.84±5.50	0.000
Duration of surgery (min)	46.82 ± 5.93	48.64±6.54	46.60±7.32	0.504

SD- Standard Deviation

Table 2: Comparison of heart rate between groups

Time	Group A Mean heart rate±SD	Group B Mean heart rate±SD	Group C Mean heart rate±SD	*P* value
0 min	83.12±15.16	86.84±9.66	87.61±8.50	0.341
5 min	85.20±15.43	83.80±9.46	84.64±8.43	0.923
10 min	82.48±15.15	79.32±9.28	81.43±8.34	0.604
15 min	79.52±15.32	75.16 ±8.79	78.28±8.24	0.372
20 min	77.04±15.43	71.04±8.77	74.65±8.68	0.181
25 min	74.08±14.52	67.64±8.37	71.74±9.41	0.125
30 min	71.24±12.68	64.51±8.05	69.30±6.83	0.048
35 min	70.40±12.33	60.86±6.94	67.46±6.68	0.000
40 min	70.80±12.46	58.23±6.36	65.14±6.70	0.000
45 min	72.00±14.10	57.43±4.76	64.32±6.81	0.000
50 min	71.84±13.31	56.06±4.05	63.84±6.58	0.000
55 min	72.11±14.43	55.71±3.87	64.12±7.68	0.000
60 min	72.26±14.69	56.24±4.90	63.49±6.54	0.000

SD- Standard Deviation

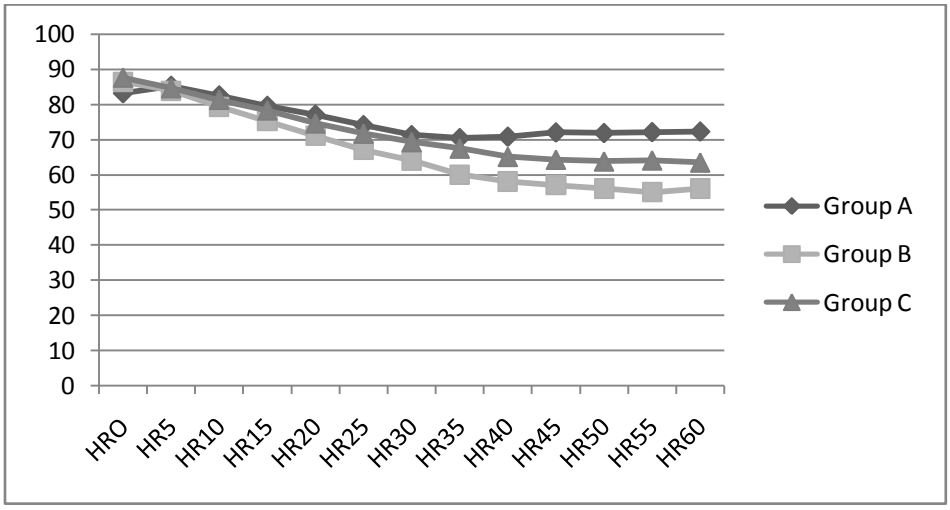

Figure 1: Mean heart rate in all groups at various time intervals

Basal heart rate of Group A,B,C were 83.1/min, 86.8/min and 87.6 /min respectively. There was no significant difference in heart rate of group A both preoperatively and intraoperatively (P>0.05), but heart rates in group B and C decreased intraoperatively from 30 min. onwards which was statistically significant [Table 2].

Systolic blood pressure decreased significantly in both Groups B and C compared to Group A (P<0.001 from 30 min onwards). The decrease was more significant in Group B and Maximum decrease was at 60 min (96.94±7.96 mm Hg) [Table 3].

