Chloroprocaine with or Without Fentanyl for Perianal Day Care Procedures Under Subarachnoid Block: A Randomized Controlled Study

Original Article

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ABSTRACT

Introduction: Chloroprocaine is a short acting local anesthetic with rapid onset and recovery making it a suitable for choice for spinal anesthesia in day care procedures. However, it provides little or no post-operative analgesia when administered alone. The present study aims to explore the effect of adding fentanyl to intrathecal chloroprocaine for subarachnoid block (SAB) for perianal day care surgery.

Materials and Methods: This was a prospective randomised controlled study conducted on 40 ASA I/II patients between 18-60yrs. after written informed consent. Patients were allocated in one of the two groups using a computer generated random number table. Group CF (chloroprocaine with fentanyl): received 40mg of 1% isobaric chloroprocaine with 20µg of fentanyl for SAB and Group CN (chloroprocaine): received 40mg 1% isobaric chloroprocaine with 0.4ml normal saline for SAB. Onset of drug, time to achieve maximum sensory and motor block, maximum level of sensory block and time to two dermatomal regression, request first rescue analgesic and home readiness were recorded.

Results: Patients receiving fentanyl as additive had delayed motor recovery (86.75±9.21min) compared to patients receiving chloroprocaine (78.16±10.02min) (p=0.08). Time to request of first rescue analgesic (p=0.001) and time to achieve home readiness was significantly prolonged with fentanyl addition as compared to chloroprocaine alone (88.20±07.38min and 82.74±07.89min respectively; p=0.032).

Conclusion: Addition of fentanyl provides prolonged analgesia but slightly delays motor recovery and time to achieve home readiness. Chloroprocaine with fentanyl is a safe alternative to chloroprocaine alone for patients undergoing day care procedures.

Key Words: Chloroprocaine, Day care surgery, Fentanyl, Perianal surgery.

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INTRODUCTION

Subarachnoid block (SAB) is a commonly used anaesthetic technique for day care ambulatory procedures. It has a rapid onset and offset, it is safe, reliable, cost effective and has minimal side effects making it a suitable choice for conducting ambulatory day care procedures as compared to general anaesthesia (GA)[1,2]. An ideal local anaesthetic (LA) agent for day care ambulatory procedures must have a short duration of sensory and motor block with minimal side-effects. Lignocaine, a short acting LA, was largely replaced because of the high incidence of Transient Neurological Symptoms (TNS)[3-6]. Others like bupivacaine and ropivacaine are less suitable for day care procedures because of prolonged sensory and motor blockade and postoperative urinary retention (POUR). So, there is a growing need to search for a suitable LA for day care ambulatory procedures.

Chloroprocaine is an amino-ester LA with very short half-life and was first introduced in 1952[7]. The drug was withdrawn from use due to reports of neurotoxicity[8]. Later studies found that preservative, sodium bisulphite was the culprit for these neurotoxic sideeffects[9]. Nowadays, a preservative-free solution of chloroprocaine for intrathecal administration has been reintroduced. It has been approved by the European Medical Agency (EMA) in 2013 as a spinal LA in short surgical procedures.1Since it is a very short acting drug, it provides little or no postoperative analgesia when given alone.

The aim of the study was to compare the effect of addition of 20µg fentanyl on the block characteristics, time to request for rescue analgesia and the time to achieve home readiness after administration of 40mg chloroprocaine

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intrathecally in patients undergoing perianal surgery under subarachnoid block.

METHODS

This study was conducted after obtaining approval from the Institutional Ethical Committee. The trial was registered with clinical trials registry (CTRI/2017/12/010811) before enrolling the participants. It was a prospective randomised, double blind study conducted between November 2017 to April 2019.

A total of 40 ASA I and II patients between 18 and 60 years undergoing elective perianal surgeries were included. Non-consenting patients, those with known hypersensitivity to local anaesthetics or fentanyl or having contraindication to SAB like coagulation disorders, local site infection, raised intracranial tension, on antiplatelet therapy, etc. were excluded from the study.

