

Comparison between Clinical Efficacies of Levobupivacaine Plain and Levobupivacaine with Fentanyl for Urological Surgeries under Subarachnoid Block

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ABSTRACT

Background and aims: Spinal anesthesia for urological operations has been frequently used, because symptoms of overhydration, transurethral resection of prostate (TURP) syndrome, and bladder perforation can be recognized. This prospective randomized study was conducted to compare the clinical efficacies of levobupivacaine with and without fentanyl in subarachnoid block with respect to onset and duration of sensory and motor block and duration of analgesia in urological surgeries.

Materials and methods: This randomized study was conducted in 100 patients of American Society of Anesthesiologists (ASA) physical status grades I and II, posted for urological surgeries. Patients were randomly allocated to two groups and were given the following drugs intrathecally as per group distribution: Group I: 2.5 mL of 0.5% isobaric levobupivacaine and group II: 2.2 mL of 0.5% isobaric levobupivacaine with 15 µg (0.3 mL) fentanyl citrate. Parameters monitored were onset and duration of sensory and motor block, hemodynamic parameters, postoperative analgesia, and side effects. Data were analyzed using Student's t-test for the continuous variables and chi-square test for categorical variables.

Results: The onset of sensory level of T10 was earlier in group II (4.74 ± 0.723 minutes) than in group I (5.7 ± 0.953 minutes). Duration of sensory block was longer in group I (292.2 ± 8.154 minutes) than in group II (260 ± 11.066 minutes). Motor block regressed earlier in group II (181.2 ± 7.73 minutes) than in group I. Hemodynamic parameters and side effects were similar in both the groups.

Conclusion: From our study, we concluded that plain levobupivacaine provided a longer duration of sensory and motor subarachnoid blockade. However, addition of fentanyl as a spinal adjuvant had a dose-sparing effect with earlier onset and early regression of motor block and no hemodynamic alterations.

Keywords: Intrathecal fentanyl, Levobupivacaine, Spinal adjuvant, Transurethral resection of prostate, Urology.

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INTRODUCTION

Urologic endoscopic procedures are performed under regional anesthesia with subarachnoid blockade on a wide variety of patients ranging from the young, physically fit to the elderly with multiple comorbidities.¹⁻³ Most of patients presenting for endoscopic urological surgery belong to the geriatric population having a coexisting cardiac, pulmonary condition, or some other comorbidities.⁴ The addition of an adjuvant to low-dose local anesthetic agent can minimize the fluctuations in the cardiovascular system associated with subarachnoid block and thus provide satisfactory anesthesia to the elderly patients without compromising safety.

Bupivacaine is available as a racemic mixture (50–50) of its two enantiomers: Levobupivacaine (S-) isomer and dextrobupivacaine (R+) isomer. The low neurological and cardiovascular toxicity of levobupivacaine has led to its application as a local anesthetic in several clinical applications.^{5,6} The sensory and motor characteristics and recovery from spinal anesthesia by using levobupivacaine are similar to bupivacaine with earlier regression of motor block.⁷⁻⁹ At low concentrations, levobupivacaine produces a differential neuraxial block wherein motor function is preserved. This may prove beneficial for ambulatory surgeries.¹⁰⁻¹²

Lipophilic opioids (e.g., fentanyl and sufentanil) are increasingly being administered intrathecally as adjuncts to local anesthetics.^{4,13} The literary evidence has established that addition of opioids provides a dose-sparing effect of levobupivacaine, with improved quality of the block and less hemodynamic variations during perioperative period.^{8,14} Intrathecal opioid used as an adjuvant enables faster onset of spinal block and the incidence of side effects is decreased. It also allows early ambulation of the patients, thereby reducing the recumbency period and duration of hospital stay for the patients.^{4,13,15}

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Hence, in our study we compared the clinical efficacies of levobupivacaine plain and with fentanyl in subarachnoid block for urological surgeries.

