Original Article

A comparative study on the effect of addition of intrathecal buprenorphine to 2-chloroprocaine spinal anesthesia in short duration surgeries

Jayaprakash Siddaiah, Vinayak S. Pujari, Ashok S. Madalu, Yatish Bevinaguddaiah, Leena H. Parate

Department of Anaesthesiology, MS Ramaiah Medical College, Ramaiah Teaching Hospital, Bengaluru, Karnataka, India

Abstract

Background and Aims: Spinal anesthesia is a safe and reliable technique for surgeries on the lower abdomen and lower limbs. Some of its characteristics like delayed ambulation and pain after block regression may limit its use, especially for short duration surgeries. 2-chloroprocaine is an amino-ester local anesthetic with an approximate duration of action of 40 minutes, which is ideal for short duration surgeries. This study aims to compare the effect of adding intrathecal buprenorphine to 2-chloroprocaine with regard to spinal anesthesia characteristics.

Material and Methods: After obtaining the institutional ethical committee clearance and clinical trial registration, informed consent was taken from 90 patients who were undergoing either lower abdominal or lower limb surgeries of less than 60 minutes duration and were then randomized into two groups. Group C received 40 mg of 1% 2-chloroprocaine and Group B received 40 mg of 1% 2-chloroprocaine with 60 mcg of buprenorphine. Sensory/motor block characteristics, first analgesic requirements, time to void, and unassisted ambulation were assessed. Student *t* test was used to analyze the metric parameters and Fisher's exact test was used to compare the categorical variables.

Results: The time of onset of sensory and motor blocks, peak sensory block, readiness for surgery, and complete regression of both sensory and motor blocks were comparable between the groups. Group B showed significantly prolonged duration of postoperative analgesia (855.82 ± 667.09 vs. 359.07 ± 253.3 minutes). 91.1% patients were able to ambulate within 100 minutes in our study.

Conclusion: We conclude that addition of buprenorphine to 2-chloroprocaine has a significant synergistic effect on prolonging postoperative analgesia.

Keywords: 2-chloroprocaine, accelerated ambulation, buprenorphine, postoperative pain, spinal anesthesia

Introduction

Spinal anesthesia is a time tested, safe, and reliable anesthetic technique for surgery of the lower abdomen and lower limbs. It is easy to administer, has rapid onset of action, low risk of infection, and low failure rates. But some of its characteristics may limit its use, which include delayed ambulation, risk of urinary retention, and pain after block regression. The choice of the correct local anesthetic for spinal anesthesia is therefore crucial in the shorter duration surgeries. Therefore an ideal spinal anesthetic for short-duration surgeries should allow rapid onset and faster offset of its own effect for early patient discharge with minimal side effects.[1,2] In addition, adequate postoperative pain control is one of the most important factors in determining safe discharge after surgery.[3]

Address for correspondence: Dr. Vinayak S. Pujari, Department of Anaesthesiology, MS Ramaiah Medical College, Ramaiah Teaching Hospital, Bengaluru - 560 054, Karnataka, India.
E-mail: drvinayak@outlook.com

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2-chloroprocaine is an amino-ester local anesthetic with a very short half-life. It has been successfully used for spinal anesthesia since 1952.[4] It was used widely for almost three decades, when many reports of neurotoxicity were reported following the use of large doses of 2-chloroprocaine for epidural anesthesia; subsequently, it was withdrawn from commercial use.[5-7] The combination of low PH (<3) and the presence of sodium bisulfite, an antioxidant, may have been responsible for the neurotoxicity.[8-11] Subsequently, the pH of the solution has been adjusted and a preservative free formulation was reintroduced into clinical use in 2005.[12] This new formulation has been safely used for spinal anesthesia in healthy volunteers and in patients without complications.[13-17]

The duration of action of 2-chloroprocaine was found to be 40 minutes, which is ideal for short-duration surgeries. But the occurrence of early postoperative pain may be undesirable. Adjuvants when added to neuraxial local anesthetics should ideally prolong the duration of intraoperative and postoperative analgesia.[18] There is a dearth of literature on the use of adjuvants with intrathecal 2-chloroprocaine; only one study wherein fentanyl has been used as an adjuvant was reported.[19] Intrathecal buprenorphine has been used to enhance the spinal analgesic effect with bupivacaine.[20]

The aim of this study is to assess the time of onset, duration of anesthesia, two segment regression, complete regression of spinal anesthesia, and time for first postoperative analgesic requirement in 2-chloroprocaine and 2-chloroprocaine with buprenorphine groups.

