Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Randomized controlled study fentanyl Vs buprenorphine as adjuvants in subarachnoid block with 2-chloroprocaine in anorectal surgery

Siddhita Deorukhakar[1], Rajendra Gosavi[2], Deepak Phalgune[3], Shripad Mahadik[4]

1 Senior resident, Dept of Anaesthesiology Poona Hospital & Research Centre, Pune. India.
2 H0D, Dept of Anaesthesiology, Consultant Anaesthesiologist, Poona Hospital & Research Centre, Pune. India.
3 Research Consultant, Dept. of Research, Poona Hospital & Research Centre, Pune. India.
4 Dept of Anaesthesiology, Consultant Anaesthesiologist, Poona Hospital and Research Centre, Pune. India.

ARTICLE HISTORY

Received: 22.07.2020

Accepted: 26.09.2020

Available online: 30.09.2020

Keywords:

Chloroprocaine, fentanyl, buprenorphine, visual analogue scale score, postoperative nausea, vomiting, subarachnoid block

***Corresponding author:**

Phone : +91-919850434220
FAX : +91-20 24338477
Email : dphalgune@gmail.com

ABSTRACT

The subarachnoid block is a safe and reliable anaesthesia technique in outpatient daycare surgeries. The aim of the present study was to compare postoperative analgesic efficacy between 2-chloroprocaine + 25 µg fentanyl, 2-chloroprocaine + 60 µg buprenorphine and 2-chloroprocaine while giving the subarachnoid block in anorectal surgery. This randomised controlled study was conducted in 105 patients. All the patients received 2-chloroprocaine 40 mg. In addition, Group A and Group B patients received 25 µg fentanyl and 60 µg buprenorphine respectively. Group C patients received only 2-Chloroprocaine.The visual analogue scale (VAS)score was recorded immediately, and at 2, 4, 6 h. Postoperative nausea and vomiting (PONV) were noted. The primary outcome measures were to compare the VAS score and the requirement of the use of rescue analgesia, whereas the secondary outcome measure was to compare the incidence of PONV. The mean VAS score was significantly lower in Group B as compared to Group A and Group C. The incidence of PONV was significantly higher in Group B (17.1 %) as compared to Group A (5.7 %) and Group C (8.6 %). The postoperative requirement of the use of rescue analgesia was significantly higher in Group A(17.1 %) compared to Group B (5.7 %). The duration of analgesia was significantly higher in Group B as compared to Group C. An addition of buprenorphine reduced a requirement of the use of rescue analgesia but was associated with an increased incidence of nausea and vomiting.

INTRODUCTION

Various methods exist for treating postoperative pain such as systemic narcotics, non-steroidal anti-inflammatory drugs, patient-controlled analgesia, regional anaesthesia techniques, epidural local anaesthetic narcotic mixtures, transcutaneous nerve stimulation and psychological. Each method has its own merits, demerits and limitations.

The subarachnoid block is a safe and reliable anaesthesia technique in outpatient daycare surgeries.[1] It provides intense analgesia with local anaesthetics by segmental neuraxial blockade but duration is short-acting. Various drugs are administered intrathecally along with local anaesthetics to prolong the duration of action in the postoperative period viz. adrenaline, neostigmine, opioid and clonidine but each has its advantages and disadvantages, limiting their use.

An ester local anaesthetic, 2-chloroprocaine having a very short half-life has been successfully used for the subarachnoid block.[2] It is a local anaesthetic with fast onset and short duration that may be used for the subarachnoid block for the ambulatory procedure of fewer than 30 minutes duration.[3] It is being used as an alternative to lignocaine for the subarachnoid block, has a motor blockade which may last upto 40 minutes and ambulation can be achieved within 90 minutes without complications. It provides adequate duration and depth of surgical anaesthesia for short procedures with the advantages of faster block resolution

and earlier hospital discharge.[4]

Fentanyl is a synthetic opioid agonist with the analgesic property. It interacts with the opioid μ receptor and binds with kappa and delta type opioid receptors. Adding fentanyl increases the duration of analgesia of the subarachnoid block without prolongation of motor block.[5]Intrathecal fentanyl doesn't prolong motor recovery and thus should not delay discharge. Fentanyl permits shorter stay in post anaesthesia care unit (PACU) and early discharge.[6]