Table 3: Comparison of SBP between groups

Time	Group A Mean SBP±SD	Group B Mean SBP±SD	Group C Mean SBP±SD	*P* value
0 min	134.75±17.33	134.21±12.94	134.21±19.83	0.994
5 min	136.03±19.82	128.52±11.41	130.07±14.63	0.211
10 min	132.66±18.03	125.14±10.74	126.03±12.82	0.136
15 min	128.82±17.37	120.29±9.18	123.61±12.56	0.084
20 min	125.73±15.96	115.10±8.31	121.49±12.56	0.015
25 min	122.91±15.22	110.27±8.41	118.20±12.88	0.002
30 min	119.46±11.98	106.26±7.66	115.62±12.76	0.000
35 min	118.58±12.83	101.85±7.84	112.36±13.58	0.000
40 min	120.24±13.36	99.56±7.64	110.68±13.63	0.000
45 min	121.33±13.10	98.49±8.04	109.61±13.55	0.000
50 min	121.72±14.16	98.04±9.12	109.26±13.28	0.000
55 min	122.03±16.55	98.03±9.73	109.78±13.40	0.000
60 min	122.23±17.31	96.94±7.96	108.42±13.18	0.000

SBP- Systolic blood pressure; SD- Standard Deviation

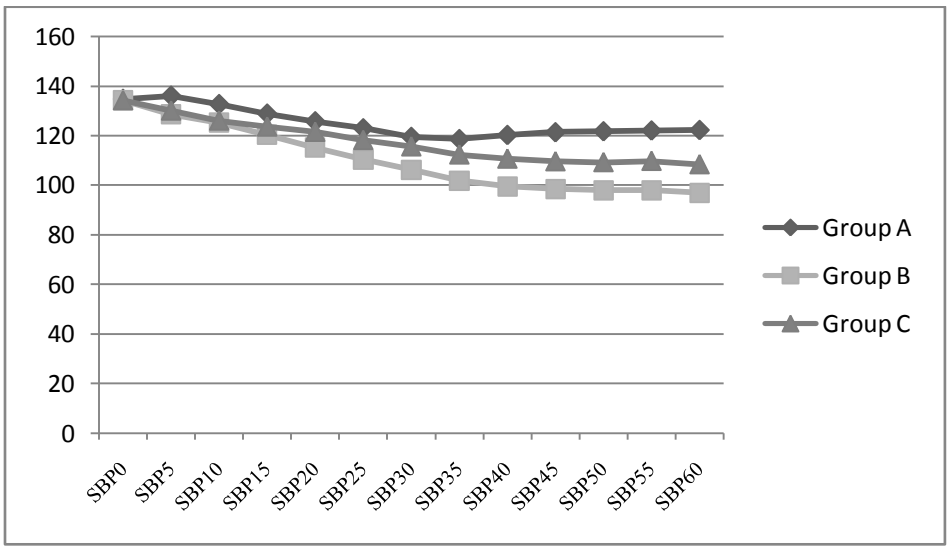

Figure 2: SBP in all groups at various time intervals

On the other hand DBP at the onset were 82.2 mm Hg, 81.5 mm Hg and 76.2 mm Hg in Group A,B and C respectively. We have seen an early decrease of DBP starting at 5 min and continuing throughout the procedure in both Group B and Group C but this is more pronounced in Group B [Table 4].

Table 4: Comparison of DBP between groups

Time	Group A Mean DBP±SD	Group B Mean DBP±SD	Group C Mean DBP±SD	*P* value
0 min	82.24±14.09	81.56±7.49	76.29±7.40	0.082
5 min	79.91±11.03	77.82±6.54	71.03±9.32	0.003
10 min	77.50±10.65	74.78±6.88	69.21±7.85	0.004
15 min	74.46±10.84	70.12±6.44	66.92±6.69	0.007
20 min	72.63±11.30	66.59±5.98	65.18±6.13	0.004
25 min	70.04±10.26	63.06±5.81	63.42±5.49	0.002
30 min	68.84±10.35	59.70±5.41	61.02±5.28	0.000
35 min	68.38±10.50	56.83±4.04	59.78±4.94	0.000
40 min	69.40±9.81	55.38±5.74	57.82±5.13	0.000
45 min	69.82±10.23	54.91±5.60	57.69±5.62	0.000
50 min	70.57±10.56	55.26±4.93	57.37±5.52	0.000
55 min	70.36±11.36	54.80±5.19	57.50±5.92	0.000
60 min	70.42±12.03	54.94±5.82	56.45±5.65	0.000