Material and Methods

90 patients of either sex aged between 18 and 65 years scheduled for elective surgeries under spinal anesthesia in our tertiary care teaching hospital were recruited for the study after approval by the institutional ethics committee [Figure 1]. The study was registered with Central Trial Registry-India with the registration number CTRI/2017/12/010900. Pre-anesthetic evaluation of patients satisfying the inclusion criteria was carried out and informed written consent was obtained. The study subjects were randomly allotted into two groups by a computer-generated random number table.

The study included elective American Society of Anesthesiologists physical status classification grade I and II patients of either sex posted for surgeries lasting less than 60 minutes under spinal anesthesia. Patients who refused to give consent, those who had absolute or relative contraindications to spinal anesthesia and pregnant patients were excluded from the study.

The patients were premedicated with tablet pantoprazole 40 mg and ondansetron 4 mg on the night before and on the morning of surgery. Upon arrival in operating room, pulse oximetry, electrocardiogram, and noninvasive blood pressure monitoring were instituted. Base line heart rate, systolic, diastolic, and mean arterial blood pressure were recorded. An 18-gauge intravenous line was secured and a 0.9% normal saline infusion was started.

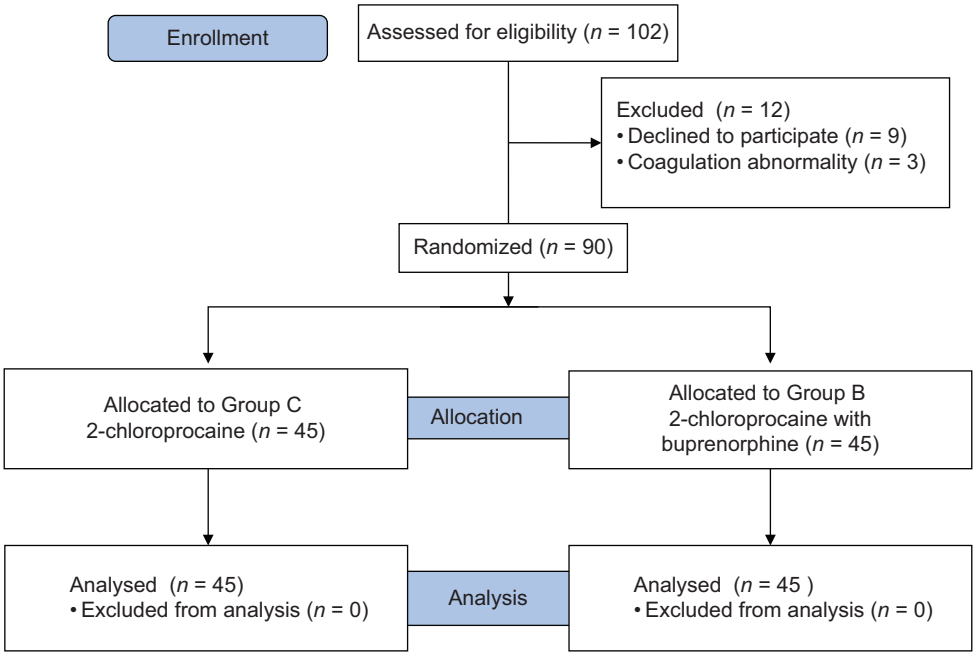

Figure 1: CONSORT 2010 flow diagram of the study

The group C patients received intrathecal 2-chloroprocaine 1% 40 mg (4 ml) (10 mg/ml solution, Clorquick, Neon laboratories limited, Andheri east, Mumbai) and the group B patients received intrathecal 2-chloroprocaine 1% 40 mg (4 ml) and 60 mcg of buprenorphine (Buprigesic, Neon lab Andheri east, Mumbai).

