

## Evaluation of Efficacy of Fentanyl as an Adjuvant to 1% 2-Chloroprocaine for Subarachnoid Block in Ambulatory Surgery: A Prospective Study

Neena Jain<sup>1</sup>, Preeti Lamba<sup>2</sup>, Rahul Bankapur<sup>3</sup>, Pooja R Mathur<sup>4</sup>, Vikas Kumar<sup>5</sup>

**Author Affiliation:** <sup>1</sup>Senior Professor, <sup>4</sup>Associate Professor, Department of Anesthesia, Jawaharlal Nehru Medical College, Ajmer 305001, Rajasthan, <sup>2</sup>Post Graduate, Department of Cardiac Anesthesia, Jawaharlal Nehru Medical College, Belgaum, Karnataka 590010, <sup>3</sup>Senior Resident, Department of Anesthesia, SDM College of Medical Sciences and Hospital, Sattur, Dharwad, Karnataka 580009, <sup>5</sup>Senior Resident, Department of Medicine, Jag Pravesh Chandra Hospital, New Delhi 110053, India.

### How to cite this article:

Neena Jain, Preeti Lamba, Rahul Bankapur, et al. Evaluation of Efficacy of Fentanyl as an Adjuvant to 1% 2-Chloroprocaine for Subarachnoid Block in Ambulatory Surgery: A Prospective Study. Indian J Anesth Analg. 2020;7(5):1113-1120.

### Abstract

**Background and Aims:** Subarachnoid block using short-acting drugs like chloroprocaine may be preferred in ambulatory surgeries. Various adjuncts are being added to local anesthetics to enhance the quality of analgesia. Fentanyl given by intrathecal route with local anesthetics has antinociceptive and synergistic effect.

Our study aimed to elucidate the effects of adding fentanyl to 1% 2-chloroprocaine on duration of sensory block and analgesia for subarachnoid block.

**Methods:** A prospective, randomized, double-blind study was conducted on a hundred patients of ASA physical status I/II, age group 18–80 years scheduled for elective infra-umbilical surgeries. Patients were allocated into two groups of 50 each to receive either 5 ml (50 mg) of chloroprocaine with 0.5 ml of normal saline (Group A) or 5 ml (50 mg) of chloroprocaine with 0.5 ml of fentanyl 25 µg (Group B). Block characteristics, duration of analgesia and complications were assessed.

**Results:** Sensory and motor block were achieved faster in chloroprocaine-fentanyl group. Duration of sensory and motor block, analgesia and return of voiding function, were significantly prolonged in Group B. No difference was noted in maximum motor block and ambulation time. Eight patients in Group B developed pruritus. Chi-Square and Student's unpaired t-test were used to analyse results, using Epi info version 7.2.1.0 statistical software.

**Conclusion:** Isobaric chloroprocaine and fentanyl mixture enhanced the duration of sensory block, analgesia and motor block without increasing ambulation time but with delay in return of voiding reflex.

**Keywords:** Fentanyl; Subarachnoid; Chloroprocaine.

### Introduction

Subarachnoid block is routinely practised technique for surgeries on the lower part of the body. Although recovery from general anesthesia using short-acting intravenous or inhalational agents may be fast, in many day-care patients, regional anesthetic techniques might be preferable for their postoperative analgesic effects.<sup>1</sup> For ambulatory

surgical procedures, the anesthetic drug should provide an enhanced recovery for fast patient discharge with minimal side effects. Lidocaine is associated with transient neurologic symptoms and cauda equina syndrome.<sup>2</sup> Chloroprocaine is being studied for day-care surgeries because of its rapid onset and short duration of action.<sup>3</sup>

Chloroprocaine belongs to ester group of local anesthetics, first introduced in 1952 and used

**Corresponding Author:** Preeti Lamba, Senior Resident, Department of Cardiac Anesthesia, JLN Medical College and KLE's Prabhakar Kore Hospital, Belgaum, Karnataka 590010.