DBP- Diastolic blood pressure; SD- Standard Deviation

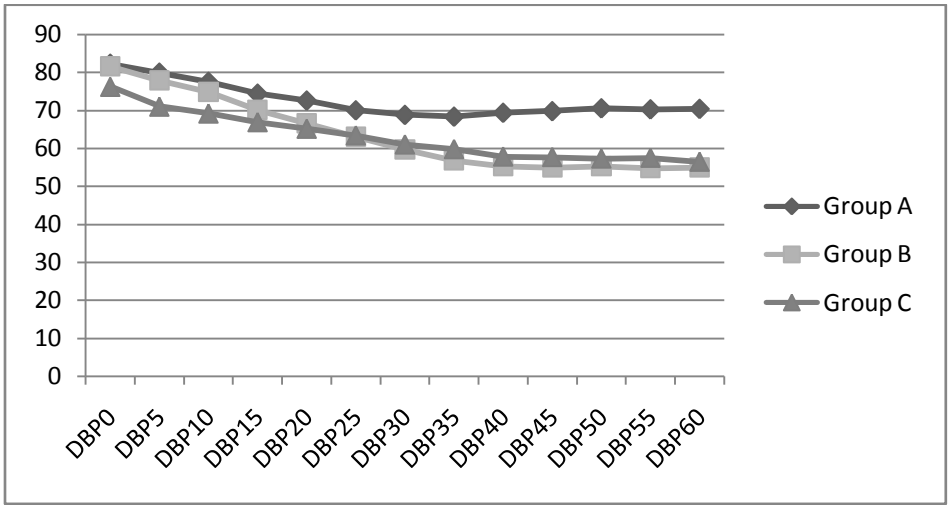

Figure 3: DBP in all groups at various time intervals

Table 5: Comparison of MAP between groups

Time	Group A Mean MAP±SD	Group B Mean MAP±SD	Group C Mean MAP±SD	*P* value
0 min	98.61±12.53	99.21±9.00	96.34±7.78	.556
5 min	98.68±13.40	94.62±7.65	90.62±9.46	.031
10 min	95.91±12.42	91.46±7.83	88.08±8.21	.020
15 min	92.62±12.42	86.80±6.83	85.68±7.16	.021
20 min	90.37±12.28	82.89±6.40	83.86±6.79	.008
25 min	87.73±11.31	78.86±6.42	81.72±6.56	.001
30 min	85.70±10.39	75.28±5.89	79.24±6.15	.000
35 min	85.07±10.89	71.87±4.95	77.26±6.05	.000
40 min	86.48±10.05	70.14±5.87	75.32±6.72	.000
45 min	86.81±10.75	69.42±6.14	74.83±6.74	.000
50 min	87.65±11.55	69.56±6.06	74.60±6.83	.000
55 min	87.46±12.46	69.2±6.38	74.82±7.31	.000
60 min	87.51±13.03	68.82±6.30	73.61±6.95	.000

MAP- Mean arterial blood pressure; SD- Standard Deviation

In case of mean arterial pressure(MAP) there was no significant change in patients of group A but MAP decreased notably in both group B and C from 25 min. onwards intraoperatively(P<0.05). The fall in MAP was greater in Group B and maximum decrease was at 60 min (68.82±6.30 mm Hg) [Table 5].