The attending anesthesiologist (who was not involved in the data collection) performed the spinal anesthesia using the test drug randomly assigned to that patient. Both the patient and the assessor (who assessed the block characteristics and collected the data) were blinded to group allocation.

Under aseptic precautions, in sitting position, after infiltration of 1 ml of 1% of lidocaine, lumbar puncture was done with a 25-gauge Quincke needle in L3-4 or L4-5 interspaces. Inj 2-chloroprocaine 1% 40 mg (4 ml) or Inj 2-chloroprocaine 1% 40 mg (4 ml) and 60 mcg of buprenorphine was injected after free flow of CSF was obtained. After spinal injection, the patients were immediately placed supine. An independent, blinded assessor evaluated the sensory and motor blockades every three minutes for 15 min, then every 15 min until complete regression of sensory and motor blocks. During surgery, the patient's blood pressure (systolic, diastolic, and mean), heart rate, and oxygen saturation were recorded.

The sensory level of the block was assessed in the caudal to cephalad direction using the pin prick method, and the C5-C6 dermatome was used as an unblocked reference point.

The sensory block characteristics such as onset of the block (sensory block at L1), peak block height, time to reach peak block height, time to reach readiness for surgery (sensory block ≥ T10), time for regression of two segments, time for regression to L1, and time for complete regression to S2 were recorded.

The motor block was assessed using the modified Bromage scale. The motor block characteristics like time to reach modified Bromage score of 3, modified Bromage score at the end of the surgery, and time to reach modified Bromage score of 0 were recorded. Additional data such as duration of surgery, duration of stay in the Post Anesthesia Care Unit, time to ambulate, time to void, and time of first postoperative analgesic requirement were recorded.

Readiness for surgery was defined as loss of pin prick sensation ≥T10. During surgery, evaluation of the motor block was suspended until the end of the procedure. If sedation was needed, Inj. midazolam 1 mg was administered depending upon the attending anesthesiologist's discretion. If the patient complained of pain, intraoperatively Inj. fentanyl 25 mcg was administered every 5 minutes upto a maximum dose of 100 mcg. The total dose of any given medication was recorded. If the patient still felt pain, general anesthesia was provided and this patient was excluded from the study. The occurrence of clinically relevant hypotension (defined as a decrease in systolic arterial blood pressure ≥20% from baseline values) was treated with intravenous injection of 6 mg ephedrine. Clinically relevant bradycardia (defined as heart rate ≤50 beatsmin^{-1}) was treated with intravenous injection of 0.3 mg atropine in increments. The total dose of ephedrine and atropine needed were recorded. The patients were monitored in the PACU (Post Anesthesia Care Unit) postoperatively and were discharged to ward once there was complete regression of motor block and the hemodynamic parameters were within normal limits.

On recovery of S2 dermatome to pin prick, the patients were encouraged to ambulate. If ambulation was successful, then they were asked to attempt to void urine. The time of injection of the drug into the intrathecal space was taken as the reference point for calculating the sensory and motor blocks, duration of analgesia, time to ambulate, and time to void. Postoperative analgesia was provided with an IV injection of paracetamol 1 gm upon patient request. Inj. tramadol 50 mg IV was given if the pain was not reduced after 15 minutes of Inj. paracetamol infusion.

Statistical Methods

Sample size calculation

Vath *et al*.[19] in their study found that complete regression of the motor block occurred at 104 ± 7 minutes in 2-chloroprocaine with fentanyl group whereas in the group without fentanyl it was 95 ± 9 minutes, which was statistically significant. The present study expecting similar results with 80% power, 90% confidence level, and effect size of 0.63 required a minimum of 82 subjects (41 in each group). To compensate for data loss and failure to adhere to protocol, 90 patients were recruited, that is, 45 in each group.