Buprenorphine is an opioid with agonist-antagonist activity and analgesic property. It is a partial agonist at the μ opioid receptor and antagonist at the kappa or delta-opioid receptors.[7] Adding buprenorphine for analgesia can provide effective pain relief with fewer significant side effects.[8]

In spinal anaesthesia adding additives to 2-chloroprocaine gives postoperative analgesia without motor blockade and hence early ambulation is possible.[9]It was reported that 40 mg of 2-chloroprocaine provided adequate spinal anaesthesia lasting 45-60 minutes.[10] The aim of the present study was to compare postoperative analgesic efficacy between 2-chloroprocaine + 25 μg fentanyl, 2-chloroprocaine + 60 μg buprenorphine and 2-chloroprocaine (control) while giving the subarachnoid block in anorectal surgery.

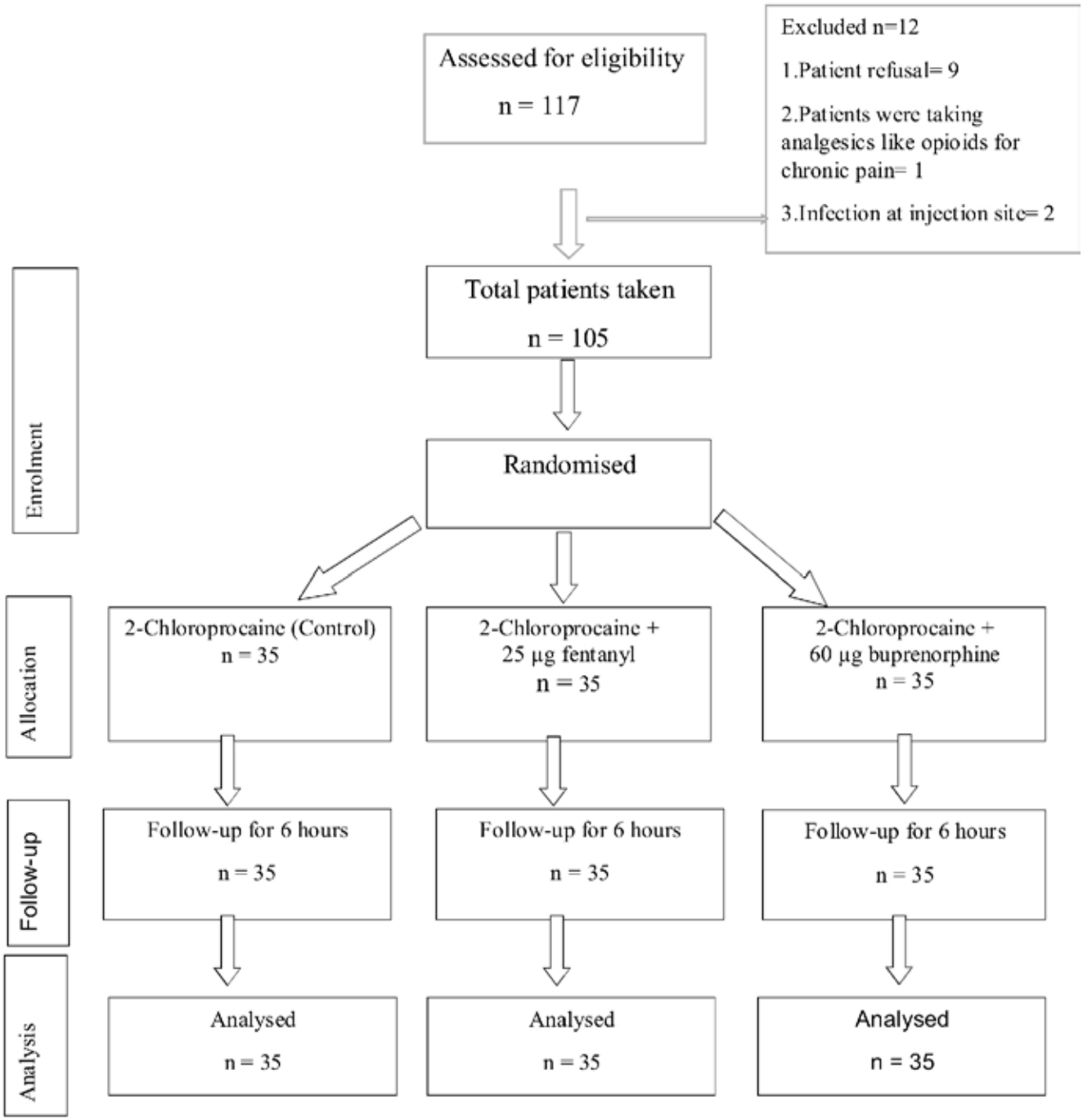

Figure 1. CONSORT FLOW DIAGRAM

MATERIALS AND METHODS

This double-blinded randomised controlled study was conducted between May 2018 and October 2019 in the operation theatre, PACU and wards of Poona Hospital and Research Centre, Pune, India. After approval from the scientific advisory committee (RECH/SAC/2018-19/0063), and the institutional ethics committee (RECH/EC/2018-19/0082), written informed consent was obtained from all the patients prior to enrollment explaining the risks and benefits of the procedure. Patients of either gender having age between 18 and 60 years posted for anorectal surgery (haemorrhoids, pilonidal sinus, anal fistula, anal fissures, etc.) of less than 1 h under the subarachnoid block, and falling into American Society of Anaesthesiologist (ASA) grades I and II were included. The patients who did not give consent, patients taking analgesics like opioids for chronic pain, patients with a history of allergy to drugs used, infection at the injection site, and patients on anticoagulants therapy were excluded from this study. Out of 117 patients assessed for eligibility, after the exclusion, 105 patients were randomly divided into three equal groups of 35 each, using computer-generated randomization code (Fig 1). We used the website https://www.sealedenvelope.com/simple-randomiser/v1/lists for creating a randomization list with a block size four. Randomization code was explained to operation theatre sister who prepared the study medication under the guidance of senior anaesthesiologist. All the patients received 2-chloroprocaine 40 mg as a fixed-dose. In addition to 2-chloroprocaine 40 mg, Group A and Group B patients received 25 µg fentanyl and 60 µg buprenorphine respectively. Group C patients received only 2-chloroprocaine (control). The patients and observer were blinded for the study.