**E-mail:** [preetilamba91@gmail.com](mailto:preetilamba91@gmail.com)

successfully for spinal anesthesia. In early 1980s neurotoxicity was observed with the accidental subarachnoid injection of large volumes of chloroprocaine during attempted epidural anesthesia, since then the drug was no longer used for subarachnoid block.<sup>4</sup> Antioxidant sodium bisulphite at low pH was accepted to be the culprit in these cases. Recently, a new preparation of isobaric 1% 2-chloroprocaine is introduced. This preparation is devoid of antioxidants and preservative. Chloroprocaine is approved as a local anesthetic by the Federal Drug Administration (FDA), but it is not approved for spinal anesthesia and so used, 'off-label'. After 2004, no case of transient neurological syndrome, and neurotoxicity was reported with the use of preservative-free chloroprocaine.<sup>4</sup>

Fentanyl inhibits afferent synaptic transmission via 'C' and 'A' types of pain fibres in substantia gelatinosa of dorsal horn of spinal cord.<sup>5,6</sup>

Based on the hypothesis that intrathecal opioids with local anesthetics improve the duration of sensory block and analgesia without significantly prolonging motor recovery, we conducted this study with the primary aim of describing the effects of adding fentanyl to isobaric chloroprocaine on the duration of sensory block and analgesia for subarachnoid block in the surgical population. Our primary outcome variable was the effect on duration of sensory block and analgesia with addition of fentanyl.

## Materials and Methods

This was a hospital-based prospective, comparative, randomized study. Study was done after getting approval from the Ethical Committee. Based on a previous study, a total of 50 subjects were taken in each group, this sample size was adequate to investigate a difference of 9 min. in the mean time of complete regression of sensory block with a pooled standard deviation of 9. The sample size was calculated at alpha error 0.05 and study power of 90%.<sup>7</sup>

All participants were explained about the procedure and a valid informed, written consent was obtained. Study groups comprised of hundred patients of either sex or age between 18 to 80 years posted for various elective infra-umbilical surgeries. Readiness for discharge on the day of surgery was considered as the criteria for ambulatory surgeries. Participants were divided into two groups with 50 patients in each using a computer-generated table of random numbers. Group A (n=50) received preservative-

free 1% isobaric 2-chloroprocaine 50 mg (5ml, Neon pharmaceuticals) with 0.5 ml normal saline (total volume-5.5 ml). Group B (n =50) received preservative-free 1% isobaric 2-chloroprocaine 50 mg (5ml) with injection fentanyl 25 µg (0.5 ml, Fendrop®-Sun pharma) (total volume-5.5ml).

Patients with ASA physical status III, IV, V, and VI, allergy to local anesthetic agents, peripheral sensorineural deficit, and infection at the site of lumbar puncture and on anticoagulants were excluded from the study. A pre-anesthetic evaluation which included relevant patient history, examination and routine investigations was done. Patients were shifted onto the operating table and intravenous line secured using 18 G cannula.

Under aseptic precautions, the subarachnoid block was given using 25 G Quincke Babcock needle in sitting position at L3-L4 or L4-L5 intervertebral level by a blinded anesthetist. Study drugs were pre-filled by a qualified anesthetist who was not associated with patient management and data collection. Both the patient and investigator were kept blinded to the contents of injection. Patients were kept in a supine position after spinal anesthesia.

Intraoperative and postoperative evaluation of outcome variables was done by anesthesiologist who was unaware of study allocation groups and contents of drug syringes. Following study parameters were evaluated: Primary outcome variable included duration of sensory block and analgesia. Onset and degree of sensorimotor block, 2-segment regression time, duration of motor block, time of ambulation, micturition time, and complications like local anesthetic toxicity, bradycardia (<50 bpm), hypotension (decrease in SBP >30% baseline or <100mm Hg), pruritus, respiratory depression, sedation, were recorded as secondary outcome variables.

Sensory block was assessed using a 23 G hypodermic needle in dermatome areas of T4 to S2 bilaterally in the midclavicular line. Sensory block onset time was the period between drug injections to the time of loss sensation to pinprick at T10 dermatome level assessed every 30 sec. for initial 3 min and then every 2 min for the next 10 min. if needed. The highest dermatome level of sensory block was described as the level achieved after 15 min. of anesthesia. Degree of sensory block was graded as, 0 = normal sensation. 1 = sensation loss to pinprick (analgesia). 2 = sensation loss to touch (anesthesia) and degree of sensory block achieved at 15 min. was noted. Sensory block regression time was assessed, starting from highest dermatome level, every 5 min. after 20 min. for the first hour

and then at 10 min. intervals until regression to S1. When sensory block regressed by two dermatomes from its highest level, this time was taken as 2-segment regression time. Regression time to S1 was considered the same as the duration of sensory block. Duration of analgesia was the time interval between onset of sensory block to the point of time when patients asked for rescue analgesia or VAS (visual analogue scale) was >3.