MATERIALS AND METHODS

This prospective randomized study was conducted following Ethical Committee Approval Seth G.S Medical College, from January 2014 to January 2016. Patients of ASA physical status grades I and II, between the ages of 18 and 60 years, weighing 40 to 70 kg with height more than 150 cm undergoing urological surgeries like TURP, transurethral resection of bladder tumors, and ureteroscopic stone retrieval surgeries were included in the study. Patients with coexisting severe cardiovascular, respiratory, or neurological disorders, known history of coagulation disorders, inflammatory skin lesions at the site of giving block, preexisting neuropathies, and allergy to local anesthetics were excluded from the study.

Following detailed preanesthetic checkup, informed written consent was obtained from patients fulfilling the required criteria. Patients were randomly divided into two groups namely groups I and II by computerized randomization. The patient was explained about the visual analog scale (VAS) score preoperatively. The surgeon, patient, and the observing anesthetist were blinded to the patient group. Patients were taken up for surgery after adequate starvation of 6 hours. After taking the patient to the operation theater, intravenous (IV) access was established. Noninvasive monitoring was attached including pulse oximeter, cardiograph and sphygmomanometer. Preloading was done with crystalloid solution 10 mL per kg of body weight. Oxygen at 4 L per minute with Hudson's mask was supplemented. The patient was positioned in sitting position. Under all aseptic precautionary measures L3–L4 or L4–L5 space was palpated and local infiltration with 2 cc of 2% lignocaine was given. Subarachnoid space was reached with 25G Quincke's spinal needle in a midline or paramedian approach and confirmed by free and clear flow of cerebrospinal fluid and negative aspiration of blood. Then study drug was injected into subarachnoid space in respective groups of patients. The patient was placed in supine position after spinal injection of drug.

Pulse rate and blood pressure were monitored every 2 minutes till the drug level fixed around 15 minutes, every 5 minutes for the next 15 minutes, and every 15 minutes thereafter for 150 minutes. Criteria for bradycardia or tachycardia and hypotension or hypertension were decrease or increase in more than 20% from the baseline respectively, but the treatment was given only if clinically indicated (mean arterial blood pressure <80 mm Hg or pulse rate <50/minute). Hemodynamic

status was monitored till regression of sensory level to S1. Incidence of nausea and vomiting was noted and treated with metoclopramide 10 mg intravenously. Midazolam in 0.5 mg increments intravenously was given as indicated for anxiolysis.

The upper and lower levels of sensory block was determined using loss of sensation to pinprick and motor block was assessed with Modified Bromage Scale (0 = no motor block, 1 = inability to raise the extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints) at timed intervals every 2 minutes for initial 15 minutes, every 5 minutes for next 15 minutes. The assessment was continued till complete regression of sensory and motor block.

The characteristics of sensory block were assessed by highest sensory level, time from injection to sensory level of T10 (minute), time of two segments regression, and time of sensory regression to S1. The characteristics of motor block were assessed by onset to Bromage 3 and regression to Bromage 1. Pain intensity was assessed by VAS and rescue analgesia in the postoperative period given in the form of IV paracetamol 1 gm over a 15 minutes infusion.

All patients from both the groups were transferred to ward where they were monitored. The postoperative pain was assessed using VAS score where "0" corresponds to no pain and "10" to maximum or worst pain.

As per statistical software nMaster 1.0

$$n = \frac{2s_p^2 [Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\mu_d^2}$$

$$= s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

where s_1^2 = standard deviation in the first group = 80.03

s_2^2 = standard deviation in the second group = 61.29

μ_d^2 = Mean difference between the samples = 40

α = Significance level = 5% $1 - \beta$ = Power = 80%

Results of the study were observed and analyzed statistically. Data were tested for normality and analyzed using Student's t-test for numerical data and chi-square test for categorical data. Statistical difference was considered significant if $p < 0.05$.

RESULTS

There were no significant differences between the two groups in demographic data and ASA classification.

Mean age in group I was 41.76 ± 11.684 years and in group II was 43.38 ± 10.212 years and difference was insignificant ($p = 0.462$). The ASA status was comparable in both groups and the difference was insignificant.

