Original Article

Comparison of analgesic efficacy of intrathecal 1% 2-chloroprocaine with or without fentanyl in elective caesarean section: A prospective, double-blind, randomised study

Address for correspondence:
Dr. Geeta Singariya,
123, Vaishali Avenue, Jhanwar Road, Jodhpur - 342 008, Rajasthan, India.
E-mail: geetamanojkamal@gmail.com

Submitted: 10-Jul-2020
Revised: 22-Aug-2020
Accepted: 01-Jan-2021
Published: 10-Feb-2021

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.IJA_816_20

Quick response code

Geeta Singariya, Kusum Choudhary, Manoj Kamal[1], Pooja Bihani, Himani Pahuja, Pradeep Saini

Department of Anaesthesiology and Critical Care, Dr S N Medical College, Jodhpur, Rajasthan, [1]Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

ABSTRACT

Background and Aims: Preservative free 1% 2-chlorprocaine is a short acting local anaesthetic agent suitable for day care surgical procedures. Potentiation of analgesic action of intrathecal local anaesthetics by the addition of opioids is well known. In this study, we investigated the effect of intrathecal fentanyl as an adjuvant to 1% 2-chloroprocaine (2-CP) in parturients undergoing elective lower segment caesarean section (LSCS). **Methods:** This prospective randomised comparative study was performed on 150 healthy, term parturients planned for elective low risk LSCS, divided into two equal groups. The group CS received 1% preservative-free 2-CP 3 ml (30 mg) + 0.5 ml normal saline and group CF received 1% preservative-free 2-CP 3 ml (30 mg) + 0.5 ml fentanyl (25 μg) with a total volume of 3.5 ml intrathecally in both groups. The duration of sensory blockade, duration of motor blockade, maximum height of sensory block, haemodynamic parameters, quality of block, neonatal outcome, patient satisfaction and any side effects were recorded. **Results:** There were no significant differences in demographic characteristics, haemodynamic parameters, onset of sensory block, onset of motor block and duration of motor block between the groups. The duration of sensory block and duration of analgesia was statistically prolonged in group CF than group CS (*P* value < 0.0001). There was no statistical difference in the Apgar score of newborns in both groups. The adverse effects (hypotension, bradycardia, nausea/vomiting, shivering and transient neurological symptoms) were comparable in both the groups. **Conclusion:** The addition of fentanyl to 1% 2-chloroprocaine intrathecally prolonged the duration of sensory block and postoperative analgesia in patients undergoing LSCS.

Key words: 2-chloroprocaine, caesarean section, fentanyl, spinal anaesthesia

INTRODUCTION

Regional anaesthesia is a safer technique compared to general anaesthesia for caesarean section for both the mother and the baby.[1] Among regional anaesthetic techniques, subarachnoid block (SAB) is the preferred one for elective caesarean section, due to its advantages like it is easy to perform, economical, rapid onset, ability to provide adequate surgical anaesthesia, less neonatal depression, fewer complications and low failure rate.[2] The ideal local anaesthetic agent should provide a rapid onset of action, faster offset of motor blockade with predictable duration, adequate postoperative pain control, low neurotoxicity potential and systemic side effects.

How to cite this article: Singariya G, Choudhary K, Kamal M, Bihani P, Pahuja H, Saini P. Comparison of analgesic efficacy of intrathecal 1% 2-chloroprocaine with or without fentanyl in elective caesarean section: A prospective, double-blind, randomised study. Indian J Anaesth 2021;65:102-7.

Preservative free 2-chloroprocaine (2-CP) is an amino-ester local anaesthetic (LA). It has properties of faster onset, excellent sensory and motor block with quick recovery time and few adverse effects.[3] The short duration of action and poor quality of postoperative analgesia limits its use in caesarean sections. Adding adjuvant drugs to intrathecal LA improves the quality and duration of the spinal blockade and prolongs postoperative analgesia. With the addition of an adjuvant, it is possible to reduce the amount of LA and thus the incidence of side-effects. The opioids continue to be the most commonly used adjuvants in clinical practice.[4] Among opioids, fentanyl is the most extensively used opioid in SAB, because of its potency, rapid onset, short duration of action with a reduced need for analgesia after the operation.[5,6]

The present study aimed to compare the analgesic efficacy and safety of intrathecal fentanyl (25 μg) as an adjuvant to low dose 1% 2-CP (30 mg) in parturients undergoing caesarean section.

