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Original Research Article

A Prospective Randomized Study to Compare Intrathecal Isobaric Levobupivacaine with or Without Fentanyl in Various Infraumbilical Surgeries

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Abstract:

Background and Aims: The subarachnoid block is the recommended anaesthetic approach for procedures below the belly button because it offers superior pain relief after the operation, efficient muscle relaxation, and is cost-effective. Levobupivacaine is more advantageous than bupivacaine because it has a reduced risk of causing cardiotoxicity, prolonged duration of sensory blockade, and a shorter duration of motor blockade. Opioids used in conjunction with intrathecal local anaesthetics improve the effectiveness of pain relief and anaesthesia both during surgery and postoperatively. The objective of the current study was to assess the effects of levobupivacaine with and without fentanyl in spinal anaesthesia.

Methods: For this study, 80 patients who were classified as belonging to the American Society of Anesthesiologists Physical Status I and II were randomly assigned to different groups. The study was conducted in a way that neither the patients nor the researchers knew which group they were in. The purpose of the study was to investigate the effects of infraumbilical surgery. Subjects were assigned at random to one of two groups. The Levobupivacaine group (n = 40) was administered 2.5 ml of isobaric levobupivacaine 0.5% along with 0.5 ml of normal saline. The Levobupivacaine + fentanyl group (n = 40) was given 2.5 ml of isobaric levobupivacaine 0.5% along with 25 µg (0.5 ml) of fentanyl. The study recorded the time at which sensory and motor block began, as well as how long it lasted. It also documented the Visual Analogue Scale score, the duration of analgesia, any changes in blood pressure and heart rate, and the adverse outcomes experienced by participants in both groups.

Results: The initiation of both sensory and motor block was notably expedited in Group LF ($P < 0.05$). The average duration of sensory blockade was substantially greater in Group LF ($P < 0.05$). The average duration of motor block was determined to be similar between the two groups, both of which had stable hemodynamics and no sedation throughout the perioperative period ($P > 0.05$). The analgesic effect lasted substantially longer in Group LF (336.5 ± 31.3 min) compared to Group L (223.65 ± 32.17 min) with a p-value of less than 0.001.

Conclusion: Using intrathecal fentanyl (25 µg) alongside isobaric 0.5% levobupivacaine can significantly enhance the block characteristics and minimize adverse effects in patients undergoing procedures below the umbilicus.

Keywords: Fentanyl; Infraumbilical surgeries; Levobupivacaine; Spinal anesthesia.

Introduction

Spinal anaesthesia is the recommended anaesthetic approach for infraumbilical surgeries due to its high credibility, cost-effectiveness, and ability to provide adequate muscle relaxation, pain relief during and after surgery. Currently, there is a growing trend towards performing an increasing number of operations as outpatient procedures. [1] For infraumbilical procedures, spinal anaesthesia commonly involves the administration of 0.5% hyperbaric bupivacaine. Nevertheless, bupivacaine has the potential to induce hemodynamic instability, a prolonged decline in motor functioning, and cardiac toxicity. Levobupivacaine is an amino-amide local anaesthetic medication that is the S-enantiomer of bupivacaine. It induces a differential neuraxial blockade, meaning it affects the nerves in a specific way. Levobupivacaine has a quicker onset for both sensory and motor block compared to other drugs in its class. It also has a longer duration of sensory block and reduced risk

of cardiotoxicity. [2] Despite advancements in understanding the physiology of acute pain, the discovery of novel opioid and non-opioid medications for pain relief, the use of various drug delivery mechanisms and routes, and the increased adoption of minimally invasive surgical procedures, postoperative pain management remains a significant problem. [3] Different intrathecal adjuvants have been employed to enhance the efficacy of analgesia and anaesthesia while simultaneously decreasing the adverse effects linked to elevated dosages of local anaesthetic used alone. [4]

The concurrent use of local anaesthetics and opioids by intrathecal administration has been found to have a synergistic effect, resulting in an extended duration of sensory block and analgesia without any further prolongation of motor block. [5] Therefore, other additives, such as fentanyl and sufentanil, have been used in combination with local anaesthetics to prolong the sensory block without increasing the motor block.