Descriptive and inferential statistical analyses were carried out in the present study. Results on continuous measurements are presented as mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Student *t* test (two tailed, independent) was used to find the significance of the study parameters on a continuous scale between two groups (intergroup analysis) on metric parameters. Leven`s test for homogeneity of variance was performed to assess the homogeneity of variance. Chi-square/Fisher Exact test was

used to find the significance of the study parameters on a categorical scale between two or more groups.

Statistical software

The Statistical software SPSS 18.0 (IBM® Statistical Package for Social Services version 18) and R environment ver. 3.2.2 were used for the data analysis and Microsoft Word and Excel were used to generate graphs, tables etc.

Results

The study was conducted from September 2017 to August 2018. There were no dropouts or case failures in our study. Age, height, weight, sex, and ASA grade [Table 1] were similar between the two groups.

The sensory block characteristics like onset of block, time to reach peak block, and time to reach readiness [Table 2] for surgery were similar between the groups. Time for regression of two segments was 38.29 ± 5.75 minutes in group C and 40.78 ± 6.91 minutes in group B with *P* value of 0.067. The mean time for regression to L1 was significantly longer in group B which was 51.27 ± 6.25 minutes compared to group C 46.60 ± 6.72 minutes with a statistically significant *P* value of 0.001. Time for complete regression to S2 was similar between the two groups. These results suggest that the patients who received 2-chloroprocaine with buprenorphine had longer time for regression to L1 when compared to patients who received 2-chloroprocaine only, suggesting that buprenorphine prolongs the duration of spinal anesthesia. Peak block heights with relation to the height of patients were comparable between the groups. In group C, 71.1%, 2.2%, 22.2%, and 4.4% of the people achieved a peak block height of T10, T9, T8, and T6, respectively, whereas in group B 75.6%, 4.4%, and 20% of the people achieved a peak block height of T10, T9, and T8, respectively.

In group C, the time to reach the modified Bromage score of 3 was 4.69 ± 2.07 minutes and the modified Bromage score at the end of the surgery was 2.69 ± 0.76. In group B, the time to reach the modified Bromage score of 3 was 4.16 ± 1.68 minutes and the modified Bromage score at the end of the surgery was 2.76 ± 0.61. The time to reach the modified Bromage score of 0 in group B was longer, 70.84 ± 9.91 minutes, when compared to group C, 67.16 ± 21.73 minutes.

The time to void [Table 3] was longer in group B which was 269.42 ± 156.61 minutes than in group C 204.42 ± 81.74 minutes. This was statistically significant with a *P* value of 0.016. But none of the patients needed urinary catheterization. The time of first postoperative analgesic requirement was also longer in group B which was 855.82 ± 667.09 minutes and in group C it was 359.07 ± 253.13 minutes with a statistically significance of *P* value of <0.001.

In group C, the mean and standard deviation of time to ambulate was 84.02 ± 18.87 minutes whereas in group B was

Table 1: Demographic characteristics

	Group C	Group B	*P*
Age in years	43.53±12.70	45.64±13.82	0.453
Male/Female Number (percentage)	19 (42.2%)/26 (57.8%)	26 (57.8%)/19 (42.2%)	0.140
Weight in kg	67.87±18.00	66.93±11.65	0.771
Height in cm	165.80±9.48	167.31±8.22	0.422
ASA Grade I/II	8 (17.8%)/37 (82.2%)	6 (13.3%)/39 (86.7%)	0.561

P≤0.05 significant

Table 2: Spinal block characteristics in minutes (mean±SD)