During the preoperative visit, all the patients were explained regarding a visual analogue scale (VAS) score. In preanaesthesia room, intravenous (IV) access was confirmed. IV fluids like ringer lactate were started as preload. The blood pressure (BP), pulseoximeter, electrocardiogram (ECG) leads were attached. Heart rate (HR), BP and mean arterial pressure (MAP) were monitored before, during and after spinal anaesthesia. The baseline readings of vitals were noted. Under all aseptic precautions, the subarachnoid block was given in a sitting position after local skin infiltration with 2 mL of 2% lidocaine using 25 G Quinke's spinal needle in L3-L4/L4-L5 space by the midline approach. After entering in the subarachnoid space, the drug was injected after confirming there was no aspiration of cerebrospinal fluid. After injecting the drug, the patient was placed in a supine position with a pillow below the head. No head down or tilt was given. Intraoperative HR, BP and oxygen saturation were monitored and recorded every 5 minutes. The side effects such as postoperative nausea, vomiting (PONV) were noted for 6 hours. The VAS score was recorded immediately (0 hours) and thereafter at 2, 4 and 6 h. The VAS score was labelled as 0-no pain, 1-3 -mild pain, 4-6 -moderate pain, 7-9-severe pain and 10-worst imaginable pain. If the VAS score $\geq$ 4, rescue analgesia Inj. diclofenac 75 mg was given intramuscularly.

The primary outcome measures were to compare VAS score and the requirement of the use of rescue analgesia,whereas the secondary outcome measure was to compare the incidence of PONV. On the basis of a previously published study, [11]a sample size of 35 patients in each group was calculated by formula [12]with 80 % power and 5 % probability of Type I error to reject the null hypothesis.

Statistical Analysis

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences for Windows, Version 20.0 from IBM Corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented as mean and standard deviation (SD). The comparison of the distribution of categorical variables such as gender, ASA grade, incidence of side effects and requirement of rescue analgesia was done using the Chi-square or Fisher's exact test. The comparison

Table 1 : Baseline characteristics

Characteristics	Group A N = 35	Group B N = 35	Group C N = 35	P value
Mean age in years ± SD	42.0± 11.4	43.6± 10.4	38.8± 12.5	0.208*
Gender (%)				
Male	18 (51.4)	18 (51.4)	21 (60.0)	0.708**
Female	17 (48.6)	17 (48.6)	14 (40.0)	
Mean BMI in Kg/m^2 ± SD	23.9± 2.3	23.8± 2.2	24.5± 3.1	0.792*
ASA grade (%)				
Grade I	19 (54.3)	19 (54.3)	25 (71.4)	0.240**
Grade II	16 (45.7)	16 (45.7)	10 (28.6)	