The onset of motor block was taken as the time interval between drug injections to the time when it reached grade 4 of the modified Bromage scale. Time taken to regain the ability to flex toes was regarded as duration of motor block. Postoperative time of return of voiding function, ambulation time and adverse effects were noted. Discharge criteria for home was defined as regression of sensory block to S1 dermatome, ability to walk without assistance (ambulation time, excluding orthopaedic procedures), return of voiding function and stable vital signs. At the time of discharge patients were prescribed oral analgesics and instructed to report any complications like headache, backache

or dysaesthesia in buttocks, thigh and lower limb up to 1 week of surgery. We followed the patients, telephonically after one week for transient neurological symptoms, and back pain.

Statistical analysis was done using Epi info version 7.2.1.0 statistical software. Chi-Square test was used to analyse categorical/nominal variables (summarized as frequency, percentage). Continuous variables in the form of mean and standard deviation were analysed using Student's unpaired t-test and Mann-Whitney U-test. Data were expressed as mean ± SD unless specified and P-value < 0.05, was considered statistically significant.

### Results

One hundred and twenty patients were assessed for eligibility. Out of these 20 patients didn't fulfil the study criteria and were excluded. A total of 100 patients were studied and there was no loss to follow-ups (Fig. 1). Demographic parameters like

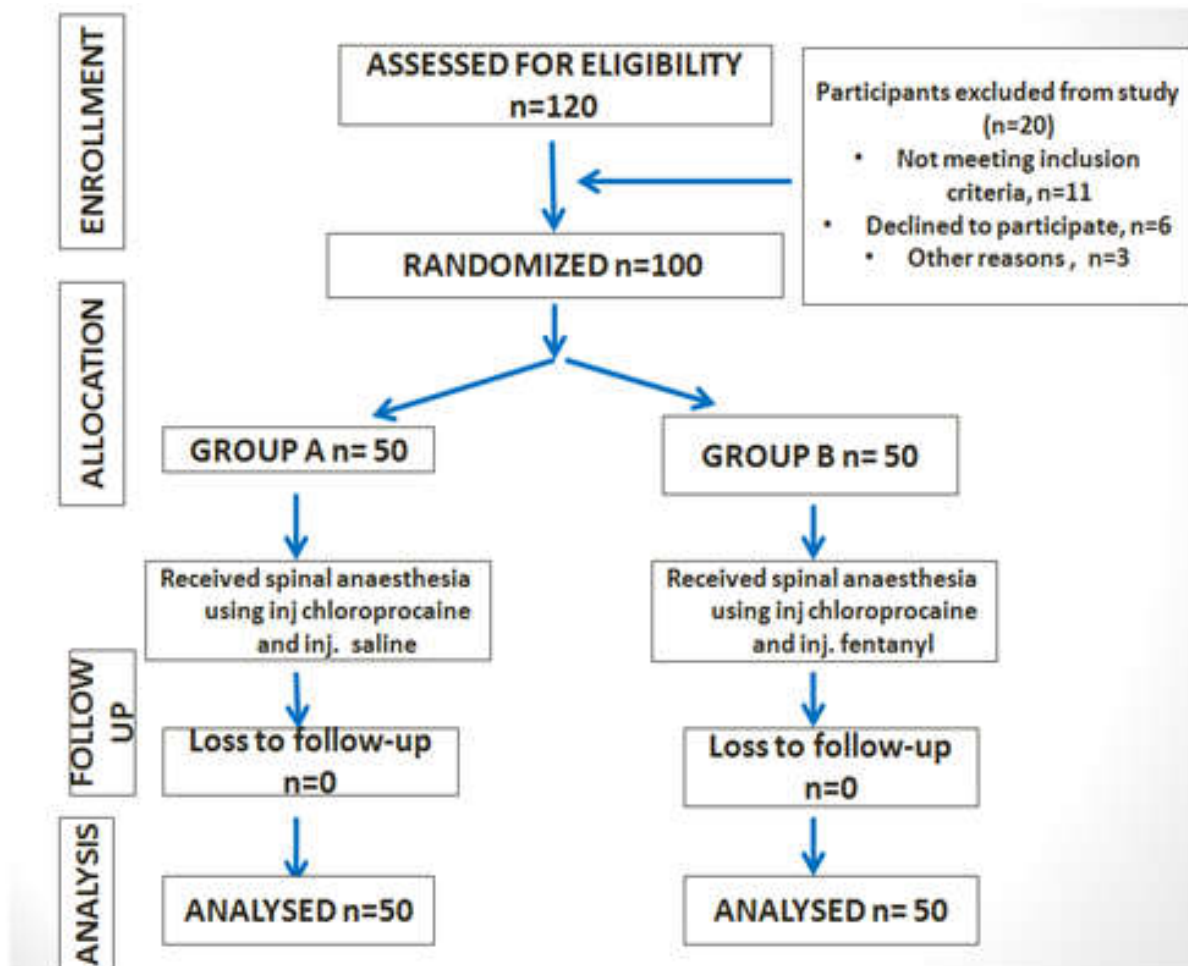
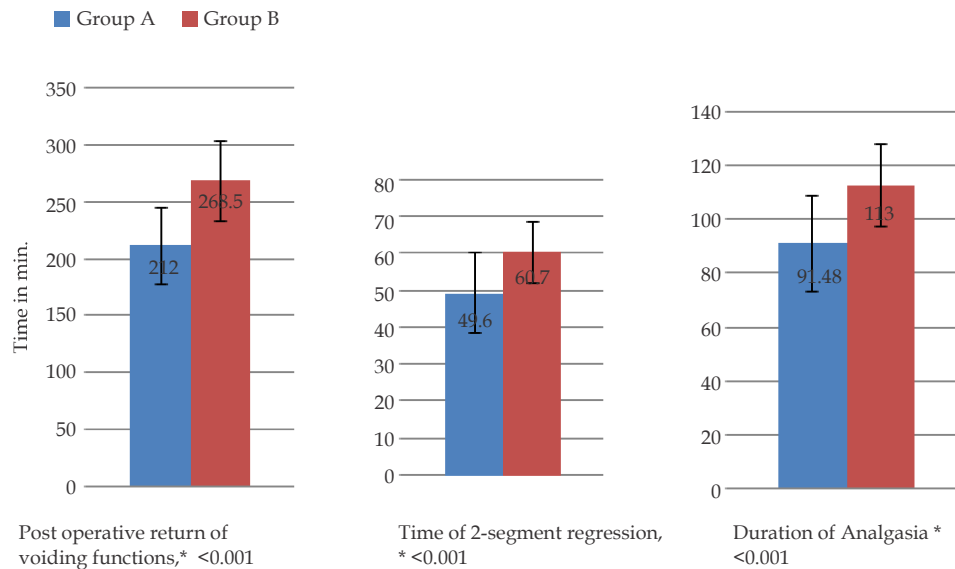


Fig. 1: Consort diagram.

**Table 1:** Demographic profile, mean duration and type of surgeries.

Demographic parameters	Group A (n=50)	Group B (n=50)	P-value
Age (yrs)	41.48 ± 13.19	41.36 ± 15.85	0.9670
Sex (M / F) (n)	35/15	32/18	0.671
Weight (kgs)	58.16 ± 3.31	57.56 ± 2.20	0.288
ASA physical status (I / II) (n)	22 / 28	19 / 31	0.684
Mean duration of surgeries (min.)	55.46 ± 9.8	52.37 ± 16.88	0.255
Type of surgeries - Mesh hernioplasty (inguinal)/ (fissurectomy, fistulectomy and others)/ Gynaecology/ Lower limb/ Urology (percentage of total)	28%/26%/4%/38%/4%	18%/18%/4%/44%/12%	0.319

Data represented as mean ± SD, n - number of patients, SD - Standard deviation, ASA- American Society of Anesthesiologists, and M: Males. F: Females, yr- years, kgs-kilograms.

