Postoperative Analgesic Effect of Wound Site Infiltration with Bupivacaine versus Ropivacaine - A Randomised Clinical Trial at VIMSAR, Burla

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ABSTRACT

BACKGROUND

Post-operative pain is a ubiquitous finding following any surgeries. It has physiological and psychological effect in patients. The source and degree of nociceptive stimulation differ among individuals and type of surgeries. In this regard, multimodal analgesic approach has been encouraged for post-operative pain relief, local infiltration of wound site being simplest among them. This procedure reduces the sensitisation and consequent hyperalgesia by cutting down afferent impulses from site of incision and injury.

METHODS

This is a single blind randomized clinical trial conducted at surgery main operation theatre, surgery indoor wards for a duration of 2 years. 60 patients posted for routine surgeries under general anaesthesia were taken as study subjects and were randomly divided into 2 groups of 30 each. Before skin closure, skin wound site was infiltrated at 1ml/cm according to the following schedule - Group B: received Inj. Bupivacaine plain (0.2 %), Group R: received Inj. Ropivacaine plain (0.2 %). All the patients were followed up for 24 hours and post-operative pain score parameters (Visual Analogue Score) were taken at 1 hour, 2-hour, 6-hour, 10 hour and 24 hours. The time duration till the requirement of first dose of rescue analgesia was noted down. Data was analysed using chi-square test, student t - test and statistical significance was set at $P < 0.05$.

RESULTS

Hemodynamic stability was more with Ropivacaine as the fall in blood pressure and heart rate was not drastic. Duration of analgesia was longer with Ropivacaine. Analgesia was better with Ropivacaine. Both the drugs caused analgesia of significant extent. No cardiotoxicity or any other adverse reaction was observed with either drug in this study.

CONCLUSIONS

Ropivacaine is having longer duration of analgesia and better analgesic effect than bupivacaine.

KEYWORDS

Postoperative, Analgesic, Wound, Infiltration, Bupivacaine, Ropivacaine

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DOI: 10.18410/jebmh/2021/353

How to Cite This Article:
Patel MK, Soren DK, Patro GSP, et al. Postoperative analgesic effect of wound site infiltration with bupivacaine versus ropivacaine - a randomised clinical trial at VIMSAR, Burla. J Evid Based Med Healthc 2021;8(23):1875-1881. DOI: 10.18410/jebmh/2021/353

Submission 15-02-2021,
Peer Review 23-02-2021,
Acceptance 21-04-2021,
Published 07-06-2021.

BACKGROUND

"Pain is whatever the experiencing person says it is and exists whenever he/she says it does"- Mc Caffery.[1] Pain is a multifarious and totally personal experience.[1]Post-operative pain has the potential for adverse effects on the physiology, psychology, wound healing, endocrine and immune activity, cardio-respiratory and thrombo-embolic diseases.[2-4] Acute pain management is a major health issue after surgery. Acute post-operative pain management is crucial to patient satisfaction and a timely discharge, to cut down health care expenses and long-term hospital viability.[5] The origin and degree of nociceptive stimulation can be different among individuals and surgeries and so multimodal analgesic approaches have been applied for pain relief to decrease in demand of opioids. With local infiltration in surgical planes, there is reduction in transmission of afferent impulse from injury site and reduces the sensitization. The risks associated with systemic administration of analgesics, risks related to central neuraxial block and the injury/injection to nearby structures in nerve/plexus blocks are avoided. Simplicity and safety are the hallmarks of the procedure.

Wound infiltration is commonly performed under monitored anaesthesia care for small incisions. For example, digital block, infiltration block to surface injuries and circumcision, herniotomy.[6] For larger incisions, larger volumes of the drug need to be infiltrated subcutaneously, also injected into extra planes e.g., hysterectomy, caesarean sections, abdominal surgeries, hip and knee replacement surgeries, breast surgeries, laparoscopic surgeries, cardiac surgeries, thoracic surgeries, bariatric surgeries etc.[7-14] Subcutaneous local anaesthesia has bacteriostatic and bactericidal actions in addition to anti-nociceptive effects.[15] For post-operative analgesia, longer acting and non-cumulating topical anaesthetic drugs are the choice. Bupivacaine is an amide-type, long-acting topical anaesthetic, reversibly attaches to neuronal membrane Na^+ channels resulting in alteration in permeability to Na^+ and membrane stabilization, inhibition of depolarization and nerve impulse transmission and a reversible loss of sensation. Ropivacaine was developed after bupivacaine was found to be related to cardiac arrest, mainly in pregnant women. Ropivacaine is less cardio-toxic than bupivacaine but having similar duration of analgesia.[16] Ropivacaine has inherent vasoconstrictive action. This study compares the analgesic efficacy of bupivacaine & ropivacaine via subcutaneous infiltration.