Table 1: Onset and duration of sensory block

| | Group I | Group II | p-value | Significance |
|--|----------------|---------------|---------|--------------------------|
| Time to T10 (minutes) | 5.7 ± 0.953 | 4.74 ± 0.723 | <0.0001 | Significant |
| Highest level (T6) (no. of pts) | 9 | 30 | <0.0001 | Significant (chi square) |
| Time to two-segment regression (minutes) | 124.4 ± 20.118 | 128.6 ± 15.78 | 0.248 | Not significant |
| Time to regression to S1 (minutes) | 292.2 ± 8.154 | 260 ± 11.066 | <0.0001 | Significant |

Table 2: Chi-square tests for highest sensory level

| | Value | df | Asymp. Sig. (2-sided) |
|------------------------------|--------|----|-----------------------|
| Pearson chi-square | 21.937 | 3 | 0 |
| Likelihood ratio | 25.305 | 3 | 0 |
| Linear-by-Linear association | 21.137 | 1 | 0 |
| N of valid cases | 100 | | |

df: Degree of freedom

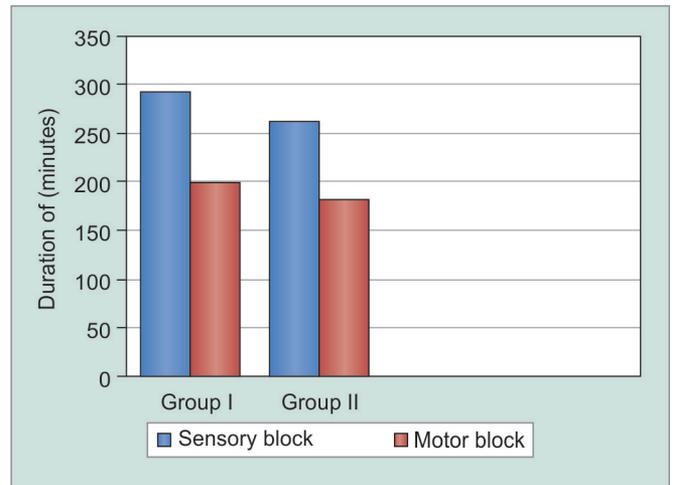
The mean time to achieve a sensory level of T10 was 5.7 ± 0.953 minutes in group I and 4.74 ± 0.723 minutes in group II (p < 0.0001). Duration of sensory block (regression to S1) was 292.2 ± 8.154 minutes in group I and 260 ± 11.066 minutes in group II (p-value < 0.0001). The highest sensory level achieved was T6 (Tables 1 and 2).

The time for regression of motor block was statistically significant in both groups with a p-value < 0.0001 which was 200.4 ± 9.026 minutes in group I and 181.2 ± 7.73 minutes in group II (Table 3, Graph 1).

In group I, four patients developed nausea and in group II, five patients had similar complaint but this difference was insignificant when analyzed statistically (Tables 4 and 5).

Hemodynamic parameters were similar in both groups before and during the operation (p > 0.05) with respect to mean arterial pressures and heart rate as shown in the graphs (Graphs 2 and 3).

The 2-hour postoperative VAS score was similar in both groups with 0.82 ± 0.983 in group I and 0.66 ± 0.961 in group II (p = 0.413; Graph 4).



Graph 1: Duration of subarachnoid block

DISCUSSION

Several studies have been published comparing the efficacy of intrathecal bupivacaine with its racemic enantiomers levobupivacaine and ropivacaine^{16,17} in cesarean sections^{11,18-20} and various lower abdominal and orthopedic outpatient surgeries on a daycare basis.^{9,21}

Lee et al^{14,22} first evaluated the effectiveness of 2.6 mL of 0.5% levobupivacaine in spinal block in urological surgeries and found that onset time, degree of sensory and motor block, and hemodynamic changes were similar to those for 2.6 mL of 0.5% bupivacaine.

