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Original Article

Anaesthesia Section

Comparison of Bupivacaine and 2-Chloroprocaine with and without Fentanyl for Subarachnoid Block in Inguinal Hernia Repair Surgery: A Randomised Controlled Study

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ABSTRACT

Introduction: Providing an adequate intraoperative anaesthesia with a prolonged pain-free interval is the prime priority of an anaesthesiologist. Since the decline in use of 2-chloroprocaine in 1956, due to side-effects of its preservative sodium bisulfite, the preservative free drug has recently witnessed a comeback in clinical practice.

Aim: To compare the efficacy of bupivacaine and 2-chloroprocaine with and without fentanyl in subarachnoid block for inguinal hernia repair surgery.

Materials and Methods: This randomised controlled study was carried out on 102 male patients of 18-65 years of age, American Society of Anesthesiologists (ASA) grade I or II, scheduled for inguinal hernia repair. The study was conducted from May 2019 to November 2020. The patients were randomly divided into three groups of 34 each. In group A, the subarachnoid block was administered with injection 0.5% bupivacaine (H) 10.5 mg. In group B, patients were administered, injection 2-chloroprocaine 40 mg diluted with 0.5 mL of saline. In group C, the patients were administered with injection 2-chloroprocaine 40 mg with 25 µg of injection fentanyl (0.5 mL). The adequacy of intraoperative anaesthesia in terms of onset and duration of sensory and motor blockade, haemodynamic parameters, postoperative urinary retention and other side-effects were evaluated. The parameters were compared using Analysis of variance test (>2 groups). If statistically significant difference was found in ANOVA, appropriate post-hoc (LSD/Bonferroni) was used to assess statistical significance of pair-wise comparisons.

Results: The mean time of onset of the motor and sensory block was faster in group B (3.57±0.66, 2.68±0.58 min), by almost 1 minute than in the bupivacaine and fentanyl group (4.57±0.79, 3.59±0.61 min) (4.99±1.01, 4.04±0.99 min) respectively. The mean difference was statistically significant (p-value <0.05). The mean duration of the motor and sensory blocks between the groups revealed statistically significant difference between groups A and B as well as groups A and C. However, between groups B and C, there was no significant difference as far as motor block duration is concerned. Group B had significantly shorter duration of the motor and sensory block amongst the three groups.

Conclusion: Addition of intrathecal fentanyl significantly prolonged the onset and duration of sensory and motor block, with minimally extending the time to complete recovery.

Keywords: Haemodynamic parameters, Motor and sensory block, Onset and duration, Postoperative urinary retention

INTRODUCTION

An ever-increasing number of day-care surgical procedures is challenging the conventionally used drugs and methods of anaesthesia. Reliable surgical anaesthesia should be fast, with rapid recovery and minimal side-effects. To produce reliable spinal anaesthesia with a reasonable recovery time, it is essential to choose the optimal drug and adequate dose for specific surgical procedures. These challenges can be reduced by the use of short acting, rapid onset drugs. A 2-chloroprocaine has seen resurgence in interest as a short-acting local anaesthetic, now that preservative-free preparations are available [1]. Due to its rapid metabolism by ester hydrolysis, it is a favourable drug in short-duration surgeries.

A variety of adjuvants, such as opioids (buprenorphine, fentanyl) and α_2 agonists (clonidine) have been used with Chloroprocaine to improve the quality of surgical block with minimum side-effects on the patients and to increase the quality of analgesia post operatively. Co-administration of opioids with central neuraxial local anaesthetics results in synergistic analgesia. Neuraxial administration of lipophilic opioids, such as fentanyl and sufentanil, provides a rapid onset of analgesia, and their rapid clearance from CSF may limit cephalic spread [2].

A dose of 25 µg fentanyl for intrathecal administration was chosen for this study. The study aimed to compare the effect of addition of fentanyl to chloroprocaine on the duration and quality of subarachnoid block for inguinal hernia surgeries, bupivacaine being a conventional local anaesthetic will be taken as a controlled group.

The primary objective was to compare the efficacy in terms of onset and duration of sensory and motor blockade and intra-operative haemodynamic parameters in each group. The secondary objective was to compare the side-effects or any complications in each group.