METHODS

This prospective, double-blind, randomised, comparative study was conducted after approval from the Institutional Ethical Committee and Clinical Trial Registry of India. The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. One hundred and fifty parturients with term pregnancy (≥36 weeks), belonging to the American Society of Anesthesiologists (ASA) physical status II, aged between 18 and 35 years, scheduled to undergo low-risk elective caesarean section under SAB, from November 2018 to October 2019 were enroled in the study. Written informed consent was obtained from each parturients. The parturients who refused to participate, having known hypersensitivity to LA, infection at the site of injection, history of bleeding disorders, parturients with pregnancy-induced hypertension, body mass index (BMI) >35 kg/m^2, parturients with cardiac or renal disease, pre-existing peripheral neuropathy or neurological deficit were excluded from the study. All parturients were randomised to one of the two groups (75 each) by using a computer-generated random number table and group allocation was done with the sealed envelope method by an anaesthesiologist who was not involved in data collection.

After arrival in the operation theatre, an 18-gauge (G) intravenous cannula was secured in the non-dominant hand and the parturients was preloaded with a 10 ml/kg ringer lactate solution over 15 min. Non-invasive blood pressure (NIBP), pulse oximeter, and electrocardiogram (ECG) were applied and baseline blood pressure (BP), heart rate (HR) and oxygen saturation (SpO_2) were recorded.

Spinal anaesthesia was administered in lateral position at the level of L3-4 or L4-5 interspace by using 25 G Quincke spinal needle under aseptic precaution. Parturients in group CS received intrathecal 1% preservative free 2-CP 3 ml + 0.5 ml normal saline (NS) and parturients in group CF received intrathecal 1% preservative-free 2-CP 3 ml + 0.5 ml fentanyl (25 μg). The study drugs were prepared by an anaesthesiologist, who was not a part of the study. The anaesthesiologist administering the study drug and the patients were blinded to the group allocation. After spinal anaesthesia, the parturients were placed in the supine position with a wedge under the right buttock. The sensory and motor blockade were evaluated each minute for the first 15 min, than every 5 min till completion of the surgery.

The sensory block was assessed by pinprick sensation using hypodermic needle and pin-prick sensation over the clavicle was taken as reference point, whereas the motor block was assessed by the modified Bromage scale (0 = no paralysis, able to flex hips/knees/ankles, 1 = able to move knees, unable to raise extended legs, 2 = able to flex ankles, unable to flex knees, 3 = unable to move any part of the lower limb) at every min till adequate sensory and motor blockade for surgery was achieved. The onset of sensory block was defined as time from intrathecal drug administration to loss of pin prick sensation at T10 level, while onset of motor blockade considered from intrathecal drug administration to Bromage scores ≥2. The surgery was commenced after achieving a sensory block height of T6 level or above. Apgar score was recorded at 1, 5, 10 min after birth for all newborns. The anaesthesiologists who administered spinal anaesthesia recorded NIBP, HR, SpO_2 and VAS every 10 min in post-operative period till patient requested for first analgesic agent. The duration of analgesia was considered from the time of subarachnoid injection of drug to the time up till visual analogue scale (VAS) for pain assessment score ≥4. The duration of sensory block was from the onset of sensory block till sensation was felt at the level of S2 dermatome, while

duration of motor block was from time to achieve Bromage scores ≥2 to time to complete recovery of motor power. The adverse events like hypotension, bradycardia, nausea, vomiting, and pruritus were recorded for first 24 h. Paracetamol 100 ml (1 gm) i.v. was administered when VAS ≥4. The occurrence of transient neurological sequelae (TNS) was assessed at days 1, 3, 7, 1 month and 6 months after surgery. This was done by an observer anaesthesiologist by making a telephone call and asking the patients about the presence of back pain radiating to buttocks, thigh, hip and calf, inability to void, or presence of residual paraesthesia/dysaesthesia in lower limbs and buttocks.

The primary outcome of the study was the duration of analgesia, while secondary outcomes were onset of sensory block (time to achieve at T10 dermatomal level), onset of motor block, duration of sensory block, duration of motor block, time to achieve T6 and T10 dermatomal level, maximum cephalad spread, time for two-segment regression, Apgar score and any adverse effects.