The study conducted by Mantouvalou et al²³ demonstrated that bupivacaine enantiomers offered better

Table 3: Onset and duration of motor block

| | Group I | Group II | p-value | Significance |
|--|---------------|---------------|---------|--------------|
| Time to achieve Bromage 3 (minutes) | 6.5 ± 1.403 | 6.92 ± 1.066 | 0.095 | NS |
| Regression to Bromage 1 (minutes) | 200.4 ± 9.026 | 181.2 ± 7.73 | <0.0001 | S |
| Duration of complete motor block (Bromage 3) | 153 ± 17.4 | 148.2 ± 10.63 | 0.099 | NS |

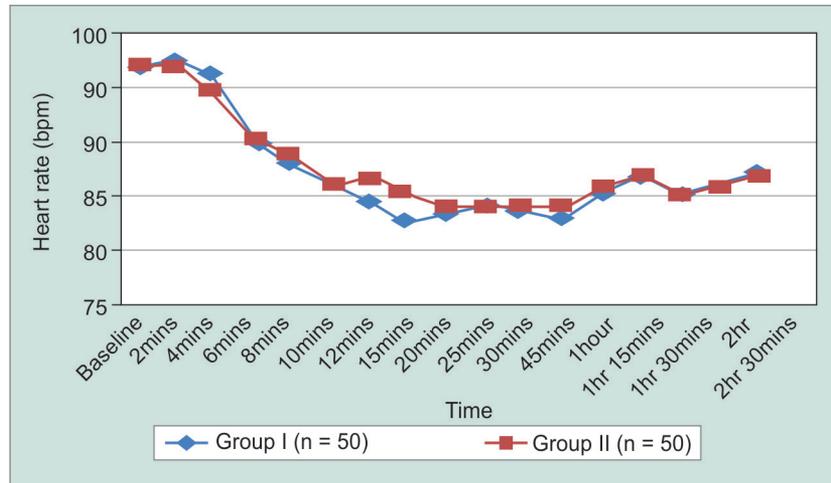
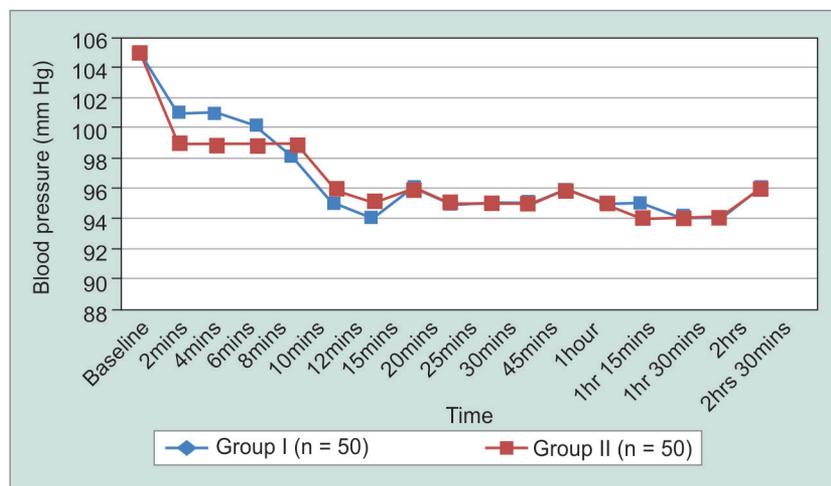
NS: Not significant; S: Significant

Table 4: Side effects

| | | | Side effect (nausea) | | Total |
|-------|-------------|--------------------|----------------------|------|-------|
| | | | Yes | No | |
| Group | LEVO | No. of pts | 4 | 46 | 50 |
| | | % within treatment | 8.0 | 92.0 | 100.0 |
| | LEVO + FENT | No. of pts | 5 | 45 | 50 |
| | | % within treatment | 10.0 | 90.0 | 100.0 |
| Total | | Count | 9 | 91 | 100 |
| | | % within treatment | 9.0 | 91.0 | 100.0 |