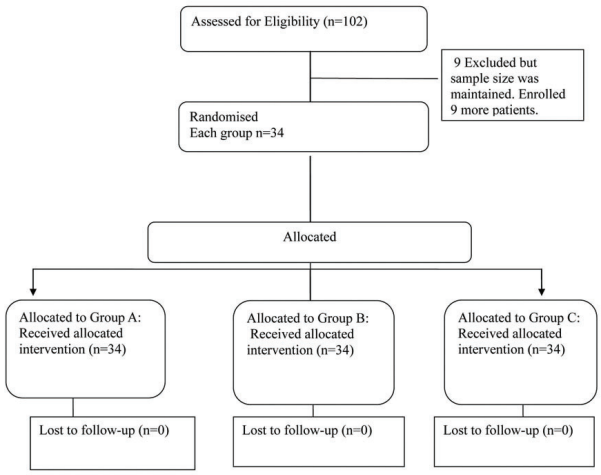
MATERIALS AND METHODS

This was a randomised controlled trial, conducted from May 2019 to November 2020. After approval from Institutional Ethical Committee (BPSGMCW/RC413/IEC/19), 102 male patients, admitted in BPSGMC (W), Khanpur, Kalan, Sonepat, Haryana, India were enrolled for the study [Table/Fig-1].

Block randomisation with a block of six subjects was taken with equal allocation to each intervention arm. So, a total of 17 blocks were taken. All possible permutations and combination of a block of six was derived and each time the block was chosen by lottery method.

Inclusion criteria: Male patients between the age of 18-65 years of age were included of ASA grade I and II, who were posted for unilateral inguinal hernia repair.

Exclusion criteria: Patients who were unwilling, were excluded. Other exclusion criteria were: patient with spine deformity, localised sepsis and raised intracranial pressure. Patients with impaired mentation, significant neurological, psychiatric, neuromuscular, cardiovascular,



[Table/Fig-1]: CONSORT flow chart.

pulmonary, renal or hepatic diseases. Female patients and patients that were morbidly obese or patients with coagulation disorders were excluded too.

Sample size calculation: Total 102 patients were divided into three groups of 34 each. The sample size was calculated based on previous study by using nMaster 2.0 software. Sample size was based on clinical trial with parallel design using superiority margin 25 minutes with the power of study being 80% and alpha error at 5%. The sample size was calculated to be 34 patients in each group [3-5].

After a thorough Pre-Anaesthetic Check-Up (PAC) and obtaining informed written consent, patients were made to fast for six hours prior to surgery. Patients were shifted to the operation theatre and i.v line were secured. Standard peri-operative monitoring was done.

Under all aseptic precautions, sub-arachnoid block was given in L_3-L_4 interspinous space, using 25G Quinke's needle, via midline approach in sitting position after local skin infiltration with 2 mL of 2% lidocaine. With free flow of CSF, group A received 10.5 mg of 0.5% bupivacaine, group B received 40 mg of 2-chloroprocaine diluted with 0.5 mL of normal saline and group C received 40 mg 2-chloroprocaine and 25 µg of fentanyl. Surgery was started after confirmation of a sensory level of T6. Injection midazolam 0.05 mg-0.075 mg/kg was given for adequate sedation. Oxygen was supplied by polymask @ 6L/min.

When adequate sensory (T6 level) and motor (Modified Bromage score 3) blockade was not achieved even after 10 minutes, General Anaesthesia (GA) was considered and patients were excluded from the study. In this study, total nine patients (three in the bupivacaine group, four in the chloroprocaine group and two in the chloroprocaine with fentanyl group) were excluded from the study because of failed blocks and due to insufficient anaesthesia (had to be administered GA to complete the surgery). The authors enrolled nine more patients to maintain the sample size of 102 as per protocol.

If regression of sensory level from T6 to T8 occurred or the patient complained of pain anytime during the course of surgery, GA was given. Time of completion of the block was taken as time 0 and onset of sensory and motor block was measured there on. Block characteristics, haemodynamic parameters and side-effects were monitored. Pulse rate, non- invasive blood pressure, respiratory rate, oxygen saturation was recorded at every 5-minute interval for the first 30 minutes and at 15 minutes interval thereafter, till the end of the surgery.