	Group C	Group B	*P*
Sensory Block			
Onset of Block (L1)	3.11±1.53	2.93±0.94	0.507
Time to reach peak block	6.62±2.25	6.76±2.12	0.773
Time to reach readiness for surgery	6.13±2.37	6.27±2.05	0.776
Time for regression of two segments	38.29±5.75	40.78±6.91	0.067
Time for regression to L1	46.60±6.72	51.27±6.25	0.001*
Time for complete regression to S2	67.47±19.35	72.00±8.36	0.153
Motor Block			
Time to reach Modified Bromage Score of 3	4.69±2.07	4.16±1.68	0.182
Modified Bromage Score at the end of the surgery	2.69±0.76	2.76±0.61	0.648
Time to reach Modified Bromage Score of 0	67.16±21.73	70.84±9.91	0.303

**P≤0.05 significant*

85.80 ± 8.06 minutes, with a *P* value of 0.563. In our study, 91.1% patients were able to ambulate within 100 minutes. Hemodynamic parameters like SBP, DBP, MAP, and oxygen saturations were comparable between two groups.

In both the groups, 12 patients had hypotension and one patient had bradycardia. In group B, one patient had itching. None of the patients had nausea, vomiting, PDPH, or other side effects [Table 4].

Discussion

In the present study, we found that addition of bupernorphine to 2-chloroprocaine prolonged the duration of spinal anesthesia and the effective duration of postoperative analgesia. The sensory and motor characteristics of spinal anesthesia were analogous in both the groups. Spinal anesthesia is the most preferred regional anesthetic technique as it is easy to perform, produces rapid onset of anesthesia, provides complete muscle relaxation, and is also economical.

Many intermediate- and long-acting local anesthetics like lignocaine, mepivacine, prilocaine, and bupivacaine have been used at lower dosage for short duration spinal anesthesia. But some of the adverse effects like risk of urinary retention, delayed ambulation, and pain after block regression may limit their use. 2-chloroprocaine is short acting and has many advantages especially for short-duration surgeries; therefore, it has been reintroduced for spinal anesthesia.[15-17,21-28]

Table 3: Duration of surgery, stay in ICU, time to void urine, time to first analgesic request, and time to ambulate in minutes (mean±SD)

	Group C	Group B	*P*
Duration of surgery	29.22±9.73	32.24±14.33	0.245
Duration of stay in the PACU	36.24±16.46	33.24±6.22	0.256
Time to void	204.42±81.74	269.42±156.61	0.016*
Time of first postoperative analgesic requirement	359.07±253.13	855.82±667.09	<0.001*
Time to ambulate	84.02±18.87	85.80±8.06	0.563

**P≤0.05 significant*

Table 4: Incidence of adverse effects

Side effects	Group C (*n*=45)	Group B (*n*=45)	*P*
Hypotension	12 (26.7%)	12 (26.7%)	1.000
Bradycardia	1 (2.2%)	1 (2.2%)	1.000
Itching	0 (0%)	1 (2.2%)	1.000
Nausea	0 (0%)	0 (0%)	1.000
Vomiting	0 (0%)	0 (0%)	1.000
Others	0 (0%)	0 (0%)	1.000

P≤0.05 significant

The addition of intrathecal buprenorphine to spinal anesthesia prolongs analgesia.[20] Buprenorphine is a highly lipid-soluble drug and has minimal risk of respiratory depression due to rostral spread. It has a high affinity for opioid receptors and, therefore, produces longer duration of analgesia compared to other agents.[18,20] All these characteristics were confirmed in our study.

In our study, we found that the time of onset of block to L1 was faster in group B in which intrathecal 60 mcg of buprenorphine was added and it was not statistically significant. The time to reach peak block was similar in both groups in our study and was slightly faster than Camponovo C *et al*. (8 minutes) where a higher dose of intrathecal 50 mg of 2- chloroprocaine was administered.[15]

Vath and colleagues found that the time for two-segment regression when 20 mcg intrathecal Inj. fentanyl was added to 40 mg 2-chloroprocaine was 48 ± 8 minutes whereas in 2-chloroprocaine 40 mg group it was 45 ± 16 minutes.[19] In our study, the two-segment regression where intrathecal buprenorphine was added was slightly prolonged, but was not statistically significant.