Table 5: Chi-square tests for side effects

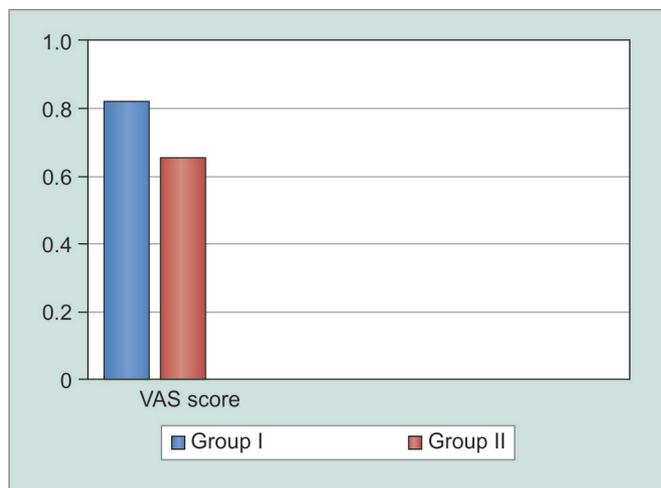
| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|------------------------------|-------|----|-----------------------|----------------------|----------------------|
| Pearson chi-square | 0.122 | 1 | 0.727 | | |
| Continuity correction | 0 | 1 | 1.000 | | |
| Likelihood ratio | 0.122 | 1 | 0.727 | | |
| Fisher's exact test | | | | 1.000 | 0.500 |
| Linear-by-Linear association | 0.121 | 1 | 0.728 | | |
| N of valid cases | 100 | | | | |

**Graph 2:** Heart rate variability**Graph 3:** Blood pressure variability

cardiovascular stability than bupivacaine alone. The lesser incidences of central nervous system and cardiovascular toxicity of levobupivacaine make it a safer drug for urological surgeries under subarachnoid block.

Cuvas et al²⁴ conducted a prospective randomized double-blinded study to compare the characteristics of spinal blocks produced by 0.5% levobupivacaine with and without fentanyl in transurethral resection and to test the hypothesis that, fentanyl added to levobupivacaine may be used as an alternative to pure levobupivacaine solution, in spinal anesthesia. Forty males, aged >60 years, ASA I–III patients scheduled for elective

transurethral resection were included. Following a spinal tap, intrathecal injection in group L (n = 20), 2.5 mL of 0.5% levobupivacaine and in group LF (n = 20), 2.2 mL of 0.5% levobupivacaine with fentanyl 15 µg (0.3 mL) was performed. The highest level of sensory block was T9 in group L, and T6 in group LF (p = 0.001). Duration of motor block was shorter in group LF than in group L (291.00 ± 81.08 minutes in group L; 213.75 ± 59.49 minutes in group LF) (p = 0.001). The study concluded that both regimes are effective, and the addition of fentanyl to levobupivacaine may offer the advantage of shorter duration of motor block and may be used as an alternative to



Graph 4: Visual analog scale score

pure levobupivacaine solution in spinal anesthesia, for transurethral resections.

In our study too we compared the characteristics and efficacy of 2.5 mL of levobupivacaine plain in group I vs 2.2 mL of levobupivacaine with 15 µg fentanyl in group II for urological procedures. The time to reach sensory level of T10 was significantly earlier in the fentanyl group (group II; $p < 0.0001$). However, the duration of sensory blockade was significantly longer ($p < 0.0001$) in group I with plain levobupivacaine. The fentanyl group achieved a higher sensory level of T6 similar to the study by Cuvas et al.²⁴

Duration of motor block was shorter and time to achieve ambulation was faster when fentanyl was used as an additive in group II. This finding was consistent with the study by Cuvas et al.²⁴

A review by Hamber and Viscomi¹⁵ conducted in 1999 concluded that the anesthesia-enhancing properties and side-effect profile of lipophilic opioids administered intrathecally suggested significant roles for these agents as adjuncts to spinal anesthesia for obstetric and out-patient procedures. Intrathecal fentanyl and sufentanil allow clinicians to use smaller doses of spinal local anesthetic, yet still provide excellent anesthesia for surgical procedures.

In our study patients in group II were administered 2.2 mL of levobupivacaine as compared with 2.5 mL in group I. The addition of fentanyl 15 µg as an additive ensured that similar sensory and motor blockade was achieved even with the lower dose of local anesthetic used. A higher sensory level was achieved and the shorter motor block ensured that patients could be made to mobilize earlier in daycare urological procedures.^{12,25}

Akan et al⁴ combined lower dose levobupivacaine with fentanyl and sufentanil which provided faster onset of sensorial block, lower frequency and shorter duration of motor block, and longer analgesia time in

TURP under spinal anesthesia. In our study, however, analgesia time was longer in the plain levobupivacaine group but onset of sensory action was hastened by the addition of fentanyl.