During the pre-anaesthetic check-up, patients were introduced to the concept of visual analogue scale (VAS) for pain assessment. The patients were kept fasting overnight. They were pre-medicated with alprazolam 0.25mg orally night before and morning of surgery. In the operating room, monitors including ECG, pulse oximeter, non-invasive blood pressure were attached. Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded and intravenous (IV) access was secured with 18G cannula. Preloading with 10ml/kg of intravenous Ringer lactate solution was done.

Patients were randomly allocated to one of the two groups using a computer-generated random number table. Group CF (chloroprocaine with fentanyl) received 40mg of 1% isobaric chloroprocaine with 20µg of fentanyl intrathecally and Group CN (chloroprocaine) received 40mg 1% isobaric chloroprocaine with 0.4ml normal saline intrathecally for subarachnoid block. Volume of the drug administered in both the groups was 4.4ml. Allocation concealment was done using sequentially numbered sealed opaque envelopes. The study drug solutions were prepared by an anaesthesiologist who was not involved in study.

SAB was performed, under all aseptic precautions via midline approach at L3-L4/L4-L5 vertebral interspace in the sitting position with 25G Whitacre needle. The patient was made supine immediately after the Intrathecal injection was complete and this time was noted as T_0.

Sensory block was assessed by the loss of pinprick sensation to 26G hypodermic needle every 2min from T_0 for the first 10min, then every 5min intra-operatively. The onset of block was defined as the time from T_0 to the loss of pinprick at T_{12} dermatome. The maximum level of sensory block was taken as the loss of pin prick at the highest dermatomal level for two consecutive observations and was noted as S_{max}. The time to achieve S_{max} from T_0 was noted as T_{max}. Further assessments in the post-operative period were performed every 15min for 60min. Time for two dermatomal regression was calculated from the time of attaining maximum block height (T_{max}) to regression by two dermatomes (T_{2d}).

The intensity and quality of the motor block were assessed using the Modified Bromage Scale, at the same time points as mentioned above. (Grade I-Complete block (unable to move feet or knees); Grade II-Almost complete block (able to move feet only); Grade III-Partial block (just able to move knees); Grade IV-Detectable weakness of hip flexion while supine; Grade V-No detectable weakness of hip flexion while supine; Grade VI-Able to perform partial knee bend).

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at T_0 followed by every 5min for first 30min and then every 10min till the completion of surgery. Postoperatively, haemodynamic parameters were recorded every 15min till home-readiness.

Hypotension was defined as a 20% decrease in SBP from the baseline or <90mmHg and was treated with fluids and vasoactive drugs (mephentermine 6mg iv). Bradycardia was defined as HR less than 50/min and was treated with 0.6mg atropine iv. Pain score was evaluated every 15min in the post-operative period using a 0-10cm Visual Analogue Scale (VAS) where zero represents no pain and 10 represents the worst imaginable pain. Duration of sensory block was defined as the time from making the patient supine to the request of first analgesic dose (when VAS ≥3). Rescue analgesia was given in the form of paracetamol 1gm iv when the patient had VAS ≥3. This time was noted as T_{res}.

In the post-operative period, when the modified Bromage Score was VI, the clinical recovery criteria for home-readiness (stable vital signs, within 20% of the baseline; ability to walk with crutches; ability to tolerate liquids by mouth; absence of nausea or pain) were assessed every 15min. Once all the criteria were met, the patient was considered eligible for home readiness[10-12]. Side effects like bradycardia, hypotension, nausea, vomiting, pruritus, urinary retention and shivering were noted and treated accordingly.

Sample size calculation and statistical analysis:

According to a previous study[13], to estimate a difference of 24min in time to regression to L1 with a standard deviation of 7min with the addition of fentanyl to chloroprocaine and 19min with chloroprocaine alone, a minimum of 8 patients were required in each group, at α=0.05 and power= 90%. Also, to estimate a difference of 9min in complete regression of the block with standard

deviation of 7min and 9min with and without the addition of fentanyl to chloroprocaine[13], a sample size of 17 cases was required in each group at α= 0.05 and power= 90%. To account for failures and dropouts, 20 cases per group were included. Normal distribution of quantitative data was tested using Kolmogorov-Smirnov test. Normally distributed quantitative data was compared using unpaired *t*-test and non-normally distributed data was compared using Mann-Whitney *U* test. Repeated measures ANOVA was used to compare the hemodynamic variables followed by Dunnet's test and Tukey's test for intragroup and intergroup analysis respectively. A *p*-value <0.05 was considered significant. All the statistical analysis was carried out in SPSS program for Windows, version 20.0.

