A comparative evaluation of equipotent doses of isobaric Levobupivacaine and Ropivacaine with neuraxial adjuvant Fentanyl for lower abdominal and lower extremity surgery

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Abstract

Introduction: Hyperbaric preparation of local anaesthetics have been used in subarachnoid block till now. Levobupivacaine and Ropivacaine, newly introduced S-enantiomer related to bupivacaine, have low cardio-neurotoxicity profile. In this study isobaric form of Levobupivacaine and Ropivacaine with Fentanyl were evaluated in terms of clinical efficacy as well as block characteristics.

Materials and Methods: In this prospective, single blind study, sixty patients of ASA grade I or II, 20-65yrs of age, of either sex, posted for lower abdominal or lower extremity surgery, were randomly administered either 3 ml Levobupivacaine (0.5%) or Ropivacaine (0.75%) with Fentanyl (25µg). Intra and postoperative block characteristic, hemodynamic parameters as well as side effects were recorded.

Results: Time to reach T10 sensory level and bromage 1 was earlier in group LF compared to group RF (p value =0.001). Peak sensory level was T6-T8 in group LF and T8-T10 in group RF. Significantly longer duration of sensory and motor block was produced in group LF (271.5 ± 5.06 and 252.16 ± 4.69 min) compared to group RF (228 ± 4.16 and 195.33 ± 3.54 min). The time to first rescue analgesia was also significantly prolonged in group LF (292.83 ± 5.28 min) compared to group RF (258 ± 4.32 min) (p value =0.001).

Conclusion: Equipotent doses of isobaric Levobupivacaine and Ropivacaine with Fentanyl (25µg) offered satisfactory anaesthesia with minimal haemodynamic variability. Levobupivacaine produced rapid onset and prolonged anaesthesia while Ropivacaine provided rapid recovery of sensory and motor block and early mobility, suitable for day care surgery.

Keywords: Isobaric, Levobupivacaine, Ropivacaine, Bupivacaine, Fentanyl.

Introduction

Subarachnoid block also known as spinal anaesthesia is a type of regional anaesthesia, used for many elective as well as emergency surgeries like lower limb surgery, infraumbilical, urological, obstetrics and gynecological surgeries.[1]

Racemic Bupivacaine is widely used amide local anaesthetic. It provides good intraoperative as well as prolonged postoperative anaesthesia, but it has cardiotoxic profile in form of arrhythmia, prolongation of QT interval and negative ionotropic effect especially after accidental intravenous injection.[2] These adverse effects are enantioselective i.e more with R(+) enantiomer.[3] S(-) enantiomer linked Ropivacaine and Levobupivacaine are two newer local anaesthetics having lower neurocardiotoxicity profile.

Ropivacaine is pure S(-) enantiomer of propyl analogue of Bupivacaine i.e. propivacaine. It blocks sensory nerves to a greater degree than motor nerves. It is less lipid soluble, long acting local anaesthetic with structural resemblance to that of Bupivacaine[4] but it is 40-50% less potent than Bupivacaine i.e. Ropivacaine in an equipotency ratio of 1.5:1 produces similar results with good preservation of motor function.[5] Increased cardiovascular safety, sensorimotor differential block and shorter elimination half-life of Ropivacaine make this local anasthetic more useful for short duration surgeries with painless and ambulatory patient in the postoperative period especially in lower abdominal and lower limb surgeries.[6]

Levobupivacaine is a S(-) enantiomer of Bupivacaine, long acting, clinically equivalent in anaesthetic potency to Bupivacaine, but with a reduced toxicity profile because of its faster protein binding rate.[3,7-9] It is given in subarachnoid block with good intraoperative anaesthesia as well as postoperative analgesia.

Structure of Ropivacaine differs from Levobupivacaine in the substitution of a propyl for the butyl group on the piperidine ring. Relative potencies of these local anaesthetic are Racemic Bupivacaine=Levobupivacaine>Ropivacaine. Ropivacaine in 0.75% and Levobupivacaine in 0.5% concentration are equipotent.

Fentanyl is frequently used intrathecal opioid adjuvants, acts on opioid receptors located at substantia gelatinosa of dorsal horn of spinal cord. This selective spinal analgesia without sympathetic block and hypotension make the patient ambulatory very early. When used with local anaesthetic in subarachnoid block, it reduces the dose and produce more cephalad level of block.