Sensory Block

Patients were assessed for loss of pinprick sensation to a 22-gauge needle for every two minutes interval for first 10 min then every five minutes till complete surgical anaesthesia. The onset of the sensory block was taken with the abolition of pin prick sensation. Full regression of the sensory block was defined as regression to the S2 dermatome.

Motor Block

Patients were assessed for motor block at two minutes interval for 10 minutes. The motor block was assessed using the Modified Bromage Scale in both the groups [6].

Duration of the motor blockade was the time from the onset of motor blockade to complete recovery of motor power. Surgery was allowed to begin once full surgical anaesthesia was established. Patients were monitored for pain using Visual Analogue Scale (VAS) on a 10-cm line where mark "0" means "no pain" and mark "10" meant "severe pain." Pain score was recorded every 30 minutes during surgery.

Postoperatively, patients were monitored for hypotension, nausea, vomiting, paraesthesia, prolonged motor blockade, urinary retention, nerve palsies, etc. Any complications observed during intraoperative or postoperative period were noted and managed as per standard protocols.

Transient neurological symptoms were defined as lower back pain radiating from the gluteal region to the lower extremities. The incidence of Transient neurological syndrome was recorded at the time of discharge from the hospital and 24 hour postoperatively [7].

Duration of analgesia was calculated from the time of the onset of sensory block till the patient complained of pain. Analgesia was given with inj. paracetamol i.v 1 gm.

STATISTICAL ANALYSIS

For normally distributed Quantitative parameters the mean values were compared between study groups using Analysis of variance test (>2 groups). If statistically significant difference was found in ANOVA, appropriate post-hoc test (LSD/Bonferroni) was used to assess statistical significance of pair wise comparisons. Categorical outcomes were compared between study groups using Chi-square test. The p-value <0.05 was considered statistically significant. IBM Statistical Package for the Social Sciences (SPSS) version 22.0 was used for statistical analysis.

RESULTS

A total of 102 male subjects were included in the final analysis. Demographic parameters and ASA grading were comparable in all groups. There was no statistically significant difference in the various vital parameters (i.e., hearts rate, respiratory rate, systolic blood pressure, diastolic blood pressure, SpO_2) measured preoperatively, intraoperatively and postoperatively at various intervals amongst the three groups. As per the study protocol, the intraoperative visual analog scale (VAS) was maintained at <3 and there was no significant difference in the intraoperative VAS scores between the three groups.

Pair-wise comparison of the mean duration of motor and sensory blocks between the groups revealed statistically significant difference between groups A and B and groups A and C. However, between groups B and C, there was no significant difference as far as motor block duration was concerned. Group B had significantly shorter duration of motor and sensory block amongst the three groups [Table/Fig-2-6].

Parameters	Group A	Group B	Group C	p-value (ANOVA)
Heart rate (beats per minute)	75.29±12.69	77±14.88	79.91±14.28	0.391
Systolic blood pressure (mm of Hg)	122.12±10.49	120.91±10.28	123.06±8.84	0.670
Diastolic blood pressure (mm of Hg)	71.68±8.04	72.24±6.08	70.15±8.53	0.507
SpO_2	98.82±0.72	98.71±0.58	98.91±0.62	0.164
Respiratory rate (breath per minute)	18.19±3.1	16.88±3.08	17±3.04	0.179

[Table/Fig-2]: Comparison of mean intraoperative vitals in each group.

Type of block	Study group			p-value post-hoc test
	Group A	Group B	Group C	
Sensory (min)	3.59±0.61	2.68±0.58	4.04±0.99	<0.001
Motor (min)	4.57±0.79	3.57±0.66	4.99±1.01	<0.001

[Table/Fig-3]: Comparison of mean onset of sensory and motor block. (ANOVA)

Block duration	Study group			p-value post-hoc test
	Group A	Group B	Group C	
Sensory (min)	209.94±51.76	100.68±25.51	133.65±8.71	<0.001
Motor (min)	192.29±47.59	92.56±24.31	107.74±11.52	<0.001

[Table/Fig-4]: Comparison of mean duration of motor/sensory block across the study groups.