We wanted to compare the time to first dose of rescue analgesic in cases of infiltration of wound site by bupivacaine and ropivacaine.

METHODS

The present study was undertaken in Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla from December 2018 to December 2020. The subjects chosen for the study were the patients scheduled to undergo routine surgeries under general anaesthesia. After obtaining approval from VIREC (registration no. ECR / 861 / Inst / OR / 2016) with ethical clearance certificate no. 095 / 19 – I – S – 096 / Dt. 25.01.2019, the study was conducted under the guidance of senior teachers of the Department of Anaesthesiology with CTRI (Clinical Trial Registry - India) registration no. CTRI / 2019 / 11 / 021943.

Inclusion Criteria

60 patients of age 18 - 60 years, American society of Anaesthesiologist (ASA) grade I and II, who were undergoing routine surgery under general anaesthesia were included in the study.

Exclusion Criteria

- Patients with history of allergy to local anaesthetics
- Pregnant women and lactating mothers
- Patients with bleeding disorders
- Patients with psychiatric disorders
- Patients with neuromuscular disorders

Sample Size Calculation

As per the article "A comparative study of intra-peritoneal ropivacaine and bupivacaine for postoperative analgesia in laparoscopic cholecystectomy: a randomized controlled trial" by the mean Visual Analogue Scale (VAS) score in bupivacaine group was 28.20 ± 3.881 while in ropivacaine group it was 23.40 ± 5.573. Applying the formula of sample size for comparing two means

$$n = (\sigma_1{}^2 + \sigma_2{}^2/K)\,(Z_{1-\alpha}/2 + Z_{1-\beta}/2)/\,\Delta^2$$

n = Sample size of Group
σ_1 = Standard deviation of Group 1 = 3.881
σ_2 = Standard deviation of Group 2 = 5.573
Δ = Difference in group means
k = Ratio = n2/n1
$Z_{1-\alpha}$ / 2 = Two - sided Z value (Z = 1.96 for 95 % confidence interval)
$Z_{1-\beta}$ = Power = 80 %

The calculated minimum sample size was 16 for each group. Considering normality, we included 30 samples in each group. the number of study subjects in bupivacaine group (Group B) was 30. The number of study subjects in ropivacaine group (Group R) was 30. Simple randomization was done using https://www.randomizer.org/ software.

Methods of Data Collection

The purpose and procedure of the study was explained to all patients and informed consent for anaesthesia and procedure was obtained. The patients were randomly allocated into either of two groups (B, R) of 30 each by randomization.

After proper pre-anaesthetic check, all patients were pre-medicated with tab. Alprazolam 0.5 mg and tab Ranitidine

150 mg orally on the night before surgery and kept nil orally for a duration of 8 hours. In the operation theatre, monitor showing heart rate, non-invasive blood pressure, electrocardiogram (ECG), oxygen saturation, and end tidal carbon dioxide were attached to the patient. Then premedication of inj. Glycopyrrolate 4 mcg/kg IV, inj. Midazolam 0.04 mg/kg IV and inj. Nalbuphine 0.2 mg/kg IV were administered 15 minutes before induction followed by pre oxygenation with 100 % oxygen followed by induction with inj. Propofol 2 mg/kg IV, till the loss of verbal response. Neuromuscular blocker was then administered in their intubating doses followed by bag and mask ventilation and then intubated with appropriately sized endotracheal tube by an expert anaesthesiologist. Anaesthesia was maintained with 2 : 1 ratio of nitrous oxide to oxygen mixture along with Sevoflurane 1 - 1.5 %.