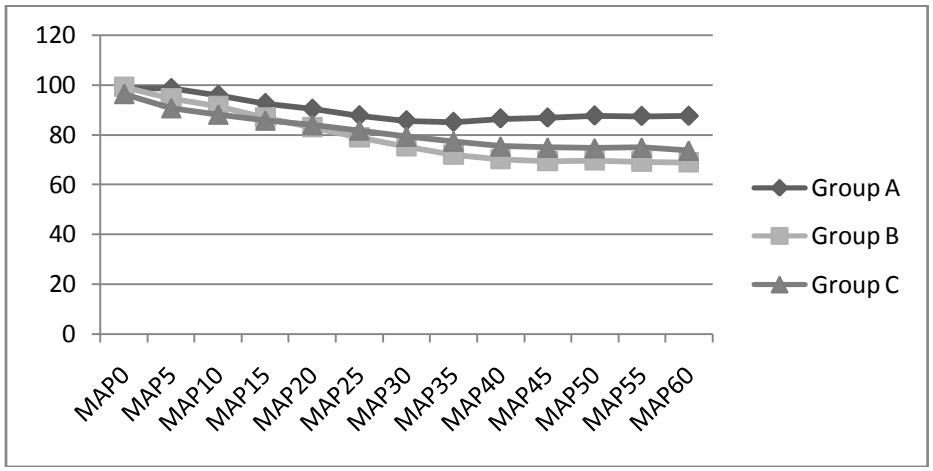

Figure 4: MAP in all groups at various time intervals

Bromage score at 10 mins of spinal anaesthesia were 1.8, 2.1, 2.1 and at the end of operation were 0.4, 3, 3 in Group A, B and C respectively. So, value was much higher in both Group B and C compared to Group A at 10 min mark (P=0.03) and at the endpoint of operation (P<0.001) [Table 5].

Table 6: Comparison of Bromage score between groups

Groups	Bromage Score at 10 min	Bromage Score at Operation end
A	1.8	0.4
B	2.1	3
C	2.1	3

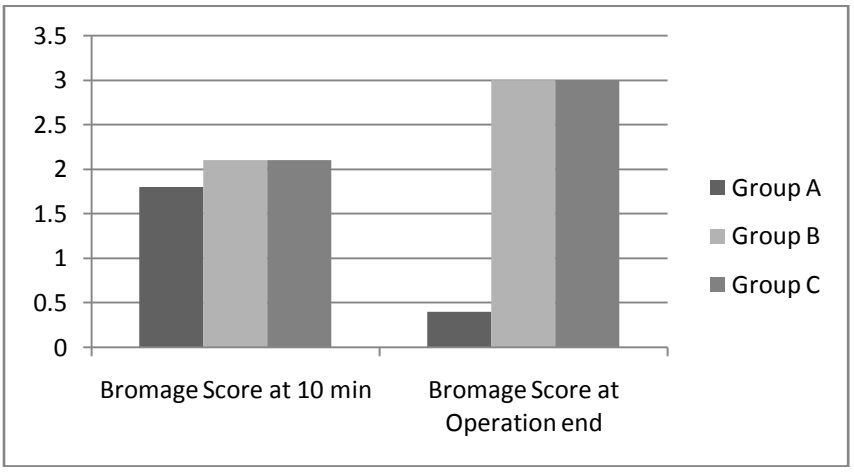

Figure 5: Bromage score comparison

So we conclude that low dose Bupivacaine (Group A) showed less haemodynamic alteration than that of Levobupivacaine (Group C) which on the other hand created less haemodynamic alteration than that of Standard dose of Bupivacaine (Group B). Alteration of motor power was also less in low dose Bupivacaine (Group A) than Standard dose of Bupivacaine (Group B) and Levobupivacaine (Group C). Similarly recovery was faster in Group A patients.

Discussion

Recent trends of geriatric anaesthesia show increased popularity of regional anaesthesia among surgeons and anaesthesiologists. Today, 0.5% heavy bupivacaine is most commonly used for spinal anaesthesia for TURP procedure.