In this study, we aimed to investigate whether adding intrathecal fentanyl to isobaric levobupivacaine would increase the duration of pain relief and sensory block without affecting motor block. We compared the effects of administering 25 µg fentanyl with 0.5% isobaric levobupivacaine (12.5 mg) to a similar dose of local anaesthetic without fentanyl in patients undergoing infraumbilical surgeries. We analysed the characteristics of the subarachnoid block, the amount of rescue analgesics needed, and any changes in hemodynamics.

Aim and Objectives: The current study aimed to assess the duration of analgesia as the main objective, while also examining the onset and duration of sensory and motor block, perioperative sedation score, perioperative and postoperative hemodynamic changes, and any adverse effects or complications as secondary objectives.

Material and Methods

This prospective, randomized, double-blinded trial comprised 80 patients, aged 18-65 years of the American Society of Anesthesiologists Physical Status I or II, was scheduled for infraumbilical procedures. The study was conducted after getting approval from the Institutional Ethics Committee. Patients who had a known allergy to the study medicines, namely local anaesthetics or opioids, and patients who had any contraindication for the subarachnoid block were not included in this study.

The sealed envelope method was employed to randomise the patients, whereby each preparation was enclosed in a separate envelope and subsequently shuffled. The investigational medication was diluted to a final volume of 3.0 ml. Subjects were administered either a dosage of 12.5 mg of levobupivacaine or a combination of levobupivacaine 12.5 mg and fentanyl 25 µg. In order to guarantee the prevention of bias, the study solutions were created by a resident anesthesiologist who had no further involvement in the study.

Every patient received a preanesthetic examination the day before to surgery and followed the institute procedure by abstaining from oral intake. Upon the patient's arrival in the operating room, the first vital signs were recorded, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO2), and respiratory rate (RR). Subsequently, the patient received a preload of ringer's lactate at a dose of 10 ml/kg. Spinal anaesthesia was provided with meticulous sterile precautions while the patient was in a seated posture. A 25G Quincke needle was used in the L2–L3 or L3–L4 interspace. Patients in Group A were administered a 2.5 ml (12.5 mg) injection of 0.5% isobaric levobupivacaine, together with a 0.5 ml injection of normal saline. On the other hand, patients in Group B got a 2.5 ml (12.5 mg) injection of 0.5% isobaric levobupivacaine, along with a 0.5 ml injection of fentanyl (25 µg).

Essential physiological measurements, such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO2), and respiratory rate (RR), were continuously monitored at 2-minute intervals for the first 10 minutes, then at 5-minute intervals until the 30-minute mark, and finally at 15-minute intervals until the conclusion of the procedure. Bradycardia and hypotension were addressed by administering an intravenous (IV) bolus of atropine 0.6 mg and ephedrine 6 mg with IV fluids, respectively, when the heart rate (HR) dropped below 60 beats per minute and the mean arterial pressure (MAP) fell below 60 mmHg. The symptoms of nausea and vomiting were alleviated by administering a 4 mg intravenous injection of ondansetron.

The assessment of motor block was conducted using the Modified Bromage score (also known as the Modified Bromage scale). The grading scale for paralysis is as follows: 0 indicates no paralysis, with the ability to flex hips, knees, and ankles; 1 indicates the ability to move knees, but unable to elevate extended legs; 2 indicates the ability to flex ankles, but unable to flex knees; and 3 indicates full inability to move any portion of the limb. The moment at which Modified Bromage Score reaches 2 is recorded as the commencement of motor block. The duration of motor block was recorded as the time taken to revert back to Modified Bromage 0. The sensory block was evaluated in the dermatomal regions from T8 to S2 using a blunt 23G