*Analysis of variance (ANOVA) test was used
**Chi-square test was used
BMI- Body mass index
ASA - American Society of Anaesthesiologist
SD- Standard deviation

Table 2 : Comparison of postoperative characteristics

Characteristics Mean VAS score ±SD	Group A N = 35	Group B N = 35	Group C N = 35	P value
0 h	0.0±0.0	0.0±0.0	0.0±0.0	0.999*
1 h	0.3±0.7	0.0±0.0	0.3±0.7	0.090*
2 h	0.4±0.8	0.0±0.0	0.7±1.4	0.017*
4 h	1.7±1.3	0.1±0.3	1.7±1.7	0.001*
6 h	2.5±1.1	0.5±1.3	2.1±1.1	0.001*
Mean heart rate per min ±SD				
0 h	78.5±11.5	80.7±11.2	76.0±11.8	0.231*
15 min	76.1±6.8	78.4±7.4	74.0±7.9	0.049*
30 min	74.5±7.2	77.2±7.1	72.6±8.0	0.038*
45 min	73.3±6.8	76.2±6.6	72.9±8.2	0.114*
1 h	72.4±6.4	75.7±7.4	71.9±6.9	0.049*
2 h	72.5±8.4	77.1±9.7	72.6±10.4	0.071*
4 h	71.1±7.5	75.3±9.4	73.5±8.8	0.025*
6 h	71.8±6.5	75.7±8.3	72.3±8.0	0.012*
Mean MAP in mm of Hg ±SD				
0 h	65.5±3.9	65.9±3.8	66.8±10.2	0.001*
15 min	64.9±3.8	65.7±3.5	65.8±8.7	0.001*
30 min	67.1±3.4	66.7±3.1	67.4±7.6	0.005*
45 min	66.6±2.7	66.5±2.6	67.0±7.2	0.001*
1 h	66.7±2.9	67.3±2.9	68.2±5.7	0.001*
2 h	67.1±3.1	66.9±3.5	66.9±3.6	0.523*
4 h	65.5±3.6	65.8±3.5	66.7±3.7	0.348*
6 h	66.2±3.1	66.2±3.1	66.7±3.2	0.783*
Incidence of PONV (%)				
Absent	33 (94.3)	29 (82.9)	32 (91.4)	0.267**
Present	2 (5.7)	6 (17.1)	3 (8.6)	
Requirement of rescue analgesia (%)				
No	29 (82.9)	33 (94.3)	23 (65.7)	0.009**
Yes	6 (17.1)	2 (5.7)	12 (34.3)	
Duration of analgesia in h ±SD	5.3±1.0	6.0±1.1	3.7±1.4	0.018*

* Analysis of variance (ANOVA) test was used
SD- Standard deviation
MAP- Mean arterial pressure
**Fisher's exact test was used
VAS- Visual Analogue Scale
PONV- Postoperative nausea and vomiting

of continuous variables such as mean age, mean body mass index (BMI), mean VAS score, mean HR, mean MAP and mean duration of analgesia was done using analysis of variance (ANOVA) test. The underlying normality assumption was tested before subjecting the study variables ANOVA test. The confidence limit for significance was fixed at 95% level with a p-value < 0.05.

RESULTS

Of 117 patients assessed for eligibility, 12 were excluded because of patient refusal (9), patients were taking analgesics like opioids for chronic pain (1),and infection at the injection site (2). One hundred five patients were randomized into three groups. All the patients received 2-chloroprocaine 40 mg as a fixed-dose. In addition to 2-chloroprocaine 40 mg, Group A and Group B patients received 25 µg fentanyl and 60 µg buprenorphine respectively. Group C patients received only 2-chloroprocaine (control). In all 35 patients were analysed in each group

There was no statistically significant difference between Group A, Group B and Group C in relation to mean age, gender, mean BMI and ASA grades (Table 1). The mean VAS score at 2 h, 4 h and 6 h was significantly lower in Group B as compared to Group A and Group C. The mean HR at 15 minutes, 30 minutes, 1 h, 4 h and 6 h was significantly higher in Group B as compared to Group A and Group C. The mean MAP at 0 h, 15 minutes, 30 minutes, 45 minutes and 1 h differed significantly across study groups. The incidence of PONV was significantly higher in Group B as compared to Group A and Group C. The requirement of the use of rescue analgesia was significantly higher in Group C compared to Group B. The duration of analgesia was significantly higher in Group B as compared to Group C (Table 2).