Pair wise comparison of block duration (min)	Mean difference	95% CI		p-value
		Lower	Upper	
A vs B	109.27	93.05	125.48	<0.001
A vs C	76.29	60.08	92.51	<0.001
B vs C	32.97	16.75	49.19	<0.001

[Table/Fig-5]: Pairwise comparison of mean duration of sensory block across the study groups.
Post-hoc test

Pair wise comparison of block duration (min)	Mean difference	95% CI		p-value
		Lower	Upper	
A vs B	99.74	84.55	114.92	<0.001
A vs C	84.56	69.37	99.75	<0.001
B vs C	15.18	-0.01	30.36	0.05

[Table/Fig-6]: Pairwise comparison of mean duration of motor block across the study groups.
Post-hoc test

Two patients in group A (5.88%) showed postoperative complication of urinary retention, which required catherization and resolved within 48 hours. No other postoperative complications were reported [Table/Fig-7].

Intraoperative complications	Study group		Group C (N=34)
	Group A (N=34)	Group B (N=34)	
Nil	34 (100%)	34 (100%)	30 (88.24%)
Pruritis	0 (0%)	0 (0%)	4 (11.76%)
Nil	32 (94.12%)	34 (100%)	34 (100%)
Urinary retention	2 (5.88%)	0 (0%)	0 (0%)

[Table/Fig-7]: Comparison of intra and postoperative complications across study group.

DISCUSSION

The current study shows that spinal anaesthesia performed with 40 mg of plain 1% chloroprocaine provides adequate anaesthesia for inguinal hernia repair surgeries lasting less than 50 minutes. However, with an adjuvant like fentanyl, it can be used for procedures lasting more than 50 minutes.

The mean time of onset of the motor and sensory block was faster in group B, by almost one minute than in the bupivacaine and fentanyl group. The mean difference was statistically significant. (p-value <0.05). Camponovo C et al., found that the mean time to motor block was 5 minutes in the chloroprocaine and six minutes in the bupivacaine group [8]. In the study by Mishra M et al., the mean time of onset of sensory and motor blockade showed no significant differences between the groups [3]. The variability in the results may be due to the difference in sample size in this study. Local anaesthetic activity is determined by pKa, lipid solubility and protein binding. It is the pKa that determines the onset of action, as it is the unprotonated form that crosses the nerve plasma membrane. Chloroprocaine is an exception to this rule. In spite of a high pKa, it is faster onset could be attributed to the higher doses which are used with minimal risk of systemic toxicity [9].

The total duration of the sensory block in group A was almost two times that of group B. Camponovo C et al., observed that 50 mg of plain 1% chloroprocaine led to a faster resolution of the sensory block as compared to 10 mg of bupivacaine {105 (60-194) min vs 225 (130-442) min} [8]. In another study, conducted by Lacasse MA et al., the duration of the sensory block was almost 2.3 times more in the bupivacaine group than in the chloroprocaine group [4]. Teunkens A et al., in their double blind randomised controlled trial, compared chloroprocaine, bupivacaine and lidocaine for spinal anaesthesia for outpatient surgeries [5]. They observed, that the time to recovery from sensory block was the fastest in the chloroprocaine group and the longest in the bupivacaine group. Both the studies were in concordance to this study. Protein binding determines the duration of the block, with highly protein bound molecules such as bupivacaine exhibiting a longer duration of action than lesser protein bound molecules such as chloroprocaine. Chloroprocaine has the lowest protein binding of all clinically used local anaesthetics, a probable mechanism for its short duration of action. Chloroprocaine is rapidly metabolised by pseudocholinesterase. The rapid metabolism also leads to quicker recovery [9].