For maintenance of muscle relaxation, one-fourth the intubating dose of each drug was given at starting of spontaneous breathing. Before skin closure, skin wound site was infiltrated @ 1ml/cm[17] according to the following schedule:

Group B (N = 30): received surgical wound site infiltration with 0.2 % Bupivacaine

Group R (N = 30): received surgical wound site infiltration with 0.2 % Ropivacaine.

After the end of surgery, blockade reversal was done with inj. Neostigmine 0.05 mg/kg IV and inj. Glycopyrrolate 0.01 mg/kg IV, after return of regular spontaneous breathing followed by extubation. All the patients were followed up at 1 hr, 2 hr, 6 hr, 10 hr, 24 hr and post-operative pain score parameters were taken.[18] The time duration till the requirement of first dose of rescue analgesia was noted down.

Statistical Analysis

The data was entered in Microsoft excel. After matching all baseline characteristics, all data was analysed using SPSS statistical software version 23.0. Demographic variables i.e., age and gender were represented using descriptive statistics. Quantitative data, the results were expressed as mean ± standard deviation (SD). Association between two qualitative data was done using chi-square test. Comparison of mean data between two groups was done using student t-test. P - value less than 0.05 was considered as statistically significant.

RESULTS

60 patients were assessed for eligibility and enrolled in the study, and none were excluded. They were randomly allocated to 2 groups of 30 each. No patient was lost to follow up in any group. All 30 patients of each group were analysed (Figure 1). There was no significant difference between the two groups with regards to demographic data, ASA grade and pre-operative values of vitals with all P values being more than 0.05, which implied that both groups were comparable. There was no significant difference between the two groups with pre-operative values showing that both groups were comparable in our study pre-operatively. We found that P - value for pulse rate was statistically significant at 10 hr and 24 hr time (0.019, 0.035 respectively) between group B (92.57, 90.27 bpm respectively) & R (86.6,83.9 bpm respectively). Mean pulse rates were more increased in group B as compared to group R and mean pulse rate of group B was tending towards upper range of normal value with time (Figure 2).

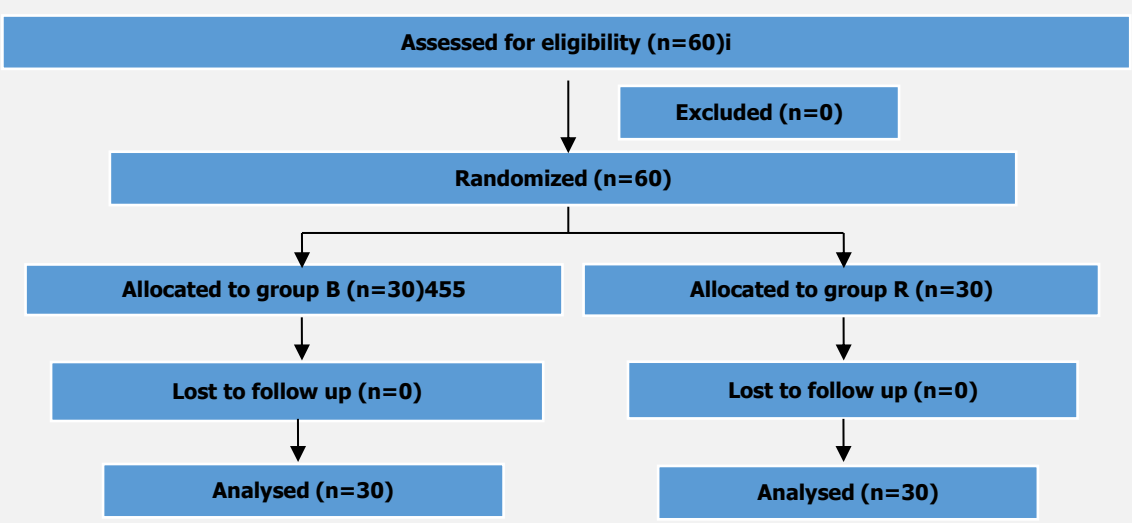

Figure 1. Consort Diagram

Group	No. of Patients	Sex		Mean Age in Years	Mean Height in cm	Mean Weight in Kg	ASA Grade	
		Male	Female				Grade I	Grade II
Group B	30	11	19	38.700 ± 14.0004	154.000 ± 8.5501	54.233 ± 10.0024	14 (46.67 %)	16 (53.33 %)
Group R	30	11	19	40.100 ± 12.3158	156.467 ± 6.7351	58.173 ± 12.0518	15 (50 %)	15 (50 %)
P value		1.000 (chi-square-test)		0.682 (student t-test)	0.219 (student t - test)	0.174 (student t - test)	0.796 (chi-square-test)	