hypodermic needle. The assessment employed a scale method where 0 indicated normal feeling, 1 indicated loss of prick sensation (analgesia), and 2 indicated loss of touch sensation (anaesthesia). The onset of sensory block refers to the period between the injection of a substance into the spinal canal and the time it takes for the substance to reach the T8 dermatomal level. The duration of sensory block is the time it takes for the sensory block to recede from the maximum level obtained, down to the S1 dermatome located in the heel. The duration of analgesia was determined as the interval between the intrathecal injection and the point at which the patient requested more pain relief. The assessment of postoperative pain was conducted using a 10-point Visual Analogue Scale (VAS), where a score of "0" represented the absence of pain and a score of "10" indicated the presence of the most intense pain. Patients were given an intramuscular injection of diclofenac sodium 75 mg as rescue analgesia when their VAS (Visual Analogue Scale) score was more than or equal to 4. The time from administration of the injection till the pain relief wore off was deemed the duration of analgesia.

The assessment of sedation during the perioperative period was conducted using the Ramsay sedation score (RSS). The grading of RSS was as follows: 1 – The patient is experiencing anxiety and agitation, or both; 2 – The patient is cooperative, aware of their surroundings, and calm; 3 – The patient only responds to commands; 4 – The patient shows a quick response to a light tap on the glabella or a loud auditory stimulus; 5 – The patient shows a slow response to a light tap on the glabella or a loud auditory stimulus; and 6 – The patient shows no response.

After the surgery, important measurements such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO2), and respiratory rate (RR) were documented. Adverse reactions (including nausea, vomiting, low blood pressure, slow heart rate, and itching) were documented at 2-hour intervals for a total of 12 hours.

Statistical analysis: According to a recent research conducted by Bidikar et al., [6], the sample size for each group was determined to be 36 patients. This calculation was based on an alpha error of 0.05 and a power of 80% to detect a predicted difference in the duration of motor block, which was estimated to be 8.6 ± 13 minutes. After accounting for a 10% dropout rate, the sample size in each group was augmented to 40. The sample size for each group was determined to be 1 based on the primary outcome measure, which was the duration of analgesia. According to the central limit theorem, it is necessary to have a minimum of 30 subjects in each group in order to observe a significant difference in results. Therefore, we have determined the sample size by considering all relevant parameters. Specifically, we have chosen the duration of motor block as the basis for calculating the final sample size. This decision was made to enhance the power and external validity of the study, as explained in the statistical analysis.

The data analysis was conducted using the statistical programme Epi Info version 7.2.1.0, developed by the CDC (Centres for Disease Control and Prevention) in the United States. The data were reported as the mean value plus or minus the standard deviation, as well as the median value, range, or number of patients. The categorical or nominal variables were represented as numbers and percentages and analyzed using the Chi-square test or Fischer's exact test, depending on the circumstances. The parameters, which are measured on a continuous scale, were analyzed using the Student's t-test comparing two groups. A p-value less than 0.05 were deemed statistically significant.

Results

The demographic characteristics, initial hemodynamic parameters, and the duration of operation were similar in both groups. [Table 1]

Table 1: Demographic variables

Variables		Group L (Mean±SD) (N=40)	Group LF (Mean±SD) (N=40)	P value
Mean age (in years)		47.84 ± 10.43	46.39 ± 14.58	0.211(NS)
Gender (M:F) (%)		30:10 (75:25)	31:9 (77.5:22.5)	0.793(NS)
Weight (in kg)		66.39 ± 8.2	66.64 ± 8.05	0.891(NS)
ASA grade (%)	Grade I	37 (92.5)	32 (80)	0.195(NS)
	Grade II	03 (7.5)	08 (20)	
Mean duration of surgery (min)		47.44 ± 7.99	49.09 ± 7.88	0.356(NS)
Baseline HR (bpm)		81. 86 ± 11.29	84. 44 ± 11.24	0.308(NS)
Baseline mean BP (mmHg)		94.02 ± 9.74	96. 21 ± 9.37	0.306(NS)
Baseline RR (per min)		13.81 ± 1.33	14.14 ± 1.15	0.301(NS)
Baseline SpO2 (%)		99.41 ± 0.72	99.21 ± 0.81	0.303(NS)