RESULTS

A total of 46 patients were enrolled in the study. Out of these five cases were excluded as they did not meet the inclusion criteria and one patient did not give consent to participate in the study. The remaining 40 patients were then randomly assigned to one of two groups comprising of 20 patients each. One patient in the CN group had a failure of SAB, resulting in a total of 39 cases being analysed (Figure 1).

The demographic profile and the duration of surgery were comparable in two groups (Table 1).

The sensory and motor block characteristics are given in Table (2).

Time to request of first rescue analgesic and time to achieve home readiness was significantly longer in group CF (Table 3).

Haemodynamic parameters like heart rate (Figure 2) and blood pressure (Figure 3) were comparable at all times between two groups intraoperatively. None of the study patients developed bradycardia (HR <50 bpm) or severe hypotension (SAP <90 mm Hg).

Incidence of side effects was also comparable between two groups (Table 4).

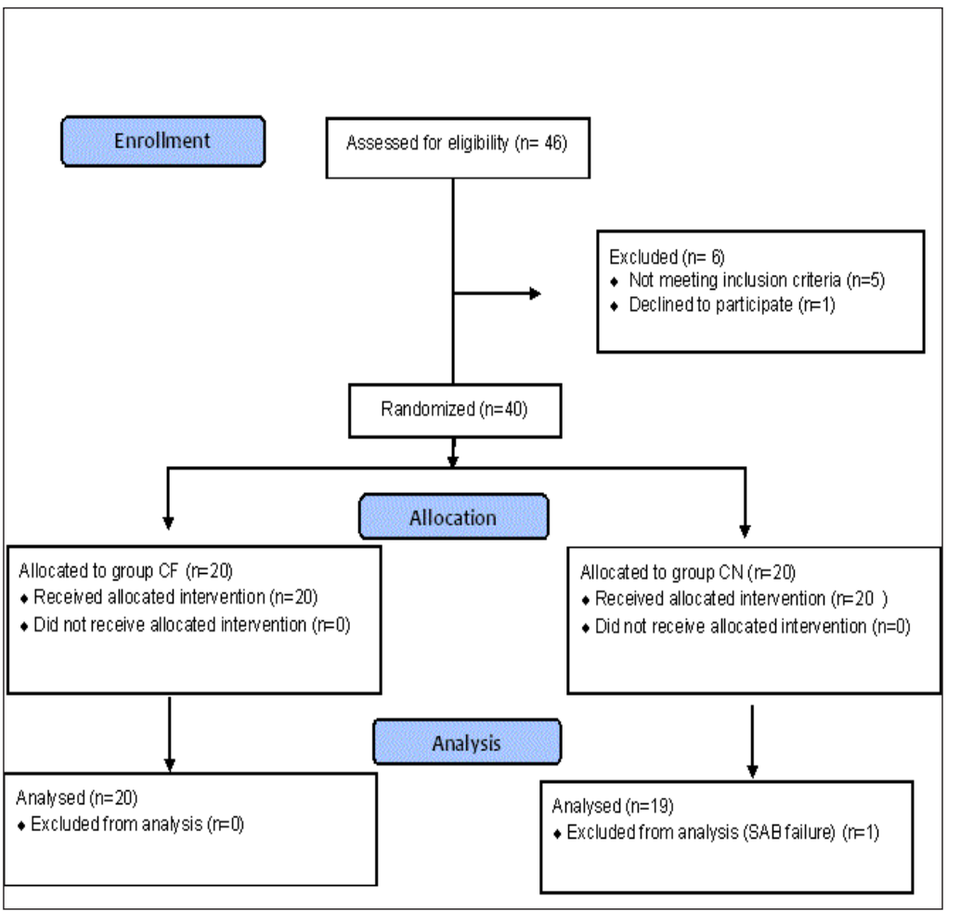

Figure 1: Consort Flow Diagram.