Postoperative pain scores and patient satisfaction were equivalent in the two groups. The incidence of side effects was also negligible. As known, spinal opioids carry the risk of respiratory depression especially in elderly patients. No respiratory depression incidence of hypoxia or pruritus was observed in either group. No shivering was observed in any of the patients, which is consistent with the study done by Chow and Cho.²⁶

So our study showed that intrathecal levobupivacaine in group I offered a longer duration of sensory and motor blockade as compared with the combination of levobupivacaine with fentanyl in group II. However, the addition of fentanyl in group II allowed lesser dose of local anesthetic and gave the benefit of earlier onset of sensory blockade. An earlier regression of motor blockade led to early ambulation of the patients. There were no differences seen in VAS scores, hemodynamic profile, and side effects.²⁷⁻²⁹

CONCLUSION

From our study we conclude that intrathecal levobupivacaine plain used for urological surgeries done under spinal anesthesia provides a longer duration of sensory and motor blockade as compared with combined use of intrathecal levobupivacaine with fentanyl. However, the use of fentanyl has a dose-sparing effect, allowing lesser dose of local anesthetic be used and also provides rapid onset of sensory block and early ambulation with no significant alterations in hemodynamic profile or side effects.

REFERENCES

1. Miller, RD. Miller's anaesthesia. 8th ed. Philadelphia (PA): Churchill Livingstone; 2015. pp. 2230-2231.
2. O'Donnell AM, Foo IT. Anaesthesia for transurethral resection of the prostate. *Contin Educ Anaesth Crit Care Pain* 2009 Jun;9(3):92-96.
3. Donat SM, North A, Dalbagni G, Herr HW. Efficacy of office fulguration for recurrent low grade papillary bladder tumors less than 0.5 cm. *J Urol* 2004 Feb;171(2 Pt 1):636-639.
4. Akan B, Yagan O, Bilal B, Erdem D, Gogus N. Comparison of levobupivacaine alone and in combination with fentanyl and sufentanil in patients undergoing transurethral resection of the prostate. *J Res Med Sci* 2013 May;18(5):378-382.
5. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anaesthesia: a systematic review. *J Anaesthesiol Clin Pharmacol* 2013 Oct-Dec;29(4):530-539.
6. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine. *Ther Clin Risk Manag* 2008 Apr;4(2): 381-392.
7. Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local