**Fig. 2:** Sensory block Characteristics.**Table 2:** Sensory block characteristics.

Study parameters	Group A (n=50)	Group B (n=50)	P- value
Onset of sensory block (min.)	2.12 ± 0.78	1.79 ± 0.72	0.010*
Percentage of patients who achieved T6/T8 as highest dermatome level of sensory block	12%/28%	48%/14%	<0.001*
Percentage of patients to achieve second degree of sensory block	40%	64%	0.028*
Mean time of regression to S1 (min.) or duration of sensory block	93.7 ± 22.23	116.7 ± 14.78	0.001.*

Data represented as mean ± SD. n - number of patients, % - percentage of total. SD - Standard deviation, min. - minutes, T6/T8-thoracic dermatome level, S1- sacral first dermatome level, '\*' denotes significant P-value.

age, sex, weight, ASA physical status, mean surgery time and type of surgeries (P = 0.319) were similar in both study groups (Table 1). Intraoperatively, none of the patients needed supplementary analgesics, general anesthesia or airway management.

Sensory block was achieved faster in Group B (1.79 ± 0.72 min.) compared to Group A (2.12 ± 0.78 min., P = 0.010) (Table 2). Regression time for 2-segments was substantially lengthened in Group B (60.7 ± 8.35 min., In Group A - 49.66 ± 10.95 min., P < 0.001). Time to demand rescue analgesia in Group

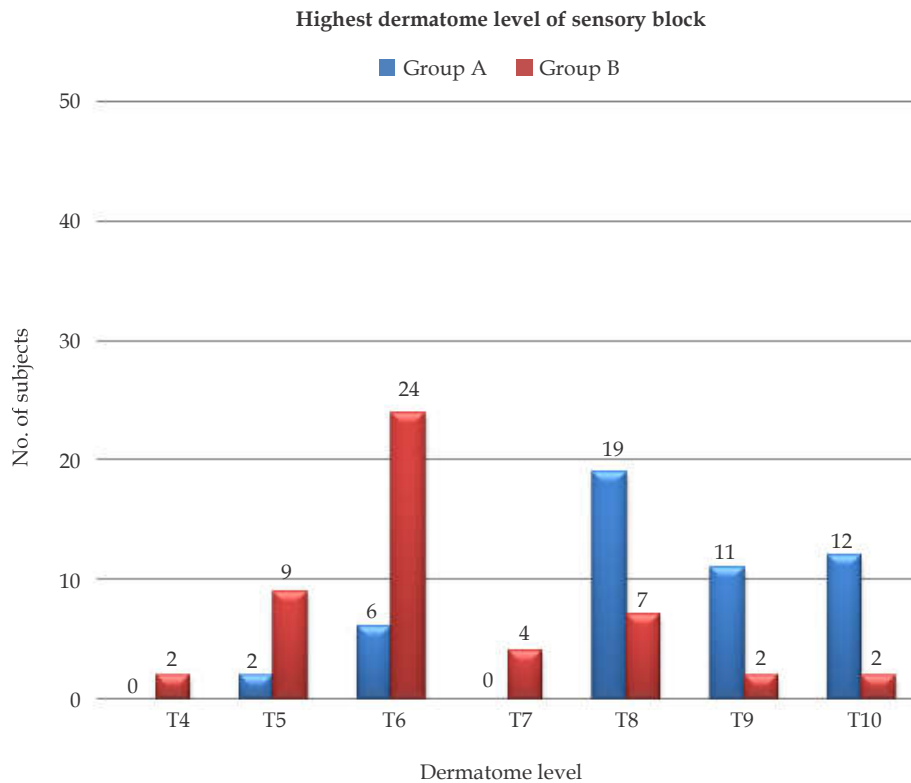
B was 113 ± 15.81 min., prolonged compared to Group A (91.48 ± 17.97 min. P < 0.001). Difference in duration of sensory block/regression time to S1 was significant. (116.7 ± 14.78 min.in Group B versus 93.7 ± 22.23 min. in Group A, P = 0.001) (Table 2, Fig. 2).

Return of voiding function was delayed in Group B (268.5 ± 35.39 min.) compared to Group A (212.2 ± 33.64 min. P < 0.001) (Fig. 2). 64% of patients achieved a 2<sup>nd</sup> degree of sensory block in Group B compared to only 40% in Group A (P = 0.028).