With these above information, this comparative study was designed to evaluate isobaric preparation of Ropivacaine (0.75%) and Levobupivacaine (0.5%) i.e. in equipotent doses with a opioid additive Fentanyl in subarachnoid block in patients posted for elective lower abdominal and lower extremity surgeries.

Materials and Methods

Study Design: In this prospective, randomized, single blinded, comparative study, institutional ethical approval was obtained, clinical trial registration (CTRI/2018/05/014012) done and after informed risk and

consent, this study was conducted in sixty patients of ASA Gr. I or II, of either sex, 20-65yrs of age, weighed between 30-80 kg, posted for elective lower extremity or lower abdominal surgeries under subarachnoid block. Patients with negative consent, ASA grade III, IV or V, requiring emergency operation, procedure taking more than two hrs, coagulation disorders, any preexisting neurological deficit, hypersensitivity to any local anaesthestic, infection near the block site, pregnant patients, and any untreated and uncontrolled systemic disease, were excluded from the study. Patients were divided into two groups (LF and RF) of 30 each and randomized using computer generated randomization. Group LF patients received 15 mg (3ml) of isobaric Levobupivacaine (0.5%) with 25µg of Fentanyl, and Group RF patients received 22.5 mg (3ml) of isobaric Ropivacaine (0.75%) with 25µg of Fentanyl intrathecally.

The spinal anaesthesia was given by the same anaesthesiologist in both the group. Intra and postoperative data was recorded by the residents who were not participated in the study.

After a detailed preanaesthetic evaluation, all the patients were given oral ranitidine 150 mg on the night before surgery. In the operation theatre after ensuring eight hour fasting, an 18G IV line was taken and patients were preloaded with Ringer's lactate solution (10 ml/kg) and given supplemental oxygen (4 L/min) with face-mask. Standard monitoring i.e. ECG, non-invasive blood pressure (NIBP) and pulse oximeter (SpO2) applied. With all aseptic precaution, lumbar puncture was performed in L2-L3/L3-L4 interspace in sitting position using a 25G Quincke spinal needle. After checking for clear and free flow of CSF, drug combination from the preloaded syringe was administered intrathecally. The injection time (T0) was noted. Patient was placed in supine position immediately. All the vital parameters like HR, SBP, DBP, SPO2 were noted every 5 min till 30 min and every 15 min till 120 min. Pinprick method was used to assess sensory block every 60 seconds from T4 downwards and surgery is allowed when the sensory block reached T10. Time of onset of sensory block (time to reach T10), peak sensory level and time to reach peak sensory level were noted. Motor block characteristic was recorded using a modified Bromage scale of 0-3 for lower limb (0 = full flexion of knees 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). GA was given in patients with partial or inadequate block and they were excluded from the study. Systolic BP less than 20% of baseline value i.e. hypotension was treated with IV fluids and 6mg of mephentermine if needed. Bradycardia (HR <50 beats/min) was closely observed and managed with IV atropine (0.6 mg). In Postoperative period patients were assessed for the total duration of sensory block (time of spinal anesthesia (T0) to the resolution of sensory blockade to S1), total duration of motor block (time interval between the onset of motor block (grade 1) up to the recovery of complete motor function (grade 0) and duration of analgesia (time interval between the onset of sensory block up to time of first rescue analgesia). The adverse effects such as nausea, vomiting, bradycardia, hypotension, pruritus, and shivering were noted.

Sample Size: The sample size was calculated using the Open Epi Software. The formula used was as follows:

$$N = \frac{\left(\sigma 1^2 + \sigma 2^2\right)\left(z1-\alpha/2 + z1-\beta\right)^2}{\left(m1 - m2\right)^2}$$

The notation for the formula are:

N = Minimum no. of cases to be included in each group

$\sigma 1$ = Standard deviation of the outcome variable in group 1

$\sigma 2$ = Standard deviation of the outcome variable in group 2

m1 = Mean of the outcome variable in group 1

m2 = Mean of the outcome variable in group 2

$z1-\alpha/2$ =1.96 = Normal variant value for 5% level of significance

$z1-\beta$ = 1.282 = Normal variant corresponding to 90% power of the study

This was applied to the study by Koltka k et al,[10] Ropivacaine and bupivacaine combined with fentanyl, to detect the difference between means 139 and 182 with a S.D. of 39 and 46, and for the power of study to be 90% and confidence interval 95%, the minimum sample size was calculated to be 21 patients in each groups. We have taken 30 patients in each group to compensate for dropouts.