Table 1. Demographic Data & ASA Grade

P - values (0.001) for systolic blood pressure were statistically significant at 24 hr time between group B (128.6 mmHg) & R (121.2 mmHg). Though the systolic blood pressure decreased up to 6hr and thereafter increased in both groups, but the variation in the values were more in group B than group R (Figure 2).

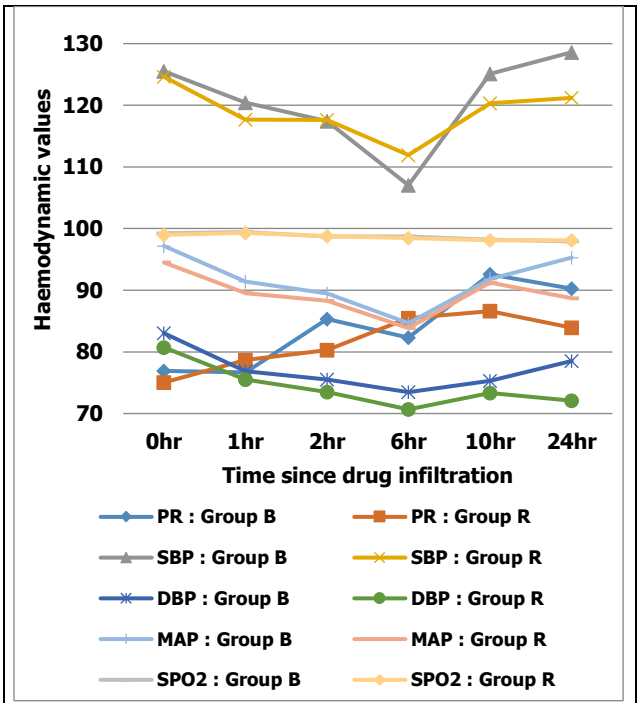

Figure 2. Haemodynamics at Different Time Frames

Group	0Hr	1Hr	2Hr	6Hr	10Hr	24Hr	Average
Group B	0.00	0.23 ± 0.430	0.73 ± 0.828	2.07 ± 0.691	2.07 ± 0.521	2.17 ± 0.531	2.07 ± 0.640
Group R	0.00	0.17 ± 0.379	0.63 ± 0.765	1.47 ± 0.900	1.80 ± 0.847	2.00 ± 0.587	1.45 ± 0.783
P - value (Student t - test)		0.527	0.629	0.005	0.147	0.253	0.002

Table 2. VAS at Different Time Frames

P - values (0.006) for diastolic blood pressure were statistically significant at 24 hr time between group B (78.5 mmHg) & R (72.1 mmHg). There was decrease in trend of diastolic blood pressure with time but in group R, the values were lying more towards normal range (Figure 2).

P - values (< 0.001) for mean arterial blood pressure were statistically significant at 24 hr time between group B (95.311 mmHg) & R (88.711 mmHg). There was decrease in trend of mean arterial pressure with time up to 6 hr followed by increase in both groups but in group R, the values were lying more towards normal range (Figure 2). There is no statistical difference between the groups for oxygen saturation at different time periods.

Mean VAS is statistically significant between the groups at 6 hr time. Also, average VAS is statistically significant between the groups (P - value < 0.05). Overall, the pain control is better in group R compared to Group B. So, ropivacaine infiltration just before skin suturing was found to have better post-operative analgesic property than bupivacaine. (Table 2)

Mean amount of drugs used (group B 27.93 ± 4.828 ml & group R 26.83 ± 4.251 ml with P - value 0.353) was statistically insignificant between the groups (Table 3). Group R (8.5163 ± 4.18941 hr) had more analgesic duration when compared to group B (6.413 ± 2.20755 hr) which was statistically significant (P - value 0.018) (Table 3).