General anaesthesia is associated with higher mortality rate in comparison to regional anaesthesia. Regional anaesthesia has some risks; fatalities are primarily related to excessive high regional blocks and toxicity of local anaesthetics. Reduction in doses and improvement in technique to avoid higher block levels and heightened awareness to the toxicity of local anaesthetics have contributed to the reduction of complications related with regional anaesthesia.

Over the last decade, spinal anaesthesia has been refined with the addition of opioids to local anaesthetic solution. The addition of morphine significantly prolongs post operative analgesia to 18-24 h, whereas the more lipophilic opioid such as sufentanil and fentanyl improve and prolong intraoperative analgesia and reduce the amount of local anaesthetics required to perform a sufficient dermatome spread and block intensity necessary for lower abdominal and pelvic surgery. By adding opioids to spinal anaesthesia, a reduction in local anaesthetic dose is possible. This reduction in local anaesthetic requirements reduces the intensity and duration of motor blockade and allows patients to ambulate faster. Initial reports on low-dose spinal anaesthesia suggest that this may also reduce hypotension.

of 7.5 mg bupivacaine for Caesarean section as this dose was associated with a decreased Nowadays, 0.5% hyperbaric bupivacaine is most commonly used for spinal anaesthesia. Recent studies have claimed successful anaesthesia with very low doses of intrathecal bupivacaine (5-9 mg) when co administered with opiods. Kiran and Singal advocated the use incidence of hypotension but again, a large number of patients rated the analgesic quality as poor. Ginosar *et al.,* (2004) reported ED50 and ED95 of hyperbaric bupivacaine in caesarean section with combined spinal epidural technique is 7.6 mg and 11.2 mg, respectively. In our study, anaesthesia was 95 % successful with 25 mcg fentanyl added to 7.5 mg hyperbaric bupivacaine. Only in two patients, it was not sufficient and local anaesthetics were administered. Due to lower cardiovascular side effect and central nervous system toxicity, use of levobupivacaine as pure S(-) enantiomer of bupivacaine has progressively increased. Epidural levobupivacaine has the advantage of decreased cardio toxicity in cases of accidental intravascular injection. Parpaglioni *et al.*, reported minimum intrathecal levobupivacaine dose to be 10.58 mg in caesarean section. Alley *et al.,* (2001) evaluated three intrathecal doses of levobupivacaine and bupivacaine (4, 6 and 8 mg) in healthy volunteers and found no differences in clinical profile of sensory and motor blocks and recovery from spinal anaesthesia. In some studies, levobupivacaine and racemic bupivacaine showed undistinguishable clinical profile in spinal anaesthesia. In selection of local anaesthetics, it is desired that the agent's onset of action is short, duration of action is longer and sensory block level to motor block level is higher. Gautier *et al.,* (2003) reported that intrathecal 0.5 % levobupivacaine had weaker motor block potency than 0.5 % bupivacaine in elective caesarean cases with CSE anaesthesia technique. Similarly Vercauterenet *et al.,* (2001) performed a study on patients who received either 0.125 % levobupivacaine or 0.125 % racemic bupivacaine and found that levobupivacaine led to less motor impairment compared to racemic bupivacaine in intrathecal labour analgesia. In our study, levobupivacaine had lesser motor potency. Bromage score at 10 min. were 2-3 in levobupivacaine and 2-3 in bupivacaine and 1-2 in low dose bupivacaine. Haemodynamics was better maintained in low dose bupivacaine group, but recovery in motor block was earlier than the other 2 groups. Intrathecal opioids administration has side effects such as nausea, vomiting, pruritus, sedation, respiratory depression and urinary retention. Highly lipid soluble opioids cause temporary pruritus whereas intrathecal morphine causes long acting and intensive pruritus. In our study, pruritus incidence was higher in levobupivacaine group, however it was not intense to be treated.

Conclusion

Intrathecal hyperbaric levobupivacaine and fentanyl combination is a good alternative to bupivacaine and fentanyl combination in TURP as it is less effective for motor block and maintains hemodynamic stability at higher sensory block levels.

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