Statistical Method: Data was analyzed using MS Excel sheet and SPSS software version 19.0. Qualitative data such as age, sex, ASA grade and side effects, were represented as numbers and percentages and calculated by Chi Square Test and Proportion test. Quantitative data such as body weight, hemodynamic parameters and onset and duration of blocks, were presented by mean ± SD (Standard Deviation). Differences between the means were analyzed by unpaired t-test. P value ≤ 0.05 was considered to be statistically significant. MS word and MS Excel were used to generate graphs and tables.

Table: 1: Demographic and anthropometric variables

Data		Groups		P value
		Group LF	Group RF	
Mean Age (yrs)		42.366	42.667	0.510
Sex	Male	26(87%)	27(90%)	0.688
	Female	4(13%)	3(10%)	
ASA Grade	I	23(77%)	22(73%)	0.766
	II	7(23%)	8(27%)	
Weight (kg) (Mean±SD)		59.83 ± 1.57	58.30 ±1.53	0.488
Duration (min) (Mean±SD)		93.16 ± 4.28	89.33 ± 4.85	0.566

Table 2: Sensory and motor block characteristic

Data	Groups		t-test	P value
	Group LF (Mean±SD)	Group RF (Mean±SD)		
Onset of sensory block (in sec)	174 ± 13.29	236 ± 11.48	-3.529	0.001
Onset of motor block (in sec)	185 ± 13.65	300 ± 13.49	-5.911	0.001
Peak sensory block (in min)	6.66 ± 0.69	6.91 ± 0.75	-0.228	0.82
Complete motor block (in min)	7.13 ± 0.75	6.23 ± 0.81	0.82	0.415
Duration of sensory block (in min)	271.5 ± 5.06	228 ± 4.16	6.64	0.001
Duration of motor block(in min)	252.16 ± 4.69	195.33 ± 3.54	9.657	0.001
Rescue analgesia (in min)	292.83 ± 5.28	258 ± 4.32	5.101	0.001

Table 3A: Side effects

Side Effects	Group		
	LF	RF	Total
Bradycardia	1	1	2
Hypotension	3	2	5
Itching	1	0	1
Nausea/ vomiting	0	1	1
Shivering	3	3	6
Total	8	7	15