DISCUSSION

The present study was undertaken to compare postoperative analgesic efficacy between fentanyl vs buprenorphine as an adjuvant with 2-chloroprocaine in anorectal surgery. The patients were randomized into three groups of 35 each. The mean VAS score at 2 h, 4 h and 6 h was significantly lower in Group B (60 µg buprenorphine group) as compared to Group A (25 µg fentanyl group) and Group C (2-Chloroprocaine group). The incidence of PONV was significantly higher in Group B as compared to Group A and Group C. The requirement of the use of rescue analgesia was significantly higher in Group C compared to Group B. The duration of analgesia was significantly higher in Group B as compared to Group C.

Zhang Y et al. in 2014 conducted a study in which different doses of 2-chloroprocaine on saddle anesthesia in perianal surgery were used to compare systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR. They reported that no significant change in HR, SBP and DBP were observed.[13] Lee YY et al. conducted a study to compare the clinical efficacy, motor block, and haemodynamic effects of using levobupivacaine alone and levobupivacaine with fentanyl for spinal anaesthesia. They reported that there were no significant differences between the two groups in the haemodynamic changes.[14]

Neeta S et al. conducted a randomized controlled study to compare intrathecal bupivacaine combined with fentanyl and sufentanil in abdominal and lower limb surgeries. The Group 1, Group 2 and Group 3 received bupivacaine with fentanyl, bupivacaine with sufentanil and bupivacaine with saline (control) respectively, intrathecally. They reported that there was no statistically significant difference in haemodynamic parameters.[15]

Prabhakaraiah UN et al. conducted a randomized, double-blind study to compare the efficacy of nalbuphine hydrochloride and fentanyl as an adjuvant to bupivacaine for spinal anesthesia in lower abdominal surgeries. The patients in the bupivacaine nalbuphine group (Group BN) received 0.8 mg of nalbuphine with 12.5 mg of 0.5% hyperbaric bupivacaine, whereas bupivacaine-fentanyl group (Group BF) received 25 µg of fentanyl with 12.5 mg of 0.5% hyperbaric bupivacaine. The postoperative VAS score was 4.8 ± 1.1 and 3.9 ± 1.0 in the Group BN and the Group BF respectively which was statistically significant (p-value = 0.0007). The number of patients demanding rescue analgesia in the early postoperative period was 18 (60.0%) in Group BN and 7 (23.33%) in the Group BF which was statistically significant (p-value = 0.004). There was no statistically significant difference in haemodynamic parameters. [16]

Bidikar M et al. compared the effects of intrathecal levobupivacaine with levobupivacaine and fentanyl in patients undergoing cesarean section. They reported that hemodynamic parameters were similar in both the groups.[17] Shim SM et al. reported that intrathecal fentanyl 15 µg for anorectal surgery under saddle anesthesia led to an improved pain score for the first six hours after surgery and decreased postoperative analgesic use.[18]Rabbiee SM et al. reported that intrathecal buprenorphine in cesarean section, prolonged the duration of analgesia without any significant changes in hemodynamic status, respiratory problems, and side effects like nausea, vomiting and itching.[19]

Akcaboy EY et al.concluded that for transurethral prostate surgery 5 mg levobupivacaine with 25 µg fentanyl provided a stable hemodynamic profile in spinal anaesthesia and that it could be used at low doses as a good alternative to bupivacaine. They further stated that the MAP and HR were comparable and stable during the surgery in both the groups.[20]

Gupta M et al. conducted a study to evaluate and compare the characteristics of the subarachnoid blockade, hemodynamic stability and adverse effects of intrathecal buprenorphine and intrathecal dexmedetomidine as an adjuvant to 0.5% hyperbaric bupivacaine for lower abdominal surgeries. They reported that there was no significant difference in SBP and DBP change over time between the two groups. [21]