NS- Not Significant (p>0.05)

The average time it took for the sensory block to begin (specifically in the T8 dermatome) was longer in the Levobupivacaine group (5.61 ± 1.54 min) compared to the Levobupivacaine + fentanyl group (4.71 ± 1.71 min), and this difference was found to be statistically significant (P = 0.016). The maximum level of sensory blockage attained in Group L and Group LF was T8 and T6, respectively, as determined by the median.

The average time it took to attain Bromage 2 motor block was longer in Group L (9.26 ± 1.65 min) compared to Group LF (7.46 ± 1.75 min), and this difference was very significant (P < 0.001). In Group LF, the sensory block lasted substantially longer (336.51 ± 31.31 min) compared to Group L (223.66 ± 32.18 min) (P < 0.001).

However, the length of motor block was similar in the two groups (144.25 ± 13.83 min in Group L and 139.89 ± 31.84 min in Group LF) (P = 0.429). [Table 2]

Table 2: Block characteristics in both groups

Parameters (min)	Group L (Mean±SD) (N=40)	Group LF (Mean±SD) (N=40)	P value
Onset of sensory block to T8 dermatome	5.61 ± 1.54	4.71 ± 1.71	0.016 (S)
Total duration of sensory block	198.71 ± 17.82	268.89 ± 21.06	<0.001 (S)
Onset of motor block to achieve ≥2	9.26 ± 1.65	7.46 ± 1.75	<0.001 (S)
Total duration of motor block	144.25 ± 13.83	139.89 ± 31.84	0.429 (NS)
Duration of analgesia	223.66 ± 32.18	336.51 ± 31.31	<0.001 (S)
Total number of doses of rescue analgesia	2.01 ± 0.962	1.09 ± 0.28	<0.0001 (S)

The evaluation of pain after surgery was conducted using the Visual Analogue Scale (VAS) score. The VAS score showed a statistically significant change from 0 hours to 6 hours (P < 0.05) and from 10 hours to 12 hours (P < 0.05). [Table 3] In Group L, patients requested the initial dosage of rescue analgesia about 4 hours, but in Group LF, the need for rescue analgesia occurred roughly 6 hours later. The analgesic effect lasted substantially longer in Group LF (336.51 ± 31.31 min) compared to Group L (223.66 ± 32.18 min) (P < 0.001). The total number of rescue analgesia doses needed within a 24-hour period was considerably lower in Group LF compared to Group L (P < 0.0001). [Table 2]

Table 3: VAS scores between groups

Time point (hour)	Median VAS Score (IQR)		P value
	Group L (N=40)	Group LF (N=40)	
0	0 (0-0)	0 (0-0)	0.022 (S)
2	2 (1-2)	0 (0-2)	<0.001 (S)
4	5 (3-6)	2 (2-3)	<0.001 (S)
6	4 (0-5)	5 (3-5)	0.006 (S)
8	0 (0-3)	0 (0-0)	0.404 (NS)
10	0 (0-3)	0 (0-0)	<0.001 (S)
12	0 (0-4)	0 (0-0)	0.028 (S)

In terms of intergroup comparison, the hemodynamic measures (HR, SBP, DBP, MAP, RR, and SpO2) showed no significant difference between the two groups (P > 0.05). Throughout the research, the heart rate (HR) remained consistent and similar to the initial levels in both groups, among the various hemodynamic measures. During the operation, two patients (5%) in Group LF and one patient (2.5%) in Group L had bradycardia. This condition was successfully treated by administering intravenous atropine.