The sample size calculation was based on a pilot study of 10 patients in each group. The difference in regression of sensory block duration up to S2 level between the two groups was 6 min, standard deviation (SD) as 11 min and 14 min, with 80% power, 95% confidence interval and level of significance 0.05. The sample size (n) was calculated as 68 for each group. To cover dropouts, we enhanced the estimated sample size by 10%, which was n = 75 parturients in each group.

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Kolmogrov Smirnov test was used to assess normality of quantitative variables. Numerical data like age, height, weight, BMI, duration of surgery along with spinal block characteristics were summarised as mean ± SD. Data on complications reported in each group were presented as numbers and percentages. Independent sample *t*-test was used to compare the baseline and spinal block characteristics between two groups. Fisher's exact test was used to compare number of complications reported between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 180 parturients were screened for eligibility. Eighteen parturients did not meet the inclusion criteria, five parturients refused to participate and seven parturients were excluded due to other reasons like non-cooperation of patient and change of surgical plan to emergency caesarean section. The 150 parturients were randomised in two groups. Five from group CS and three from group CF were excluded from the analysis because of failed/partial spinal block (total eight parturients) [Figure 1].

The parturients in both groups were similar with respect to demographic data and duration of surgery [Table 1]. The difference in HR, BP and SpO_2 was not statistically significant in both the groups throughout the perioperative period. The time to achieve block height of T10 (onset of sensory block), time to achieve block height of T6, maximum dermatomal cephalad spread, the onset of motor block and the duration of motor block were comparable in both the groups [Table 2]. The mean duration of sensory block was prolonged in group CF in comparison to group CS, with the difference being statistically significant (101.1 ± 14.61 versus 72.13 ± 10.33 min, $P < 0.0001$). The mean duration of analgesia was prolonged in group CF compared to group CS, with the difference being statistically significant (115.20 ± 25.54 min versus 79.59 ± 10.74 min, $P < 0.0001$) [Table 2]. The adverse effects namely hypotension, bradycardia, nausea, vomiting, pruritus, shivering, sedation and respiratory depression were comparable in both the groups [Table 3]. There was no statistical difference in the Apgar score of newborns in both the groups. In this study, none of the parturients reported TNS in the follow-up period.

DISCUSSION

The principal findings of our study were that the addition of 25 μg of fentanyl to 2-CP (30 mg) for spinal anaesthesia prolonged the sensory blockade and duration of postoperative analgesia. The onset of sensory block and time to achieve T6 dermatomal spread, maximum cephalad dermatomal spread, onset

Table 1: Demographic data and duration of surgery

Parameters	Group CS (*n*=70) mean±SD	Group CF (*n*=72) mean±SD	*P*
Age (years)	24.2±3.2	24.0±3.3	0.7
Height (cm)	159.3±6.0	159.4±5.0	0.9
Weight (kg	68.1±5.7	66.6±5.0	0.1
BMI (kg/m^2)	26.9±2.4	26.3±2.6	0.1
Duration of surgery (min)	38.2±4.8	39.6±4.6	0.8

Data represented as mean±Standard Deviation (SD) and unpaired Student's *t*-test was used for intergroup comparison. The *P*<0.05 considered as significant. *BMI: body mass index