Vath and colleagues found that the time for regression to L1 was 77 ± 7 minutes in 2-chloroprocaine with fentanyl group whereas it was 53 ± 19 minutes in the 2-chloroprocaine group which was statistically significant.[19] A similar statistically significant prolongation was found in our study suggesting that buprenorphine prolongs the duration of spinal anesthesia.

In our study, the time for a complete sensory regression to S2 was similar to other studies where complete sensory regression was 92 minutes,[17] 105 (range 90–124) minutes,[19] 108 (range 95–121) minutes,[24] and 146 ± 38 minutes when only 40 mg 2-chloroprocaine injected intrathecally.[26]

The motor block characteristics were similar in both the groups suggesting that buprenorphine has no effect on motor blockade. In our study, we found that the time to ambulate was similar in both groups. 91.1% patients among the two groups were able to ambulate within 100 minutes; similar results were found by Sell and colleagues.[26] In contrary to our results, fentanyl has been found to prolong both the duration of motor blockade and the time to ambulate.[19]

In our study, the time to void urine was delayed by an hour in the group that received intrathecal buprenorphine. This similar result of prolongation of time of voiding by addition of intrathecal opioid was also found by Vath *et al*.[19] when they added fentanyl intrathecally to 2-chloroprocaine. Time

to void urine in a few studies was found to be 198 (120–271) minutes, 271 ± 96 minutes, 204 ± 61.8 minutes, and 306 ± 114 minutes.[19,25,27,28] Several studies on animals and humans have consistently shown that spinal opioids influence bladder functions and cause urinary retention. Buprenorphine, a partial agonist with poor affinity for μ and δ, has a poor effect on detrusor contraction and urethral sphincter. The urodynamic effects of intrathecal opioids are mainly caused by the action of the opioid receptors on the spinal cord and the cerebral structures.[29,30]

The first postoperative analgesic request was more than two times longer after the addition of 60 mcg of buprenorphine to 2-chloroprocaine. A similar result was found in the study conducted by Dinakar Rao and colleagues in which they intrathecally added 60 mcgs of buprenorphine to 0.5% bupivacaine. The mean postanalgesic time was 933 minutes in buprenorphine with bupivacaine group whereas it was 188 minutes in the 0.5% bupivacaine group.[20]

Our results are consistent with the previous findings that intrathecal opioids have a synergistic effect with local anesthetic agents. Animal models have similarly shown a synergistic relationship between opioids and local anesthetics in analgesia, allowing for adequate analgesia without motor blockade using subtherapeutic doses of local anesthetic. Although intrathecal local anesthetics are nonselective in their blockade of afferent and efferent pathways, addition of opioids has an effect on the afferent nociceptive fibers without an effect on the sympathetic efferent fibers. Opioid antinociception is mediated by the activation of opioid receptors in the substantia gelatinosa. They act both presynaptically by inhibiting the release of excitatory neurotransmitters and postsynaptically by interfering with K+ currents resulting in neuronal hyper polarization.[18] Fentanyl is able to depress C-fiber reflexes alone, whereas the opioid-local anesthetic combination resulted in the depression of both A δ and C reflexes without efferent effect.[30]

In our study, we found that there was no statistical significance in the hemodynamic parameter changes between two groups. The only drawback of using intrathecal buprenorphine was that the time to void was delayed by more than 60 minutes, but none of the patients in our study needed urinary catheterization. The main limitation of this study is that we have not compared 2-chloroprocaine with 0.5% bupivacaine which is the most commonly used local anesthetic in spinal anesthesia.

Moreover, we have not compared intrathecal buprenorphine with fentanyl or other adjuvants.

Conclusion

The addition of intrathecal buprenorphine to 2-chloroprocaine for spinal anesthesia significantly prolongs the two-segment sensory regression, regression to L1, and postoperative analgesia. Buprenorphine prolonged the duration of analgesia by more than eight hours without having any effect on ambulation. We conclude that the addition of buprenorphine to 2 chloroprocaine has a significant synergistic effect in prolonging postoperative analgesia without delaying ambulation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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