The statistical analysis showed that there was no significant difference between the two groups (P = 1.00). One patient (2.5%) in Group L experienced hypotension, but no patients in Group LF had hypotension. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were consistent with their initial levels throughout the duration of the trial. There was no occurrence of respiratory depression in any of the patients in either of the groups. There were no reported adverse effects, such as nausea, vomiting, pruritus, sedation, headache, or backache, in any of the patients during the postoperative period in both groups.

Discussion

The current study illustrates that the addition of 25 µg fentanyl to 12.5 mg intrathecal 0.5% levobupivacaine results in a prolonged period of pain relief, beyond that achieved with 12.5 mg of 0.5% levobupivacaine alone for procedures below the umbilicus. In addition to a longer duration of analgesia, there was also a quicker beginning of

both the loss of sensation and movement. Another benefit was a shorter period of loss of movement and a decrease in the amount of further pain medication needed.

Postoperative pain is a frequently reported and painful issue among patients. It exacerbates the stress reaction caused by surgery, impedes early walking, and may lengthen the duration of hospitalization. An optimal anaesthetic strategy should prioritize pain control in the postoperative phase, hence reducing complications and patient distress. Once the neurobiology of pain and pharmacology of existing medications were comprehended, a significant advancement took place in the treatment of postoperative pain.

Diverse organizations have utilized and developed various intrathecal adjuvants with diverse modes of action over time. Opioids such as morphine, fentanyl, sufentanil, hydromorphone, buprenorphine, and tramadol have been utilized as supplementary substances to local anaesthetics, yielding different levels of effectiveness. [7] Levobupivacaine, an amino-amide medication used as a local anaesthetic, has been found to produce varying effects on the nervous system. Specifically, it has a quicker start and longer-lasting numbing effect on sensory nerves, while causing a shorter period of muscle paralysis and reduced risk of heart-related side effects. [8] Fentanyl exerts a nociceptive effect by targeting both μ1 and μ2 receptors located in the dorsal horn of the spinal cord, therefore enhancing the blocking of sensory signals coming from the peripheral nerves. When used as an adjuvant, Fentanyl enhances the effects of local anaesthetics, resulting in improved pain relief and anaesthesia during surgery, as well as better pain relief after surgery. This occurs without any notable adverse effects.

In this study, it was shown that Group LF had a considerably quicker start of sensory block and achieved maximal sensory and motor block more quickly compared to Group L. The levobupivacaine and fentanyl groups exhibited a considerable prolongation in the duration of sensory block and postoperative analgesia, without extending the motor block, in comparison to the plain levobupivacaine group. In Group LF, the highest degree of sensory response reached was T6, whereas in Group L it was T8. However, both groups had a maximum motor block of Bromage 2. In the postoperative period, Group LF took longer to reach a VAS score greater than 3 compared to Group L. Additionally, Group LF ingested fewer doses of rescue analgesics during a 24-hour period.

In a study conducted by Bozdogan Ozyilkan et al. [9], the effects of several combinations of levobupivacaine were evaluated. The combinations included levobupivacaine 0.5% 2.2 ± 0.2 ml, levobupivacaine 0.5% 2.2 ± 0.2 ml with 2.5 mg sufentanyl, and levobupivacaine 0.5% 2.2 ± 0.2 ml with fentanyl 10 μg. The researchers determined that the groups receiving sufentanyl and fentanyl experienced a faster start of sensory blockage compared to the control group. Our investigation revealed comparable outcomes regarding the average time it took for the sensory block to begin in the fentanyl group. The more rapid onset of fentanyl may be due to the combined impact of opioids with local anaesthetic drugs. Group LF had a faster onset of motor block. The early occurrence of motor block in Group LF, as opposed to Group L, in this study may be attributed to the synergistic impact of opioids combined with local anaesthetics. The findings of this study are similar to those of Attri et al. [10], who conducted a comparison between levobupivacaine 0.5% 10 mg and levobupivacaine 0.5% 10 mg plus fentanyl 25 μg for infraumbilical operations. They discovered that the fentanyl group experienced a substantially faster onset of motor block.