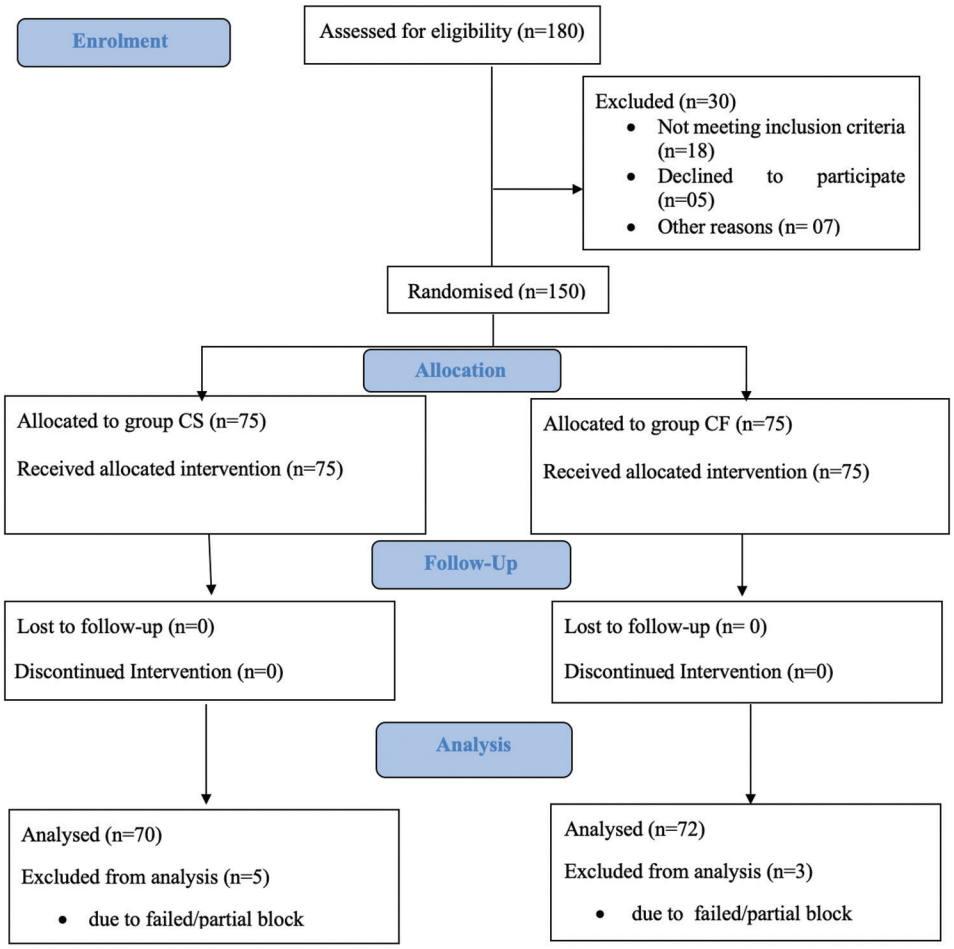

Figure 1: Consort flow diagram

Table 2: Spinal block characteristics

	Group CS (*n*=70)	Group CF (*n*=72)	*P* from independent *t*-test
Mean time to achieve T10 sensory block (min)	4.23±0.92	4.13±1.13	0.78
Mean time to achieve T6 sensory block (min)	5.16±1.05	5.39±1.34	0.15
Mean time to achieve maximum cephalad spread (min)	5.97±0.87	6.22±2.09	0.22
Maximum cephalad sensory level (Median)	T6 (T4-T8)	T6 (T4-T8)	
Mean time for two segment regression (min)	57.96±6.48	57.83±8.52	0.99
Mean duration of sensory block (min)	72.13±10.33	101.1±14.61	<0.0001
Mean onset of motor block (min)	4.5±0.74	4.4±1.12	0.55
Mean duration of motor block (min)	69.8±13.66	70.4±14.44	0.33
Mean duration of analgesia (min)	79.59±10.74	115.2±25.54	<0.0001

P<0.05 is indicative of significant difference between the two groups

and duration of motor block and adverse events were comparable in both the groups.

2-CP has a rapid onset of action, with an excellent sensory and motor block. 2-CP has a shorter duration of action due to very low protein binding and rapid metabolism by pseudocholinesterase.[3,7-9] Several older studies have highlighted the issues of safety and potential neurotoxicity with preservative of 2-CP.[10,11] The acidic solution and the preservative bisulfite were associated with a higher incidence of complications.[11] However, use of preservative-free 2-CP has shown good results without complications.[3,12] Rapid onset of sensory block (3–5 min) and complete resolution of the sensory block in 70–150 min after intrathecal 2-CP (30–60 mg) makes it an attractive option for SAB in day care surgeries.[8,12,13] Use of 2-CP in low-risk caesarean section in healthy parturients has been found to reduce the length of stay in the post-anaesthesia care unit (PACU), benefit early breast feeding initiation,

Table 3: Comparison of complications

	Group CS (*n*=70)	Group CF (*n*=72)	*P*
Hypotension	5 (7.14%)	4 (5.56%)	0.74
Bradycardia	1 (1.43%)	1 (1.39%)	1.00
Nausea/vomiting	5 (7.14%)	4 (5.56%)	0.74
Shivering	9 (12.8%)	6 (8.33)	0.42
Pruritus	0 (0.00)	5 (6.94)	0.06