Neeta S et al., Prabhakaraiah UN et al., Bidikar Met al., Shim SM et al., Rabbiee SM et al., Akcaboy EY et al.,and Gupta M et al. reported that there were no hemodynamic changes by adding buprenorphine as an adjuvant in spinal anesthesia. [15-21]

Khan FA et al. reported that buprenorphine gave prolonged analgesia than fentanyl and the requirement of the first rescue analgesia was also earlier in the fentanyl group than buprenorphine.[22] Candido KD et al. reported that buprenorphine as an adjuvant to local anesthetics gave prolonged analgesia for brachial plexus block.[23] Sapkal PS et al. concluded that intrathecal buprenorphine gave better analgesia than clonidine. [24] The present research substantiated the findings of the studies conducted by Singh AP et al., Arora MV et al., and Kaur N et al. [25-27]

Sapkal PS et al. reported that nausea was noted in 17.5% of patients in the buprenorphine group and 7.5% of patients in the clonidine group. Vomiting was present in 5% of patients in the buprenorphine group while none of the patients in the clonidine

group had vomiting.[24] Schnabel A et al. reported that buprenorphine significantly increased the risk of PONV in perioperative nerve blocks.[28]

Limitations

The potential limitations of the study merit consideration. This study was conducted in a single center with a small sample size which included only stable ASA I or II patients, therefore our findings cannot be extrapolated to the patients with significant comorbidities. Our study excluded the paediatric and geriatric population, so the safety and efficacy of the drug in these age groups need to be studied. In our study, surgery duration was less than one hour, so not useful for long-duration surgeries. Multicentric studies with a large sample size are needed to substantiate our findings.

CONCLUSION

The mean VAS score was significantly lower in Group B (buprenorphine) as compared to Group A(fentanyl) and Group C(only 2-chloroprocaine). The incidence of PONV was significantly higher in Group B as compared to Group A and Group C. The postoperative requirement of the use of rescue analgesia was significantly higher in Group A compared to Group B. The duration of analgesia was significantly higher in Group B as compared to Group C.

Conflict of interest: Dr. Siddhita Deorukhakar, Dr. Rajendra Gosavi, Dr. Deepak Phalgune and Dr. Shripad Mahadik declare that they have no conflict of interest. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work