**Table 3:** Motor block characteristics.

Study parameters		Group A (n=50)	Group B (n=50)	P- value
Onset of motor block(min.)		3.07 ± 0.77	2.43 ± 0.61	<0.001*
Maximum motor block (modified Bromage)	Grade	Number of patients		0.126
	1	2	0	
	2	9	3	
	3	15	22	
	4	24	25	
Duration of motor block(min)		81.17 ± 26.75	97.58 ± 16.23	<0.001*
# Time of ambulation		177.6 ± 38.11 (n = 32)	180.4 ± 51.17 (n = 31)	0.808

# Patients undergoing orthopaedic surgeries were excluded, Data represented as mean ± SD, n - Number of patients. '\*\*' denotes significant P-value.



**Fig. 3:** Dermatome level achieved by the subjects.

(Table 2). Patients who couldn't achieve 2<sup>nd</sup> degree of sensory block, had no complaints of pain in either group, surgery was tolerated without discomfort, anxious patients were only motivated and explained about the short duration of surgery.

In Group B peak dermatome levels of 'T6 / T8 / T10' were achieved in '48% / 14% / 4%' of patients while in group A this value was '12% / 38% / 24%' respectively. This difference was statistically significant (P < 0.001) (Table 2, Fig. 3).

Motor block onset time in Group A was 3.07 ± 0.77 min. while in Group B it was 2.43 ± 0.61 min. (P < 0.001). Maximum motor block (modified Bromage) was comparable in both Groups. Motor

block duration in Group B- 97.58 ± 16.23 min. was significantly longer than Group A- 81.17 ± 26.75 min. (P < 0.001). No difference was noted in mean ambulation time among the Groups (P = 0.808). Patients undergoing orthopaedic surgeries (n=18 in Group A, n=19 in Group B) were excluded, for the analysis of ambulation time (Table 3).

Mean arterial pressure, arterial oxygen saturation and pulse rate were comparable and stable among both study groups intraoperatively and postoperatively. Eight patients (16%) in Group B developed pruritus compared to nil in Group A. Pruritus was self-limiting and patients were reassured (P = 0.010). All patients except those undergoing orthopaedic procedures, where



ambulation is not relevant, (total number = 37 in both the groups) were able to fulfil discharge criteria to home on the day of surgery. None of the patients had complaints of back pain, transient neurological symptoms on telephonic follow-ups after one week of anesthesia. There were no other postoperative complications in either group.

## Discussion

Recent trend is growing towards ambulatory surgeries where the goal is early recovery and fast ambulation. A combination of isobaric drug with an opioid can fulfil this goal.<sup>8</sup> The primary finding of our study was that combining 25 µg of fentanyl to 50 mg chloroprocaine for subarachnoid block prolonged sensory as well as motor block. These findings are divergent from the presumed hypothesis. Difference in sensory block characteristics which included its duration, onset, peak dermatome level achieved, degree, 2-segment regression time, duration of analgesia and post-operative return of voiding function, was statistically significant. For motor block also, onset was earlier and duration was significantly lengthened. But, maximum motor block (modified Bromage) and ambulation time were found similar in both study groups. None of the patients developed neurological or other side effects except for pruritus which was noted in 16 % of patients receiving chloroprocaine and fentanyl.

So far, chloroprocaine and chloroprocaine-fentanyl combination were compared only in one study conducted on 8 healthy volunteers using chloroprocaine in a dose of 40 mg and fentanyl 20 µg.<sup>4,7</sup> We selected higher dose of chloroprocaine (50 mg) and fentanyl (25 µg).

Onset time of sensory and motor block was substantially earlier in chloroprocaine-fentanyl group. Onsets of action of local anesthetics depend on their pKa values. Higher pKa means slower the onset of action. Chloroprocaine is an exception to this because it has the fastest onset despite high pKa (9.1).<sup>3</sup> This suggests that other factors like the ability to diffuse through connective tissues, baricity and change in baricity due to the addition of adjuncts may alter drug's onset of action.