Agrawal and colleagues [11] conducted a comparison between levobupivacaine 15 mg + normal saline 0.5 ml and levobupivacaine 15 mg + fentanyl 25 μg. The study revealed that the fentanyl group experienced a longer period of sensory block. Similarly, Attri and colleagues [10] in their study demonstrated that the fentanyl group had a considerably longer duration of sensory blackout compared to the control group. In this investigation, the length of time that the sensory block lasted was also greatly extended. Maniyar and colleagues [12] conducted a comparison between levobupivacaine 7.5 mg by itself and levobupivacaine 5 mg combined with fentanyl 25 μg. They discovered that the length of time for motor block was identical in both groups. Our finding aligns with the results of our investigation and is also consistent with several other studies in the existing literature. [13, 14, 15, 16] The extended motor block may cause discomfort during the postoperative period, hence it does not appear to be advantageous in terms of patient satisfaction.

Bidikar and colleagues [6] conducted a comparison between levobupivacaine 10 mg and a combination of levobupivacaine 7.5 mg and fentanyl 12.5 μg. The study revealed that the fentanyl group had a considerably longer duration of analgesia compared to the group that received levobupivacaine alone. Rajsekaran and colleagues [17] did a research on women giving birth, comparing the effects of levobupivacaine 10 mg + normal saline 0.3 ml with levobupivacaine 10 mg + fentanyl 15 μg. The study found that the fentanyl group experienced considerably longer pain relief compared to the levobupivacaine group.

The results of this investigation are comparable to those of another study. The extended duration of

pain relief seen in this trial may be attributed to the administration of a greater dosage of both local anaesthetic and fentanyl. Attri et al. [10] similarly discovered comparable outcomes for the length of pain relief. In terms of hemodynamic parameters, this study's findings align with the research conducted by Attri et al. [10] and Gadkari et al. [18], which demonstrated no significant changes in hemodynamics. The study found that the VAS score was considerably lower in Group LF compared to Group L. The Visual Analogue Scale (VAS) ratings exhibited considerable variations during the whole postoperative duration. In Group LF, the total amount of rescue analgesic needed after the operation was much lower compared to Group L. In Group L, the majority of patients (37) only required one dosage of rescue analgesic. During this trial, one patient (2.5%) in Group L experienced hypotension, while none of the patients in Group LF had hypotension. Bradycardia was detected in 1 patient (2.5%) in Group L and in 2 patients (5%) in Group LF. There was no statistically significant disparity in the level of sedation during surgery and the occurrence of postoperative problems, such as low blood pressure, slow heart rate, itching, nausea, and vomiting, between the two groups. This study supports the findings of Bozdogan Ozyilkan et al. [9] and Koppal et al. [19]

This study primarily examined the impact of fentanyl as an additional substance to levobupivacaine when injected intrathecally. The objective was to assess how this combination affects the effectiveness of subarachnoid block. However, it is important to acknowledge that there are a few limitations to this study. The patient did not receive any premedication, hence their cooperation was required.

Only one dose of intrathecal fentanyl (25 μg) was administered as an adjuvant, and the dosage of the drug was not adjusted based on the patient's height or weight. Early ambulation would be the clinical significance of the shorter duration of motor block caused by the combination of levobupivacaine and fentanyl. Levobupivacaine has a low incidence of cardiotoxicity based on its pharmacological characteristics. Additional research is required to assess and enhance the effectiveness and safety of various dosages of fentanyl when used as a supportive agent alongside isobaric levobupivacaine.

Conclusion

Our findings indicate that the addition of intrathecal fentanyl (25 μg) to isobaric 0.5% levobupivacaine can effectively enhance the duration of analgesia, reduce the need for additional pain medication, and expedite the onset of both sensory and motor block. Furthermore, this combination maintains stable hemodynamics without prolonging the motor block and exhibits minimal adverse effects in patients undergoing infraumbilical surgeries.