- anaesthetics, ropivacaine and levobupivacaine. *Acta Biomed* 2008 Aug;79(2):92-105.
8. Goyal A, Shankaranarayan P, Ganapathi P. A randomized clinical study comparing spinal anesthesia with isobaric levobupivacaine with fentanyl and hyperbaric bupivacaine with fentanyl in elective caesarean sections. *Anaesth Essays Res* 2015 Jan-Apr;9(1):57-62.
 9. Herrera R, De Andrés J, Estañ L, Olivás FJ, Martínez-Mir I, Steinfeldt T. Hemodynamic impact of isobaric levobupivacaine versus hyperbaric bupivacaine for subarachnoid anesthesia in patients aged 65 and older undergoing hip surgery. *BMC Anaesthesiol* 2014 Oct;14:97.
 10. Dizman S, Turker G, Gurbet A, Mogol EB, Turkcan S, Karakuzu Z. Comparison of two different doses of intrathecal levobupivacaine for transurethral endoscopic surgery. *The Eurasian J Med* 2011 Aug;43(2):103-108.
 11. Gunusen I, Karaman S, Sargin A, Firat V. A randomized comparison of different doses of intrathecal levobupivacaine combined with fentanyl for elective caesarean section: prospective, double-blinded study. *J Anesth* 2011 Apr;25(2):205-212.
 12. Attri JP, Kaur G, Kaur S, Kaur R, Mohan B, Kashyap K. Comparison of levobupivacaine and levobupivacaine with fentanyl in infraumbilical surgeries under spinal anaesthesia. *Anesth Essays Res* 2015 May-Aug;9(2):178-184.
 13. Kuusniemi KS, Pihlajamäki KK, Pitkänen MT, Helenius HY, Kirvelä OA. The use of bupivacaine and fentanyl for spinal anaesthesia for urologic surgery. *Anesth Analg* 2000 Dec;91(6):1452-1456.
 14. Lee YY, Muchhal K, Chan CK, Cheung ASP. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. *Eur J Anaesthesiol* 2005 Dec;22(12):899-903.
 15. Hamber EA, Viscomi CM. Intrathecal lipophilic opioids as adjuncts to surgical spinal anaesthesia. *Reg Anesth Pain Med* 1999 May-Jun;24(3):255-263.
 16. Chaudhary A, Bogra J, Singh PK, Saxena S, Chandra G, Verma R. Efficacy of spinal ropivacaine *versus* ropivacaine with fentanyl in transurethral resection operations. *Saudi J Anaesth* 2014 Jan;8(1):88-91.
 17. Cappelleri G, Aldegheri G, Danelli G, Marchetti C, Nuzzi M, Iannandrea G, Casati A. Spinal anaesthesia with hyperbaric levobupivacaine and ropivacaine for outpatient knee arthroscopy: a prospective, randomized, double-blind study. *Anesth Analg* 2005 Jul;101(1):77-82.
 18. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic T, Vanderck B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine and bupivacaine for Caesarean section. *Br J Anaesth* 2003 Nov;92(5):684-689.
 19. Turkmen A, Moralar DG, Ali A, Altan A. Comparison of the anaesthetic effects of intrathecal levobupivacaine + fentanyl and bupivacaine + fentanyl during caesarean section. *Middle East J Anesthesiol* 2012 Feb;21(4):577-582.
 20. Bremerich DH, Fetsch N, Zwissler BC, Meininger D, Gogarten W, Byhahn C. Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for Caesarean section. *Curr Med Res Opin* 2007 Dec;23(12):3047-3054.
 21. Chattopadhyay S, Halder B, Saha GC, Karmakar S, Pahari S. Comparison of two concentrations of isobaric intrathecal levobupivacaine for vaginal hysterectomy. *Indian J Pain* 2013;27(3):154-158.
 22. Lee YY, Muchhal K, Chan CK. Levobupivacaine *versus* racemic bupivacaine in spinal anaesthesia for urological surgery. *Anaesth Intensive Care* 2003 Dec;31(6):637-641.
 23. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anaesthesia: comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. *Acta Anaesthesiol Belg* 2008 Jun;59(2):65-71.
 24. Cuvas O, Basar H, Yeygel A, Turkyilmaz E, Sunay MM. Spinal anaesthesia for transurethral resection operations: levobupivacaine with or without fentanyl. *Middle East J Anesthesiol* 2010 Feb;20(4):547-552.
 25. Karsli ND, Subaşı D, Terzioğlu B, Turan G, Ekinci O. ED50 and ED95 of intrathecal isobaric levobupivacaine coadministered with fentanyl for transurethral resections: randomized, double-blind trial. *Drug Res* 2015;65(1):24-29.
 26. Chow TC, Cho PH. The influence of small dose intrathecal fentanyl on shivering during transurethral resection of prostate under spinal anaesthesia. *Acta Anaesthesiol Sin* 1994 Sep;32(3):165-170.
 27. D'Ambrosio A, Spadaro S, Mirabella L, Natale C, Cotoia A, De Capraris A, Menga R, Salatto P, Malvasi A, Brizzi A, et al. The anaesthetic and recovery profile of two concentrations (0.25% and 0.50%), of intrathecal isobaric Levobupivacaine for combined spinal-epidural (CSE) anaesthesia in patients undergoing modified Stark method caesarean delivery: a double blinded randomized trial. *Eur Rev Med Pharmacol Sci* 2013 Dec;17(23):3229-3236.
 28. Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small-dose dilute bupivacaine: better anaesthesia without prolonging recovery. *Anesth Analg* 1997 Sep;85(3):560-565.
 29. Hindle A. Intrathecal opioids in the management of acute postoperative pain. *Contin Educ Anaesth Crit Care Pain* 2008 Jun;8(3):81-85.