Table 3B: Side effects

Side Effects	N	Frequency	Proportion test	P- Value
LF	30	8	0.095	0.98
RF	30	7		

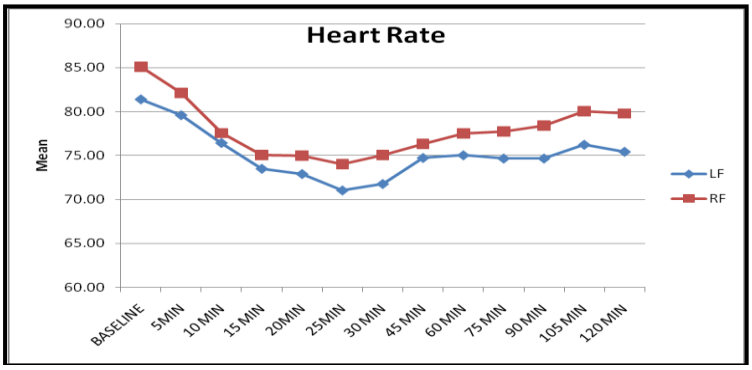

Fig. 1

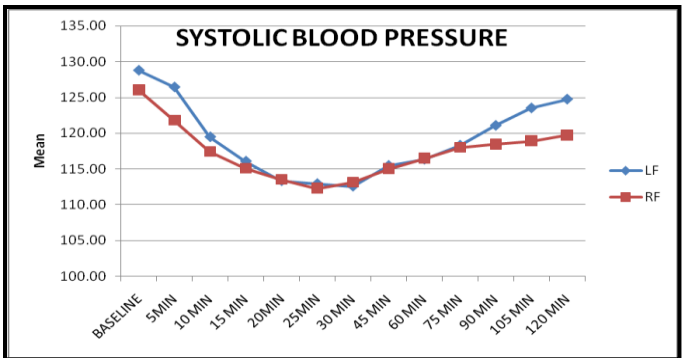

Fig. 2

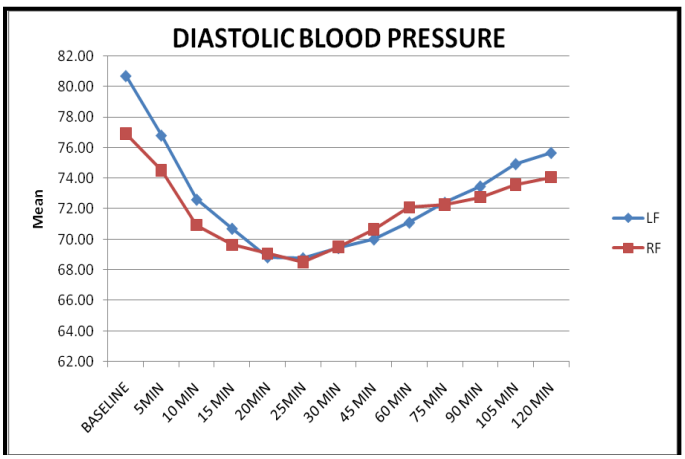

Fig. 3

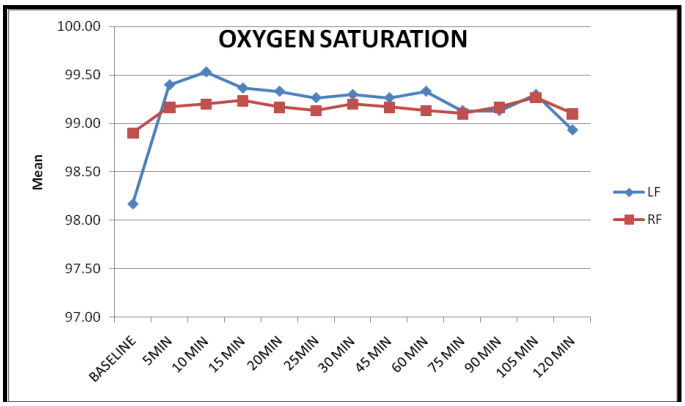

Fig. 4

Results

The mean age was 42.36 and 42.66yrs, the mean weight was 59.83 and 58.3 Kg and mean duration of surgery was 93.16 ± 4.28 and 89.33 ± 4.85 min in group LF and RF respectively. There were no significant differences regarding the demographic and anthropometric variables of the study population i.e. age, sex, weight, ASA grade and duration of surgery between the two groups (p value >0.05). Desired level was achieved in all the patients in our study. The mean time to achieve T10 dermatomal level was 174 ± 13.29 sec in group LF and 236 ± 11.48 sec in group RF. Similarly time to bromage1 was185 ± 13.65 sec in group LF and 300 ± 13.49 sec in group RF (p value =0.001). Peak dermatomal height achieved was T6-T8 in group LF and T8-T10 in group RF. The mean time to achieve peak sensory level was 6.66±0.69 min in group LF and 6.91±0.75 min in group RF (p value > 0.05) and mean time to achieve complete motor block i.e. bromage 3 in group LF was 7.13±0.75 and in group RF was 6.23±0.81 (p value > 0.05). Total mean duration of sensory block was comparatively more in group LF (271.5 ± 5.06 min) than in group RF (228 ± 4.16 min) with p value 0.001. Time for recovery of motor block to bromage 0 was significantly prolonged in group LF (252.16 ± 4.69 min) as compared to group RF (195.33 ± 3.54 min) p value =0.001. Duration of analgesia was also significantly (p value =0.001) longer in group LF (292.83 ± 5.28 min) as compared to group RF (258 ± 4.32 min).

Hemodynamic parameters were also comparable between the two groups at various time intervals. HR, systolic and diastolic blood pressure decreased with time in both the groups, but the difference was not significant between the groups. Hypotension was seen in 3 patients in group LF and 2 patients in group RF whereas incidence of bradycardia was similar in both groups i.e. in 1 patient in each group.

The incidences of post dural puncture headache (PDPH) or any other side effects were not seen in two groups and were not statistically significant as evident from proportion test (p value 0.98).