Table 1: Demographic profile and duration of surgery in two groups:

Parameter	Group CF (*n*= 20)	Group CN (*n*= 19)	*p*-value
Age (years)	35.70±12.61	34.63±11.98	0.788
Weight (kg)	67.75±9.71	64.79±10.79	0.361
Height (cm)	165.4±5.57	166±6.07	0.750
Sex Ratio (Male:Female)	18:2	17:2	
Duration of surgery (min)	50±13.76	51.58±17.56	0.756

Values are represented as Mean±SD (age, weight, height and duration of surgery) or ratio(sex ratio); *P*-value <0.05 is considered significant.

Table 2: Demographic profile and duration of surgery in two groups:

Parameter	Group CF (*n*= 20)	Group CN (*n*= 19)	*p*-value
Onset of sensory block (min)	4.25±4.52	4.21±2.64	0.974
Time to achieve maximum sensory block height (min)	12.20±5.63	10.84±4.90	0.428
Maximum level of sensory block $^{\epsilon}$	T8[T6-T8]	T8[T6-T10]	0.248
Time to achieve maximum motor block (min)	10.90±05.51	12.16±05.39	0.476
Time to 2 dermatomal regressions (min)	41.0±10.2	39.21±10.84	0.599
Time to achieve complete motor recovery (min)	86.75±09.21	78.16±10.02	0.008*

Values are represented as Mean±SD or Median [IQR]; *P*-value <0.05 is considered significant (*).

Table 3: Time to First Rescue Analgesic and Home readiness:

Parameter	Group CF (*n*= 20)	Group CN (*n*= 19)	*p*-value
Time to First Rescue Analgesia (mins)	108.95±13.01	86.68±10.85	<0.001*
Time to achieve home readiness (min)	88.20±07.38	82.74±07.89	0.032*

Values are represented as Mean±SD; *P*-value <0.05 considered significant (*).

Table 4: Incidence of side effects in the two groups:

Side-effects	Group CF (*n*= 20)	Group CN (*n*= 19)
Pruritus	2(10%)	0
Nausea	0	0
Vomiting	0	0
Shivering	1(5%)	2(10.5%)
Urinary retention	0	0

Values are represented as number of patients in each group (percentage in the respective group).

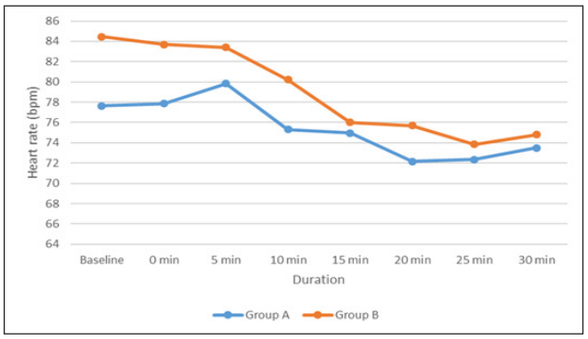

Figure 2: Heartrate (Intraoperative).

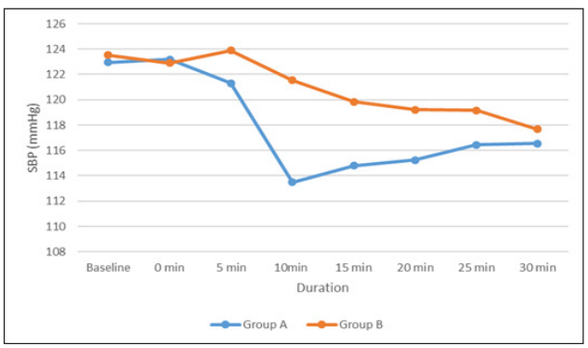

Figure 3A: Systolic Blood Pressure (Intraoperative).