Data represented as number (%). *P*<0.05 considered as significant. Fisher exact test used for analysis

improve maternal satisfaction due to better and early mother-baby bonding and help in the maintenance of the new born's temperature.[9] Literature suggests a dose ranging between 30-60 mg of 2-CP for procedures lasting 60 min or less, while 10 mg is considered as no-effect dose.[14] Different doses (30-60 mg) of 2-CP have been compared for intrathecal administration for below umbilical surgeries lasting less than 60 min. It is observed that 40 and 50 mg of 2-CP provides adequate SAB for outpatient procedures lasting 45-60 min and 30 mg produces a spinal block of insufficient duration.[7,13] The LSCS can be conducted under spinal anaesthesia with either a large dose of 2-CP or a small dose of the same agent with addition of fentanyl as an adjuvant. The use of a high dose of 2-CP may be associated with prolonged duration of motor blockade, which may not be desirable. The addition of fentanyl to a smaller dose of 2-CP results in a shorter duration of the motor blockade and a longer duration of sensory block and analgesia. It is well documented that parturients require a smaller dosage of LA in SAB compared to non-pregnant patients because of mechanical factors such as changes in spine curvature, distension of epidural veins as a result of the aorto-caval compression by the gravid uterus and increased sensitivity of neurons to LA.[15] Maes *et al.* used 2-CP 40 mg with and without sufentanil (1 μg) in subarachnoid block for low risk caesarean section.[9] Since, there is no recommendation regarding the appropriate intrathecal dosage of 2-CP in parturients, we selected a lower dose (30 mg) of 2-CP keeping in mind the above mentioned concerns.

Intrathecal LA and opioids act synergistically but on different receptors, as LA blocks afferent and efferent pathways, while opioids affect only afferent nociceptive fibers. Synergistic effect of intrathecal opioids can greatly enhance analgesia of sub-therapeutic doses of LA.[16,17] The use of subarachnoid opioids in spinal anaesthesia for caesarean section enhances spinal block and produces effective and prolonged postoperative analgesia. Reducing the dose of LA used in spinal anaesthesia can decrease some of the side effects such as maternal hypotension, high spinal block, and prolonged motor block.[6]

Fentanyl has a high affinity for opioid receptors; therefore, it produces a longer duration of analgesia compared to other agents. Fentanyl can depress C-fiber reflexes, whereas the opioid local anaesthetic combination results in the depression of both Aδ and C fiber mediated reflexes without efferent effect.[5] Most authors have reported that fentanyl doses from 12.5 to 25 μg are safe and enhance spinal blockade, during caesarean and immediate postsurgical analgesia, without increasing side effects. In our study, we used 25 μg fentanyl with 2-CP. Though the time to dermatomal regression was comparable in both groups in our study, the sensory regression and duration of postoperative analgesia were significantly prolonged without intensifying the motor blockade. Many previous studies have focused on the use of intrathecal fentanyl as it provides a more intense sensory block without untoward effects.[5,6,17]

We found negligible incidences of hypotension, bradycardia, nausea, vomiting, pruritus, shivering, sedation, and respiratory depression in our study parturients undergoing caesarean section. Also, the Apgar score of the newborns remained comparable in both groups. Though earlier studies[6,8] did not use the same concentration, volume of LA and opioid intrathecally as used in our study, their results were similar to our study. In our study, we administered a small dose of a newly marketed formulation of preservative-free 1% 2-CP for spinal anaesthesia. The small dose is believed to lower the risk of neurotoxicity.[7,9] We also did not find neurologic complications in any of the parturients. Existing literature highlights the use of 2-CP in day care surgeries; in fact, very few studies on 2-CP for non-day care surgeries are available. Our study showed that 2-CP can be used for spinal anaesthesia for low risk LSCS safely.

The limitations of our study are that we did not compared 2-CP with 0.5% bupivacaine heavy, which is commonly used for LSCS. We could have compared two different doses of 2-CP with fentanyl because there is no recommendation for intrathecal dose of 2-CP. We did not have a back-up of an epidural catheter to provide anaesthesia in case the surgery got prolonged. Hence, if the surgical procedure had got prolonged, the parturients might have got exposed to the risks of general anaesthesia (GA). Luckily, none of our parturients needed GA. We could have

used non-steroidal analgesic agents or epidural analgesia to improve the postoperative analgesia. The duration of surgery in our study was short (around 38 to 43 minutes in both groups) and the cases were low risk cases. Hence, our results cannot be extrapolated to high risk LSCS cases and centres where the surgeon is slow in operating.