References

1. Kataria AP, Jarewal V, Kumar R, Kashyap A. Comparison of levobupivacaine and levobupivacaine with dexmedetomidine in infraumbilical surgeries under spinal anesthesia Anesth Essays Res. 2018;12:251–5.
2. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review J Anaesthesiol Clin Pharmacol. 2013; 29:530–9.
3. Garimella V, Cellini C. Postoperative pain control Clin Colon Rectal Surg. 2013; 26:191–6.
4. Grewal A. Dexmedetomidine: New avenues J Anaesthesiol Clin Pharmacol. 2011; 27:297–302.
5. Mehta N. Adjuvant drugs to local anesthetics Topics in Local Anesthetics 2020. London IntechOpen Available from: https://www.intechopen.com/chapters/71663doi:10.5772/intechopen.91980.
6. Bidikar M, Mudakanagoudar MS, Santhosh MC. Comparison of intrathecal levobupivacaine and levobupivacaine plus fentanyl for cesarean section Anesth Essays Res. 2017; 11:495–8.
7. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends World J Clin Cases. 2017; 5:307–23.
8. Sivakumar S, Manickam MD, Krishna B. 0.5% Isobaric Levobupivacaine, 0.5% Isobaric Levobupivacaine with Fentanyl and 0.5% Hyperbaric Bupivacaine. Comparative study in infraumbilical surgeries IOSR J Dent and Med Sci. 2016; 15:79–85.
9. Bozdogan Ozyilkan N, Kocum A, Sener M, Caliskan E, Tarim E, Ergenoglu P, et al Comparison of intrathecal levobupivacaine combined with sufentanil, fentanyl, or placebo for elective caesarean section: A prospective, randomized, double-blind, controlled study Curr Ther Res Clin Exp. 2013; 75:64–70.
10. 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;9:178–84.
11. Agrawal AP, Khan M, Agrawal M, Singh R, Krishan G, Mitra S. A comparison of the intrathecal isobaric 0.5% levobupivacaine with fentanyl and isobaric 0.5% ropivacaine with fentanyl for lower abdominal and lower Limb surgeries: A prospective randomised double

blind controlled study Ann Int Med Dent Res. 2018; 4:1–5.
12. Maniyar F, Trishala J, Praveen KO. Spinal anesthesia for transurethral resection of prostate: Levobupivacaine with or without fentanyl Int J Anesth Res. 2016; 4:358–62.
13. Cuvas O, Basar H, Yeygel A, Turkyilmaz E, Sunay MM. Spinal anesthesia for transurethral resection operations: Levobupivacaine with or without fentanyl Middle East J Anaesthesiol. 2010; 20:547–52.
14. 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 cesarean sections Anesth Essays Res. 2015;9:57–62.
15. 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;18:378.
16. Lee JH, Chung KH, Lee JY, Chun DH, Yang HJ, Ko TK, et al Comparison of fentanyl and sufentanil added to 0.5% hyperbaric bupivacaine for spinal anesthesia in patients undergoing cesarean section. Korean J Anesthesiol. 2011; 60:103–8.
17. Rajasekaran S, Murugaiah S, Anandan A, Ramalingam A. Comparison of intrathecal levobupivacaine and levobupivacaine with fentanyl in caesarean section - a randomised trial Indian J Clin Anaesth. 2017; 4:298–303.
18. Gadkari C, Singh P, Jirapure R, Bhure A. Comparison of efficacy of interathecal 0.5% isobaric levobupivacaine with fentanyl versus 0.5% isobaric bupivacaine with fentanyl for inguinal hernia repair J Contemp Med Res. 2019;6:A12–7.
19. Koppal R, Naik D, Mathpati V, Hulkund S. A comparative study of intrathecal 0.5% isobaric levobupivacaine with fentanyl and 0.5% isobaric levobupivacaine with nalbuphine in infraumbilical surgeries: A randomized double blind clinical trial Indian J Clin Anaesthesia. 2019; 6:203–8.