Addition of fentanyl as adjuvant to 2-chloroprocaine prolonged the mean duration of the sensory block of chloroprocaine by 30 minutes in the group C (133.65±8.71 mins). This was in concordance, with the study conducted by Vath JS and Kopacz DJ in which complete block regression of chloroprocaine was prolonged with the use of fentanyl [10]. Walker SM et al., and Singh H et al., in their studies have similarly demonstrated a synergistic relationship between opioids and local anaesthetics in analgesia [11,12]. Although intrathecal local anaesthetics are nonselective in their blockade of afferent and efferent pathways, the addition of opioids has an effect on the afferent nociceptive fibers without an effect on sympathetic efferent fibers. Fentanyl is able to depress C-fiber reflexes alone, whereas the opioid-local anaesthetic combination results in depression of both Aδ and C reflexes without efferent effect, a probable mechanism for the prolongation and effectiveness of the block [11].

Campanovo C et al., compared 1% chloroprocaine 50 mg with 10 mg of bupivacaine. The mean duration of complete motor block 2 times in the bupivcaine group [8]. Vath JS and Kopacz DJ compared chloroprocaine with and without fentanyl. They concluded that the mean duration of complete motor block duration was 104±7 minutes in the fentanyl group and 95±9 in the chloroprocaine group [10]. Lacasse MA et al., compared 40 mg of chloroprocaine and 7.5 mg (0.75%) bupivacaine. They observed that the total duration of motor block was 76 minutes in the chloroprocaine group and 119 minutes in the bupivacaine group [4]. Teunkens A et al., conducted a double blind randomised controlled trial to compare chloroprocaine, bupivacaine and lidocaine for spinal anaesthesia in patients undergoing knee arthroscopy in an outpatient setting. They concluded that among the three groups chloroprocaine group had the fastest offset time [5].

In this study, 4 out of 34 patients in group C, complained of pruritus in the intraoperative period which was not significant enough and required no treatment. Incidence of pruritis was also observed in the study done by Vath JS and Kopacz DJ [10,13]. In the bupivacaine group, two patients were catheterised because of urinary retention in the postoperative period. Gys B et al., compared the effect of prilocaine, chloroprocaine and bupivacaine for abdominal wall herniorrhaphy. Their study concluded that Bupivacaine had a rather slow recovery with a risk of urinary retention than 2-chloroprocaine [14]. Urinary retention following spinal anaesthesia is well documented in the literature, and its incidence in the overall surgical population was found to be around 3.8% in a study conducted by Baldini G et al., [15]. Identification of risk factors for urinary retention in this population has resulted in discrepant conclusions.

In this study, no obvious case of Transient neurological syndrome was reported in the observation period. This finding further confirms, the lack of neurotoxicity of the preservative-free chloroprocaine formulations, as was observed in the study using, 1% chloroprocaine by Palas T, in 2000 patients undergoing various surgeries. They concluded that, with the use of chloroprocaine adequate surgical anaesthesia can be achieved without any signs of TNS [16]. No incidence of TNS with chloroprocaine, in over 4,000 patients was reported by Eberhart LH et al., when compared with lidocaine or Bupivacaine [17].

Limitation(s)

Since the study was performed in a small geographical location, the results of this study may not be representative of population in different geographic location. The impact of patient related risk factors such as obesity and age on the duration of the motor and sensory blockade could not be studied. Identification of these individual risk factors for difference in duration of the blockade may have warranted a much larger sample size.

CONCLUSION(S)

Chloroprocaine is an attractive alternative to low dose bupivacaine for spinal anaesthesia in patients undergoing inguinal hernia repair surgeries lasting less than 50-minutes. Use of 2-chloroprocaine as a sole anaesthetic agent in spinal anaesthesia provides a rapid onset of sensory and motor blockade when compared to low dose bupivacaine, however some degree of pain in later stages of surgeries is a possibility. Moreover, addition of fentanyl as an adjuvant to chloroprocaine during intrathecal administration prolongs the duration of the blockade and improves the quality of analgesia, thereby, obliviating the need for GA in such scenarios.

The use of chloroprocaine is associated with fewer post operative side-effects like urinary retention in comparison to low dose bupivacaine. Hence, chloroprocaine may be safely used for ultrashort and short ambulatory surgeries with a time interval lasting ≤60 minutes, however, for surgeries with a longer duration, bupivacaine still remains the local anaesthetic of choice for intrathecal administration.

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