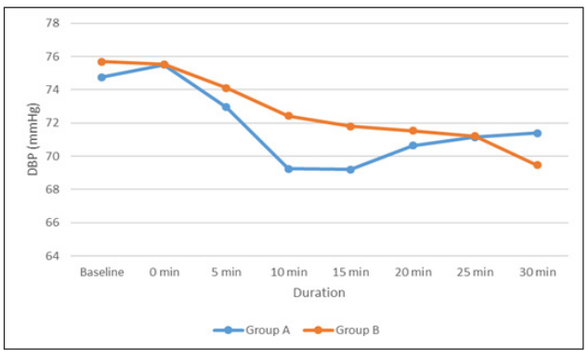

Figure 3B: Diastolic Blood pressure (Intraoperative).

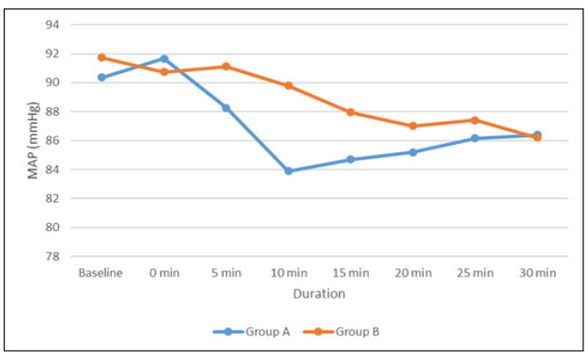

Figure 3C: Mean Arterial Pressure (Intraoperative).
MAP: Mean Arterial Pressure.

DISCUSSION

With the increasing number of surgical procedures being conducted on day care basis, there is a need for an appropriate anaesthesia technique. An ideal technique should have rapid onset, short duration of action, quick and predictable recovery, better safety and should provide good postoperative analgesia. The pharmacological properties of Chloroprocaine make it suitable for use in such cases[1]. However, it does not provide any postoperative analgesia. Addition of opioids as adjuvants to local anaesthetics is known to prolong the duration of postoperative analgesia[14-16]. So, this study was aimed to determine whether chloroprocaine with fentanyl was better than chloroprocaine alone for day care procedures.

We found that the addition of fentanyl to chloroprocaine did not affect the onset of sensory block, time to achieve the maximum level of sensory block, time to achieve maximum motor block and time to two dermatomal regression. However, there was a statistically significant, prolongation in the time to request of first rescue analgesic, time to achieve complete motor recovery and time to achieve home readiness.

Studies have shown that addition of fentanyl to local anaesthetics does not affect the onset of sensory block[16]. In the study by Vaghadia *et al.,*[17], the median time of onset of sensory block of chloroprocaine with fentanyl (12.5µg) was 4.1min (1.6-16.5min) as compared to 2min (1-20min) in our study. The onset action of the drug was faster in our study probably due to the higher volume of intrathecal solution used. The results from many other studies cannot be compared to our study because of different definition of onset of block used[12,18-20].

Various clinical trials have reported that the maximum level of sensory block with chloroprocaine 40mg was up to the mid-thoracic level between T7-T10[12,13,19,21], and few reported higher thoracic levels up to T4 and T5 also[20,22]. Few available studies with chloroprocaine-fentanyl combination have shown the maximum height of sensory block was between T5 and T8[13,17]. The results of our study are in concurrence with these studies. The addition of fentanyl did not affect the maximum level of sensory block.

The mean time to achieve maximum level of sensory block was earlier in our study as compared to many previous studies[13,18,21,22]. This difference could be due to the larger volume of intrathecal drug administered in our study i.e., 4.4ml compared to 2.0 to 2.25ml in the previous studies. Vath *et al.,* found that addition of fentanyl did not affect the time to reach the peak block height[13]. This finding was similar to our study. However, the time to peak height was longer (17±6min) in their study as they administered a lower volume of drug i.e., 2.4ml compared to 4.4ml in our study (CF group: 10.84±4.90min).

The mean time to two dermatomal regression with chloroprocaine has been reported as 50±18min,18 45±8min13 and 40±10min[22] in various studies. The time to two dermatomal regression found in our study (CN group: 39.21±10.84min) was similar to Vath *et al.,*[13], and Warren *et al.,*[22]. Our findings on the mean time to two dermatomal regression were also similar to the findings of Vath *et al.,*[13].