Group	Number of Drugs Used in ml	Analgesia Duration in Hr
B	27.93 ± 4.828	6.4130 ± 2.20755
R	26.83 ± 4.251	8.5163 ± 4.18941
P - value (student t - test)	0.353	0.018

Table 3. Mean Amount of Drugs Used in ml (0.2 % Concentration) & Mean Analgesia Duration in Hr

DISCUSSION

Over the past three decades, patient care related to surgery has steadily been improved. This is due to advancement of medical technology, surgical methods, introduction of new anaesthetic agents and techniques. Advanced technology & monitoring, better drugs, proper evaluation of patients and the evolution of peri-operative care are the key factors for the anaesthetic safety.

Surgical incision causes pain signal formation, also produces inflammation secondarily which further amplifies post-operative pain. Infiltration of local anaesthetics at the incision site can hinder pain signal transmission. It is a safe, easy approach and avoids side effects of systemic analgesics like opioids, NSAIDS. The evidence in this contest are mixed with studies like Lohsiriwat et al. 2004;[19] Lowenstein et al. 2008;[20] Sihoe et al. 2007[21] showing significant pain reduction while other studies Fayman et al. 2003;[18] Hilvering et al. 2011;[22] Metaxotos et al. 1999;[23] Venmans et al. 2010[24] did not find a reduction in pain or had mixed results. The effectiveness in post-operative pain is still debatable in human studies. The use of continuous infusion of local anaesthetics into the surgical site may have some demonstrated efficacy. Infiltration of local anaesthetics prior to surgical incision has been more vastly studied in comparison to local anaesthetic infiltration prior to closure.[19-24] So in our study we have taken into consideration for drug infiltration prior to wound closure to enlighten our knowledge further.

Altuntas et al.[25] compared local anaesthetic infiltration in the trocar insertion sites with intra-peritoneal instillation. They concluded local anaesthetic infiltration in a trocar site was easy, effective on postoperative analgesia and because it is a method with low morphine consumption and low side effect frequencies and possibly the pain of patients was mostly incisional–parietal pain. Our study also involved infiltration of skin incision site comparing two local anaesthetics.

Vigneau et al.[26] evaluated in cancer breast surgery for infiltration anaesthesia. Ropivacaine infiltration provided effective control of pain during first few hours following surgery and thereafter no benefit. Our study was also done to know the effectiveness of infiltration of ropivacaine and bupivacaine in comparison with each other.

Moiniche et al.[27] in systematic review, has evaluated the effect of incisional local anaesthesia for control of postoperative pain in those studies where abdominal incisions were performed excluding laparoscopic surgery. They found the effect was short-lived (2 – 7 h) in most studies. But, a significant dose response relationship was observed in the studies of Johansson et al where the largest dose (highest concentration) of the local anaesthetic caused the most pronounced pain relief. In our study, the results support that drug infiltration has analgesic effect for 6 hours in bupivacaine and 8 hours for ropivacaine.

Kakagia et al.[28] in a double-blind study in bilateral otoplasties, ropivacaine in one ear and bupivacaine in the other ear was used for surgical site infiltration. They noted similarity regarding pain scores intra-operatively and in postoperative period at 2, 6 and 10 hours. They recommended ropivacaine as an effective replacement for bupivacaine. In our study, we also compared bupivacaine with ropivacaine infiltration and found out ropivacaine to be better in term of quality and duration.

Fayman et al.[18] found that overall analgesia achieved with bupivacaine and ropivacaine infiltrations was not statistically different. They recommended the use of ropivacaine in high-dose infiltration breast analgesia, as it is reported to be less cardiotoxic than bupivacaine. We also carried out the study comparing both drugs comparing the efficacy in other types of surgeries also. Fayman et al. analysed VAS pain scores at 1, 2, 6, and 10 hours after surgery likewise we have also collected data at same time also with at 0 hour and 24 hours.

This study titled "Postoperative Analgesic Effect of Wound Site Infiltration with Bupivacaine Versus Ropivacaine: A Randomised Clinical Trial" was performed on 60 ASA grade I and II patients between 18 - 60 years of age posted for routine surgeries under general anaesthesia in VIMSAR, Burla during the period of 2018 to 2020. All collected data was tabulated in Microsoft Excel 2007. Data was analysed using SPSS version 23 using appropriate statistical tests. The observations were compared between the two groups and with the observations of other authors who had done similar work. Age, weight, and height was compared using the student t-test while sex and ASA grade was compared using the chi-square test. The mean age, sex, weight, height, and ASA grade were similar across both the groups ($P > 0.05$).