Discussion

Various local anaesthetic drugs are used intrathecally to achieve sensory and motor block. In order to decrease adverse effects associated with currently used local anaesthetic drugs and to improve safety and clinical profile of spinal anaesthesia, new local anaesthetic drugs and intrathecal additives are being investigated. After restriction of intrathecal use of lignocaine, the only drug used was racemic Bupivacaine. Although bupivacaine is the novel drug for spinal anaesthesia, cardiovascular adverse effects such as hypotension, bradycardia and arrhythmias are observed with this. Also severe cardiac and neurotoxicity can occur in accidental intravascular injection of large doses. These adverse effects are linked to R(+) isomer of bupivacaine. So S-enantiomers related to Bupivacaine i.e. Levobupivacaine and Ropivacaine are introduced and suitable alternative for regional anaesthesia. These isomers are having a safer pharmacological profile[11,12] with less cardiovascular and neurological adverse effects.[8,13] The faster protein binding rate of Levobupivacaine is attributed to its decreased toxicity.[14] While Ropivacaine is less likely to penetrate large myelinated motor fibres because of its is less lipophilicity than Bupivacaine; therefore, it has selective action on Aδ and C pain-transmitting nerve fibres rather than Aβ fibres, which are involved in motor function so differential sensorimotor blockade results. Studies have shown the potency ratio between Ropivacaine and Levobupivacaine is 0.68-0.83.[15-17] Literature is available where Levobupivacaine and Ropivacaine were used in varying doses and baricity and also compared with racemic Bupivacaine but results are inconsistant in these studies and the varying doses of drug produced different finding in different studies. It is observed that isobaric local anaesthetic preparation are suitable for surgeries below T10 level but surgeries requiring higher level either needs higher volume of local anaesthetic or intrathecal additives with local anaesthetics.[18] The use of lipophilic intrathecal opioid enhances the quality of intraoperative analgesia and also decreases the dose of local anaesthetic required to achieve desired dermatomal level and dense sensory block. This reduced amount of local anaesthetic decreases the intensity and duration of motor block and provide early mobility. Currently there are only fewer studies which used intrathecal additive Fentanyl with isobaric preparation of Ropivacaine and Levobupivacaine in equally potent doses and compared their block characteristic. This prospective, single blind, comparative study was conducted to observe block characteristics of isobaric Ropivacaine 0.75% and Levobupivacaine 0.5% i.e. in equipotent doses combined with Fentanyl for lower abdominal and lower extremity surgeries.

In present study the group LF achieved sensory level of T10 and bromage grade 1 block significantly earlier as compared to group RF. Similar results were stated by Gautamsingh et al (2017),[18] Jain et al (2017),[19] Dr A Das et al(2015),[20] Indumathi et al (2014),[21] Mantouvalou et al(2008),[22] Mehta et al(2007).[23] In contrast to this, Athar M et al (2016)[24] observed earlier onset with Ropivacaine than Levobupivacaine. This difference in the result can be due to use of different doses, different adjuvants as well as different criteria for assessment. While Ritika Jindal et al (2016),[25] Vampugalla PS et al (2015)[5] and Fasciolo et al(2011)[26] observed comparable results with Levobupivacaine and Ropivacaine.

In our study group LF achieved higher peak sensory level than group RF. The mean time to achieve peak dermatomal level and Bromage grade 3 was comparable between two groups. Gautamsingh et al (2017),[18] Dr A Das et al(2015)[20] and Malinovsky et al (2000)[27] observed higher level of sensory block with Levobupivacaine compared to Ropivacaine. Kyung-Mi Kim et al (2013)[28] revealed that in intrathecal Ropivacaine group peak sensory level was lower than Levobupivacaine in labor analgesia. Similarly McNamee et al (2016)[29] and Koltka K et al (2009)[10]concluded that Ropivacaine is associated with lower sensory level than Bupivacaine. All of these studies correlate with our results for height of sensory block. In contrast to our study, Ritika Jindal et al (2016)[24] and Athar M et al (2016)[24], Vampugalla PS et al (2015),[5] J. F. Luck et al (2002)[30] observed similar extent of sensory level with Levobupivacaine and Ropivacaine. Marriet et al (2016)[31] and Ogun et al(2016)[32] and Mantouvalou et al (2008)[22] also found a similar cephalad extent of sensory block with bupivacaine and Ropivacaine. This difference might be due to the use of Fentanyl as adjuvant in our study which produced good quality of block and also extra volume of this additive led to a higher spread of local anaesthetic.