The mean duration of analgesia was prolonged by 22 min. in fentanyl receiving patients which was statistically significant but this small duration may not of much practical importance. In chloroprocaine-fentanyl group, 64% of patients achieved a 2<sup>nd</sup> degree of sensory block compared to only 40%

of patients of chloroprocaine-saline group. Both these findings can be attributed to the synergistic action of fentanyl with local anesthetics.<sup>5</sup> Opioid-local anesthetic combination reduces transmission through both, 'A δ' (fast pain) and 'C' (slow pain) fibres.

Onset time of sensory and motor block, duration of analgesia, degree of sensory block and maximum motor block achieved, were not investigated in previous study with chloroprocaine and fentanyl.<sup>4</sup> Prolongation in an average time of the 2-dermatome regression of sensory block was divergent from the previous study, which may be attributed to the selection of a higher dose of chloroprocaine (50 mg) and fentanyl (25 µg) in our study.<sup>7</sup>

Peak dermatome level, duration of sensory and motor block, time of postoperative return of voiding function were significantly higher in chloroprocaine-fentanyl group and were consistent with findings of previous similar study.<sup>7</sup> The mean time of the return of voiding function was prolonged by 56 min. in fentanyl group which may translate to a slight delay (56 min.) in discharge. In our study it was not enough to surpass requirement of ambulatory surgery. Ambulation time was reported similar in both groups (after exclusion of patients undergoing orthopaedic procedures).

Duration of action of local anesthetics is directly related to lipid solubility and protein binding. Relative lipid solubility of unchanged chloroprocaine is 2.3 that is very low as compared to more commonly used drug bupivacaine and that is why chloroprocaine is short-acting.<sup>3</sup> It is already described in former studies that chloroprocaine has the shortest recovery profile compared with bupivacaine, lidocaine, prilocaine and mepivacaine.<sup>9,10</sup> Discharge criteria vary for different surgical procedure. In day-care surgeries discharge criteria include the return of voiding function, ability to ambulate and haemodynamic stability. In review analysis of chloroprocaine, it is obvious that the use of varying doses of chloroprocaine can result in wide variation in voiding times ranging from 95 to 271 min.<sup>4</sup> Return of voiding function depends on many factors such as preoperative hydration status, age of patient (enlarged prostate in males), type of surgery (perianal procedures, inguinal herniorrhaphy, urological procedures - can increase voiding time) and this finding can't be solely credited to use of fentanyl.

Transient neurological symptoms and respiratory depression were not seen in any of the patients of either group. It was consistent with findings of previous study combining chloroprocaine with

fentanyl, where authors didn't report any case of neurological complications even in lithotomy position with the use of spinal chloroprocaine while higher incidence was noted in lignocaine-fentanyl combination.<sup>11</sup>

Sixteen percent of participants in group B developed pruritus ( $P < 0.010$ ), itching was minimized with reassurance and judicious use of anti-pruritic therapy. Pruritus was also seen in other studies combining fentanyl with local anesthetics for spinal anesthesia and is one of the common side effects.<sup>12</sup> As with other complications of neuraxial opioids like respiratory depression, pruritus is likely dose-dependent and may need further studies.

Superiority of chloroprocaine spinal anesthesia over total intravenous anesthesia is shown in a previous study.<sup>13</sup> Recently, a multicentre observational study was conducted on 615 patients receiving chloroprocaine spinal anesthesia where authors observed chloroprocaine as a short-duration anesthetic and a strong contender for ambulatory surgeries.<sup>14</sup>

We suggest that isobaric, 50 mg 1% 2-chloroprocaine is safe and reliable for spinal anesthesia in infra-umbilical surgeries of predicted duration less than < 50 min. Fentanyl added with spinal chloroprocaine enhances the duration of postoperative analgesia and provides satisfactory operating conditions for surgeries lasting around 90 min. Isobaric chloroprocaine and fentanyl combination may be a good choice for subarachnoid block in day-care surgical procedures.

Our study is not without limitation. Addition of fentanyl was associated with prolongation of the time of the return of voiding reflex. Although prolongation in the duration of sensory block by 22 min. is statistically significant, it may not of much practical benefit. We selected a wide surgical population where an assessment of analgesia, the return of voiding reflex and ambulation time may have been confounded by type of surgeries, in turn leading to imprecision. In future, the efficacy of chloroprocaine in different dose combination with adjuvant should be investigated in a group of patients undergoing 'particular' types of surgeries.