REFERENCES

1. Gebhardt V, Mueller-Hansen L, Schwarz A, Bussen D, Weiss C, Schmittner MD. Chloroprocaine 10 mg/ml for low-dose spinal anaesthesia in perianal surgerya randomised dose finding study. Act Anaesthesiol Scand. 2017; 61:241-9.
2. Ghisi D, Bonarelli S. Ambulatory surgery with chloroprocaine spinal anesthesia: A review. Ambulatory Anesth. 2015;2015:111-20
3. Casati A, Fanelli G, Danelli G, Berti M, Ghisi D, Brivio M et al. Spinal anesthesia with lidocaine or preservative-free 2-chlorprocaine for outpatient knee arthroscopy: a prospective, randomized, double-blind comparison. Anesth Analg.2007;104:959-64.
4. Lacasse MA, Roy JD, Forget J, Vandenbroucke F, Seal RF, Beaulieu D et al. Comparison of bupivacaine and 2-chloroprocaine for spinal anesthesia for outpatient surgery: a double-blind randomized trial. Can J Anesth. 2011;58:384-91.
5. Vath JS, Kopacz DJ. Spinal 2-chloroprocaine: the effect of added fentanyl. AnesthAnalg. 2004;98:89-94.
6. Gupta A, Axelsson K, Thörn SE, Matthiessen P, Larsson LG, Holmstorm B et al. Low-dose bupivacaine plus fentanyl for spinal anesthesia during ambulatory inguinal herniorrhaphy: a comparison between 6 mg and 7. 5 mg of bupivacaine. Act Anaesthesiol Scand. 2003;47:13-9.
7. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2:395-402.
8. Xia X, Xiu F, Ma Z. The effect of buprenorphine combined with bupivacaine for epidural analgesia in patients underwent transurethral resection of the prostate. Jiangsu Med J. 2006;32:27.
9. Korhonen AM, Valanne JV, Jokela RM, Ravaska P, Korttila K Intrathecal hyperbaric bupivacaine 3 mg+ fentanyl 10 µg for outpatient knee arthroscopy with tourniquet. Act Anaesthesiol Scand. 2003;47:342-6.
10. Casati A, Danelli G, Berti M, Fioro A, FanelliA, Benassi C et al. Intrathecal 2-chloroprocaine for lower limb outpatient surgery: a prospective, randomized, double-blind, clinical evaluation. AnesthAnalg. 2006;103:234-8.
11. Gurbet A, Turker G, Girgin NK, Aksu H, Bahtiyar NH. Combination of ultra-low dose bupivacaine and fentanyl for spinal anaesthesia in out-patient anorectal surgery. J Int Med Res. 2008;36:964-70.
12. Harvey Motulsky. Intuitive Biostatics. NewYork: Oxford University Press;1995
13. Zhang Y, Bao Y, Li L, Shi D. The effect of different doses of chloroprocaine on saddle anesthesia in perianal surgery. Acta Cir Bras. 2014;29:66-70.
14. .Lee YY, Muchhal K, Chan CK, Cheung AS. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. Eur Journal Anaesthesiol. 2005;22:899-903.
15. Neeta S, Upadya M, Gosain A, Manissery JJ. A prospective randomized controlled study comparing intrathecal bupivacaine combined with fentanyl and sufentanil in abdominal and lower limb surgeries. Anesth Essays Res. 2015;9:149.
16. Prabhakaraiah UN, Narayanappa AB, Gurulingaswamy S, Kempegowda K, Vijaynagar KA, Hanumantharayappa NB, et al. Comparison of nalbuphine hydrochloride and fentanyl as an adjuvant to bupivacaine for spinal anesthesia in lower abdominal surgeries: A randomized, double-blind study. Anesth Essays Res. 2017;11:859.
17. Bidikar M, Mudakanagoudar MS, Santhosh MC. Comparison of intrathecallevobupivacaine and levobupivacaine plus fentanyl for cesarean section. Anesth Essays Res. 2017;11:495.
18. Shim SM, Park JH, Hyun DM, Jeong EK, Kim SS, Lee HM. The effects of adjuvant intrathecal fentanyl on postoperative pain and rebound pain for anorectal surgery under saddle anesthesia. Korean J Anesthesiol. 2018; 71:213.
19. Rabiee SM, Alijanpour E, Jabbari A, Rostami S. Benefits of using intrathecal buprenorphine. Caspian J Internal Med. 2014;5:143.
20. Akcaboy EY, Akcaboy ZN, Gogus N. Low dose levobupivacaine 0.5% with fentanyl in spinal anaesthesia for transurethral resection of prostate surgery. J Res Med Sci. 2011;16:68.
21. Gupta M, Shailaja S, Hegde KS. Comparison of intrathecaldexmedetomidine with buprenorphine as

adjuvant to bupivacaine in spinal anaesthesia. J ClinDiagn Res. 2014;8:114.

22. Khan FA, Hamdani GA. Comparison of intrathecal fentanyl and buprenorphine in urological surgery. J Pak Med Assoc. 2006 ;56:277-81.

23. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. Reg Anesth Pain Med. 2002 ;27:162-7.

24. Sapkal PS, Kulkarni KD, Rajurkar SS, Nandedkar PD. Comparative study of intrathecal clonidine and intrathecal buprenorphine for postoperative analgesia after lower limb orthopedic surgery. Int J Cur Res Rev. 2013;5(06).

25. Singh AP, Kaur R, Gupta R, Kumari A. Intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries. J Anaesthesiol Clin Pharmacol. 2016;32:229

26. Arora MV, Khan MZ, Choubey MS, Rasheed MA, Sarkar A. Comparison of spinal block after intrathecal clonidinebupivacaine, buprenorphinebupivacaine and bupivacaine alone in lower limb surgeries. Anesth Essays Res. 2016;10:455

27. Kaur N, Goneppanavar U, Venkateswaran R, Iyer SS. Comparative effects of buprenorphine and dexmedetomidine as adjuvants to bupivacaine spinal anaesthesia in elderly male patients undergoing transurethral resection of prostrate: A randomized prospective study. Anesth Essays Res. 2017;11:886

28. .Schnabel A, Reichl SU, Zahn PK, Pogatzki-Zahn EM, Meyer-Frießem CH. Efficacy and safety of buprenorphine in peripheral nerve blocks: a meta-analysis of randomised controlled trials. EurJ Anaesthesiol. 2017;34:576-86.