Group LF showed comparatively longer duration of sensory block than group RF. The similar finding was stated by Gautamsingh et al (2017),[18] Jain et al (2017),[19] Ritika Jindal et al(2016),[25] Athar M et al (2016),[24] Dr A Daset al(2015),[20] Vampugalla PS et al (2015),[5] Koltka K et al (2009),[10] Mantouvalou et al(2008),[22] Manuel Marron-Pena, MD; Jaime Rivera-flores et al (2008),[33] Mehta et al(2007),[23] Gianluca Cappelleri et al (2004),[34] Helena Kallio et al (2004),[35] J. F. Luck et al (2002),[30] Delfino J. et al (2001)[36] who compared Ropivacaine and Levobupivacaine and concluded that resolution of sensory blockade was earlier in Ropivacaine group.

The mean duration of motor block in Group LF was significantly higher than the group RF, which is well supported by earlier studies by Gautamsingh et al(2017),[18] Jain et al (2017),[19] Ritika Jindal et al (2016),[25] Athar M et al (2016),[24] Vampugalla PS et al (2015),[5] Dr A Das et

al(2015),[20] Koltka K et al (2009),[10] Manuel Marron-Pena, MD; Jaime Rivera-flores et al (2008),[33] Mantouvalou M et al(2008),[22] Mehta A et al (2007),[23] Gianluca Cappelleri et al (2004),[34] Helena Kallio et al (2004),[35] J. F. Luck et al (2002) [30] and Delfino J. et al (2001).[36]

Fasciolo A et al (2011)[26]and Breebaart M. et al (2001)[37] observed comparable results in regards to duration of sensory and motor block with Ropivacaine and Levobupivacaine. It might be due to the lesser dose taken by them compared to our study. While Indumathi T et al (2014)[21] observed that recovery of sensory and motor blocks was earlier with Levobupivacaine which might be due to the use of Magnesium as an adjuvant in their study.

Mean duration of analgesia was longer in group LF than in group RF in the present study. The first rescue analgesic time was significantly shorter with Ropivacaine than with Levobupivacaine. Our findings correlate well with the study by Athar M et al (2016),[24] Kyung-Mi Kim et al (2013),[28] Mantouvalou et al(2008)[22] and Delfino J. et al (2001)[36] who found significantly shorter duration of analgesia in Ropivacaine group. Vampugalla PS et al (2015)[5] and Fasciolo A et al (2011)[26] observed that duration of analgesia between Levobupivacaine and Ropivacaine was comparable. While Manuel Marron-Pena, MD; Jaime Rivera-flores et al (2008)[33] concluded that hyperbaric Ropivacaine provides longer lasting residual analgesia and faster recovery of motor block which may be due to use of hyperbaric Ropivacaine in that study.

The incidence of adverse effects including nausea/vomiting, hypotension, bradycardia, itching and shivering between the two groups were not statistically significant. Ritika Jindal et al (2016),[25] Athar M et al(2016)[24], Mehta A et al (2007)[23] and J. F. Luck et al(2002)[30] support our findings. While Jain et al (2017)[19] found hypotension more frequently in Levobupivacaine group than Ropivacaine group and Gautamsingh et al (2017)[18] found bradycardia more frequently in Ropivacaine group.

Strength of the Study

The strengths of this study include use of equipotent doses, absence of any drop-outs and absence of any major side effects.

Limitations of the Study

1. A better comparative study would have been resulted if Bupivacaine was added as a third group in the study.
2. This study was single blinded i.e. both the investigators & analyser were aware of group allocation. So observer bias could not be ruled out.
3. We have not mesured height of the patients in our study, which may influence the results.

Conclusion

Equipotent doses of isobaric Levobupivacaine (15 mg) and Ropivacaine (22.5 mg) with neuraxial adjuvants Fentanyl (25µg) administered effective surgical anaesthesia in lower abdominal and lower extremity surgeries with less hemodynamic variations and side effects. Levobupivacaine-Fentanyl can be considered better in view of early onset and longer duration of blockade and postoperative analgesia while Ropivacaine-Fentanyl having advantage of faster recovery of sensory and motor block and early mobility can be a better choice for day care surgery.

Conflict of Interest: None.

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