CONCLUSION

Our study concluded that intrathecal preservative-free 1% 2-chloroprocaine (30 mg) with fentanyl (25 μg) as an adjuvant results in a prolonged duration of sensory blockade and postoperative analgesia, with similar duration of motor blockade and incidence of complications when compared to preservative-free 1% 2-chloroprocaine (30 mg) without an adjuvant, in patients undergoing elective lower segment caesarean section.

Acknowledgements

I acknowledge the contribution of Dr Shobha Ujwal, Senior Professor & Head, Department of Anaesthesiology & Critical Care, Dr S N Medical College, Jodhpur and Dr Satya Narayan Seervi, Senior resident, Department of Anaesthesiology & Critical Care, Government Medical College, Pali for guidance and preparation of this manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yeoh SB, Sng BL, Sia ATH. Anaesthesia for lower-segment caesarean section: Changing perspectives. Indian J Anaesth 2010;54:409-14.
2. Gandhi KA, Jain K. Management of anaesthesia for elective, low-risk (Category 4) caesarean section. Indian J Anaesth 2018;62:667-74.
3. Goldblum E, Atchabahian A. The use of 2-chloroprocaine for spinal anaesthesia. Acta Anaesthesiol Scand 2013;57:545-52.
4. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases 2017;5:307-23.
5. Vath JS, Kopacz DJ. Spinal 2-Chloroprocaine: The effect of added Fentanyl. Anesth Analg 2004;98:89-94.
6. Uppal V, Retter S, Casey M, Sancheti S, Matheson K, McKeen DM. Efficacy of intrathecal fentanyl for cesarean delivery: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. Anesth Analg 2020;130:111-25.
7. Hejtmanek MR, Pollock JE. Chloroprocaine for spinal anesthesia: A retrospective analysis. Acta Anaesthesiol Scand 2011;55:267–72.
8. Camponovo C, Wulf H, Ghisi D, Fanelli A, Riva T, Cristina D, *et al*. Intrathecal 1% 2-chloroprocaine vs 0.5% bupivacaine in ambulatory surgery: A prospective, observer blinded, randomized, controlled trial. Acta Anaesthesiol Scand 2014;58:560-6.
9. Maes S, Laubach M, Poelaert J. Randomised controlled trial of spinal anesthesia with bupivacaine or 2-chloroprocaine during caesarean section. Acta Anaesthesiol Scand 2016;60:642-9.
10. Moore DC, Spierdijk J, VanKleef J, Coleman D, Love G. Chloroprocaine neurotoxicity: Four additional cases. Anesth Analg 1982;61:155–9.
11. Taniguchi M, Bollen AW, Drasner K. Sodium bisulfite: Scapegoat for chloroprocaine neurotoxicity? Anesthesiology 2004;100:85–91.
12. Saporito A, Marcello C, Perren A, Regina DL, Cafarotti S, Borgeat A, et al. Does spinal chloroprocaine pharmacokinetic profile actually translate into a clinical advantage in terms of clinical outcomes when compared to low-dose spinal bupivacaine? A systematic review and meta-analysis. J Clin Anesth 2019;52:99–104.
13. Ghisi D, Bonarelli S. Ambulatory surgery with chloroprocaine spinal anesthesia: A review. Ambulatory Anesthesia 2015;2:111-20.
14. Kopacz DJ. Spinal 2-chloroprocaine: Minimum effective dose. Reg Anesth Pain Med 2005;30:36–42.
15. Kestin IG. Spinal anaesthesia in obstetrics. Br J Anaesth 1991;66:596-607.
16. Axelsson K, Gupta A. Local anesthetic adjuvants: Neuraxial versus peripheral nerve block. Curr Opin Anaesthesiol 2009;22:649-54.
17. Bhaskara B, Prabhakar SA, Rangadhamaiah R. Intrathecal 1% 2-Chloroprocaine with fentanyl in comparison with ropivacaine (0.5%) with fentanyl in day care perianalsurgery. Prospective randomized comparative study. Anesth Essays Res 2019;13:471-5.