We also found that the time to achieve maximum motor block was not affected by addition of fentanyl. Our results were consistent with the study of Yoos *et al.,*[21]. Other authors who studied the chloroprocaine-fentanyl combination have not reported this parameter. However, studies done with other local anaesthetics have shown that addition of fentanyl does not affect the time to achieve maximum motor block[14].

Previous studies report the mean time for motor recovery with chloroprocaine alone to range from 67±13min[13], 76±25min[18], 78±20.4min[19], 91±14min[21]. Our results are similar to these findings. We also found that the addition of intrathecal fentanyl resulted in a statistically significant (p= 0.008) but clinically insignificant increase in the time for complete motor recovery (86.75±9.21min). Similar time was reported by Vath et al also (81±16min)[13].

The definition of duration of sensory block varied from one study to another. Previous studies have found that the mean sensory block duration with chloroprocaine 40mg ranged between 95-113min[13,19,21,22]. In our study, we found that the mean duration of sensory block was 86.68±10.85min in CN group, which is shorter than these studies. This was probably because of the lower concentration of chloroprocaine i.e., 1% in our study versus 2% used in the previous studies. Vath *et al.,* reported that the addition of fentanyl (20µg) significantly prolonged the complete regression of sensory block with chloroprocaine (40mg) in volunteers[13]. Our results are similar to their findings where the duration of sensory block in chloroprocaine-fentanyl combination was significantly longer than chloroprocaine alone (p<0.001).

There is a large variability in time of home discharge reported by various researchers[12,13,18,23]. As per the study by Vath *et al.,* this was as early as 95±9min[13] but according to Lacasse *et al.,* it was as late as 225±56min[18]. The longer time taken for achieving home discharge was probably due to the more stringent discharge criteria set in their study, which included unassisted ambulation and spontaneous voiding. We observed only ambulation with crutches and voiding was a discharge criterion in our study. This may be the reason of shorter time to discharge and home readiness found in our study. As previously reported[13], addition of fentanyl to chloroprocaine resulted

in a statistically significant increase in the time to home readiness. However, clinically this difference was only around 6 minutes.

All patients remained haemodynamically stable throughout the intraoperative period (Figures 2 and 3). Within group variability can be attributed to the sympathectomy as a result of subarachnoid block. Incidence of adverse effects was limited to shivering in three patients (two in CN group and one in CF group) and pruritus in two patients in combination group. Shivering tends to occur in patients undergoing surgery either under SAB or GA24 but the addition of intrathecal opioids is known to decrease the incidence of shivering[24-26]. Pruritus is also a known side effect of intrathecal opioids[27-29].

Our study has a few limitations. The discharge criteria in the study did not include time to unassisted ambulation and spontaneous voiding. This was because the patients in our study were shifted to a postoperative ward and were not discharged from the hospital after meeting the criteria for home readiness. Thus the time to achieve home readiness was quite early compared to other studies in literature. For the same reason cost-analysis could not be done. As there was no follow up questionnaire, the incidence of TNS could not be studied.

CONCLUSION

From the above findings, we conclude that 20µg fentanyl added to intrathecal 40mg 1% chloroprocaine provided good post-operative analgesia with only a small and insignificant delay in the time to achieve home-readiness without significant haemodynamic alterations compared to 40mg chloroprocaine alone in patients scheduled for perianal day care procedures under subarachnoid block.

LIST OF ABBREVIATIONS

SAB: Subarachnoid Block; **GA:** General anaesthesia; **LA:** Local anaesthetic agent; **TNS:** Transient neurological symptoms; **POUR:** Postoperative urinary retention; **PDPH:** Post-dural puncture headache; **CP:** Chloroprocaine; **CN:** Chloroprocaine + Normal saline; **CF:** Chloroprocaine + Fentanyl; **EMA:** European medical agency; **VAS:** Visual Analog Scale; **IV:** Intravenous; **IT:** Intrathecal; **ASA:** American society of Anaesthesiologists; **SPSS:** Statistical package for social sciences; **ANOVA:** Analysis of variance; **SD:** Standard deviation; **HR:** Heart rate; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **MAP:** Mean arterial pressure.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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