There was no significant difference in the pre-operative heart rates, systolic blood pressures, diastolic blood pressures, mean arterial pressures and oxygen saturations between the subjects of both the groups. The data was analysed with the help of the student t-test. Mean number of drugs used is statistically insignificant between the groups with P - value > 0.05 using student t - test. Taking the amount of drug used into consideration, both groups were comparable. Hemodynamic variables like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded at 0 hr, 1 hr, 2 hr, 6 hr, 10 hr and 24 hr. The data was analysed using independent t-test.

Hazarika et al.[29] studied heart rate in postoperative period up to 24 hours in lumbar laminectomy patient where wound site infiltration was done using either bupivacaine plus magnesium (BM) or ropivacaine plus magnesium (RM). They found peak heart rate between 6th and 7th hour in Group BM and between 7th and 8th hour in Group RM. In our study peak heart rate was observed at 10^{th} hour in both the groups. The mean pulse rates were comparable up to 6 hr with P value > 0.05 but it was different at 10 hr and 24 hr with P - value < 0.05 which is statistically significant. Mean pulse rate was more increased in group B as compared to group R and mean pulse rate of group B was tending towards upper range of normal value with time. There was no incidence of bradycardia or severe tachycardia in either of the groups. So, ropivacaine infiltration was maintaining better pulse rate than bupivacaine in post-operative period.

The systolic blood pressure decreased up to 6 hr and thereafter increased in both groups, but the variation in the values was more in group B than group R. Decrease in BP may be due to drugs effects followed by increase in BP may be due to fade of drug effects and also due to pain. There was decrease in trend of diastolic blood pressure with time in both groups but in group R, the values were lying more towards normal range. The diastolic blood pressure difference was statistically significant at 24 hr time which may be due to better analgesic and more duration action of ropivacaine.

There was decrease in trend of mean arterial pressure with time up to 6 hr followed by increase in both groups but in group R, the values were lying more towards normal range. Almost all previous studies (except Hazarika et al.)[29] have focused on post-operative pain scores, none of them have given importance to postoperative vitals which was taken into consideration in our study and found that ropivacaine has better control of vitals in postoperative period than bupivacaine. We defined duration of analgesia as the time period from skin infiltration of drug to the requirement of rescue analgesia that is VAS score of 4 or more.

Fayman et al.[18] in their study found that mean VAS pain scores after infiltration with bupivacaine were predominantly lower than after infiltration with ropivacaine, though the difference was only marginally different with $P = 0.069$. But in our study, Group R had more mean analgesic duration when compared to group B and lower VAS score with ropivacaine group with statistically significant value at 6 hr and also average VAS was statistically low in ropivacaine than bupivacaine. So, ropivacaine infiltration just before skin suturing was found to have better post-operative analgesic effect than bupivacaine.

Thornton et al.[16] compared the use of ropivacaine 0.2 % with bupivacaine 0.25 % for axillary brachial plexus block in children undergoing hand surgery and there was no significant difference between the two groups in pain scores, the time to first dose of codeine phosphate or in analgesic requirements in the first 24 hr.

Fayman et al.[18] in their study also found that use of a higher dose of ropivacaine is likely to have removed the clinical advantage noted for the bupivacaine group. They recommended the use of ropivacaine in high-dose infiltration breast analgesia, also focused on to the adequacy of field infiltration of local anaesthesia. Ka-WaiTam[30] in their review

of trials found that, a higher concentration or larger volume of ropivacaine (4.75 mg/mL solution 40 mL) did not yield stronger analgesic effects than did lower doses (7.5 mg/mL solution 20 ml. In our study, even 2 mg/ml solution of about 26.83 ml (mean) yielded the analgesic effect as required. Calculation of rescue analgesia dose, assessment of VAS score in movement are the limitations of our study.

Further study can be done by taking consideration of another group with either only systemic analgesics or combination of skin infiltration with systemic analgesics and in multi-centric trial using large population.

CONCLUSIONS

Ropivacaine infiltration along the skin wound before skin closure results in longer duration of analgesia and better analgesic effect than bupivacaine.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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