## Conclusion

Addition of 25 µg fentanyl to 50 mg isobaric 1% 2-chloroprocaine for spinal anesthesia resulted in prolonged sensory block, duration of analgesia and motor block without prolongation of ambulation time but with delay in return of voiding reflex.

*Conflicts of interest:* Nil.

*Acknowledgement:* Nil.

## References

1. Kulkarni S, Harsoor S S, Chandrasekar M, Bhaskar S B, Bapat J, Ramdas EK, Valecha UK, Pradhan AS, Swami AC. Consensus statement on anesthesia for day care surgeries. *Indian J Anaesth* 2017; 61:110-24.
2. Alley EA, Mulroy MF. Neuraxial anesthesia for outpatients. *Anesthesiology Clin* 2014; 32:357-69.
3. John F. Butterworth, David C. Mackey, John D. Wasnick, G Edward Morgan, Maged S Mikhail. Local Anesthetics. In: Morgan and Mikhail's Clinical Anesthesiology, 5<sup>th</sup> Ed. New Delhi: McGraw Hill; 2014.p. 267-9.
4. Ghisi D, Bonarelli S. Ambulatory surgery with chloroprocaine spinal Anesthesia: a review. *Ambulatory Anesthesia* 2015; 2:111-20.
5. Nayagam HA, Singh N R, Singh H S. A prospective randomised double blind study of intrathecal fentanyl and dexmedetomidine added to low dose bupivacaine for spinal anesthesia for lower abdominal surgeries. *Indian J Anaesth* 2014; 58: 430-5.
6. John F. Butterworth, David C. Mackey, John D. Wasnick, G Edward Morgan, Maged S Mikhail. Local Anesthetics. In: Morgan and Mikhail's Clinical Anesthesiology, 5<sup>th</sup> Ed. New Delhi: McGraw Hill; 2014.p.189-90.
7. Vath JS, Kopacz DJ. Spinal chloroprocaine: the effect of added fentanyl. *Anesth Analg* 2004; 98:89-94.
8. Upadya M, Neeta S, Manissery JJ, Kuriakose N, Singh RR. A randomized controlled study comparing intrathecal hyperbaric bupivacaine-fentanyl mixture and isobaric bupivacaine-fentanyl mixture in common urological procedures. *Indian J Anaesth* 2016; 16:44-9.
9. Gebhardt V, Kiefer K, Bussen D, Weiss C, Schmittner MD. Retrospective analysis of mepivacaine, prilocaine and chloroprocaine for low-dose spinal anesthesia in outpatient perianal procedures. *Int J Colorectal Dis.* 2018; 33:1469-77.
10. Teunkens A, Vermeulen K, Van Gerven E, Fieuws S, Velde M, Rex S. Comparison of 2-Chloroprocaine, Bupivacaine, and Lidocaine for Spinal Anesthesia in Patients Undergoing Knee Arthroscopy in an Outpatient Setting: A Double-Blind Randomized Controlled Trial. *Regional Anesthesia and Pain Medicine* 2016; 41:576-583.
11. Vaghadia H, Neilson G, Lennox PH. Selective spinal anesthesia for outpatient transurethral prostatectomy (TURP): randomized controlled comparison of chloroprocaine with lidocaine. *Acta Anesthesiol Scand* 2012; 56:217-23.

12. Kumar K, Singh SI. Neuraxial opioid induced pruritus: An update. *J Anesthesiol Clin Pharmacol* 2013; 29:303-7.
13. Gebhardt V, Zawierucha V, Schöffski O, Schwarz A, Weiss C, Schmittner MD. Spinal anaesthesia with chloroprocaine 1% versus total intravenous anaesthesia for outpatient knee arthroscopy. *Euro J Anaesthesiol* 2018; 3:774-81.
14. Capdevila X, Aveline C, Delaunay L, Bouaziz H, Zetlaoui P, Choquet O et al. Impact of Chloroprocaine on the Eligibility for Hospital Discharge in Patients Requiring Ambulatory Surgery Under Spinal Anesthesia: An Observational Multicenter Prospective Study. *Adv Ther* 2020; 37:541-51.

