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Original article

COMPARATIVE STUDY BETWEEN 2-CHLOROPROCAINE AND COMBINATION OF 2-CHLOROPROCAINE WITH FENTANYL FOR SPINAL ANAESTHESIA

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Abstract

Background: *Using fentanyl as an adjuvant in spinal anesthesia has well been documented. Fentanyl being an opioid additive prolongs the duration of neuroaxial blockade without significantly increasing the time to ambulation.* **Aim:** *To assess the effect of fentanyl as an adjuvant used with 2-chloroprocaine on sensory and motor onset and offset block time, time for ambulation and complication rate.* **Methodology:** *A randomized comparative study was conducted for a period of 6 months in the department of anesthesiology at Kirupananda Variyar medical college and hospital, Salem. A total of 100 patients (50 in each group) posted for elective surgeries in the age group between 20 and 60 were enrolled as our study subjects. Group A patients received intrathecal injection of 3 mL of 1% 2-Chloroprocaine (30 mg) mixed with 0.5 mL of Normal saline and Group B patients received 3 mL of 1% 2-Chloroprocaine (30 mg) mixed with 0.5 mL of Fentanyl solution containing 50 micrograms per mL (25 mcg). Bilateral sensory and motor block onset and regression time was monitored.* **Results:** *Time for regression of sensory block, recovery of motor block and time to void urine was comparatively more among group B (2-chloroprocaine with fentanyl) than group A (2-chloroprocaine) and the difference was found to be statistically significant ($p < .05$). The length of stay in post-anesthesia ICU and the patient satisfaction score did not show a statistical significant difference between the two groups. Similarly no change was noted in hemodynamic parameters and in the incidence of adverse events.* **Conclusion:** *We conclude that the addition of fentayl to 2 chloroprocaine has a significant synergistic effect in prolonging postoperative analgesia without prolonging the time for ambulation.*

Keywords: *2-chloroprocaine; fentanyl; spinal anesthesia; motor and sensory block*

Introduction

From 20th century till today, spinal anesthesia is considered to be the safest and highly reliable technique for most of the lower abdomen and perineal surgeries. Requirement of short duration neuraxial blockade has shown more popularity due to its increasing day care and ambulatory surgeries.[1] However the conventional drugs such as bupivacaine are not very suitable for short duration anaesthesia as bupivacaine has a long half life and when used in smaller doses has unpredictable duration of block[2]. Later, the interest was towards lignocaine, which was tempered due to the risk of transient neurologic symptom, then emerged 2-Chloroprocaine as a viable candidate for short duration spinal[3].

In early 1950's Foldes and McNall had shown how preservative free 2-Chloroprocaine was practical and effective in spinal anesthesia. However it failed to gain significant attention among anesthetists because few reports in 1980's had showed that it induced permanent neurological sequelae in few patients. But on further investigation it was showed that low PH of less than 3 and Chloroprocaine containing bisulfite preservative was the reason for neurological complications. In 2005 research had shown that after adjusting the PH of the solution that is going to be used along with a preservative free 2-Chloroprocaine, no complications related to neurological system had occured.[4] The rapid onset and reliable offset of 2-Chloroprocaine has enabled faster mobilization of patients and thereby making day care surgery more feasible and conve-

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nient. The mean duration of action of 2-Chloroprociane was found to be 40 minutes based on the literature review. One of the major disadvantage of using 2-Chloroprocaine is the early occurrence of post-operative pain which could be addressed by adding an adjuvant which would ideally increase the duration of analgesia both during intraoperative and postoperative period[5].

Using fentanyl as an adjuvant for most of the spinal anesthetic agents has well been documented. Fentanyl being an opioid additive prolongs the duration of neuroaxial blockade without significantly increasing the time to ambulation[6–8]. Thus addition of opioids to 2-Chloroprocaine allows its use for slightly longer duration surgeries. The common adverse events that were reported due to addition of an opioid to anesthetic agent was pruritis and post-operative urinary retention[9–11].

Fentanyl being a short acting opioid has very minimal risk in causing respiratory depression at a very low doses being used in spinal anaesthesia[12]. As of today very few studies had been conducted combining fentanyl as an adjuvant with 2-Chloroprocaine and so the present study was undertaken to assess the effect of fentanyl as an adjuvant used with 2-Chloroprocaine on sensory and motor onset and offset block time, time for ambulation and complication rate.

Methodology

A randomized comparative study was conducted for a period of 6 months in the department of anesthesiology at Kirupananda Variyar Medical College Hospital, Salem. The study was started after getting the ethical clearance from the institution. A total of 100 patients posted for elective lower abdomen or perineal surgeries of shorter duration (< 45 mins) with ASA physical status of either I or II in the age group between 20 and 60 were enrolled as our study subjects. After enrolling all the patients each patient was assigned a unique identity number. Following that, an unblinded anaesthetist derived a computer-generated randomized list in which each unique identity number of the patient was linked to either 2-CP alone or 2-CP with fentanyl. As all the surgical procedures were day care procedures no premedication or sedation was given. All patients were kept on fasting for 6 hours prior to the surgery. A 18 gauge intravenous line was placed and 6 ml/kg of crystalloid was infused over 15 mins. Maintenance infusion was given at the rate of 8 mL/Kg/Hr for the first hour and then followed by 2 mL/Kg/Hr thereafter.

Spinal anesthesia was performed using Quinke Babcock spinal needle (BD-Quincke-Spinal-Needles-by-BD – Medline ind), 25 gauge at L3-L4 space in a sitting posture and the patient was immediately made to lie supine after administration of drug. The drug combination was randomly assigned to the patient – Group A patients received intrathecal injection of 3 mL of 1% 2-Chloroprocaine (30 mg) mixed with 0.5 mL of Normal saline and Group B patients received 3 mL of 1% 2-Chloroprocaine (30 mg) mixed with 0.5 mL of Fentanyl solution containing 50 micrograms per mL(25 mcg). The 2-Chloroprocaine solution used for intrathecal administration was a preservative free solution which was manufactured under the name Chlorquik 1% 5 ml amp by Neon lab. India.

The following parameters were monitored in the patients: time for attaining sensory block of T 10, time taken to achieve maximum level of sensory block, regression of sensory block to S2 level, attaining motor block – bromage grade 4, recovery for motor block – to attain bromage grade I, duration of surgery, time to ambulate, time to void urine, time to discharge, heart rate, blood pressure(MAP), pain assessment / patient satisfaction – VAS score, adverse effects like vomiting & pruritus and retention of urine. Bilateral sensory block was assessed in cephalad to caudad direction by using pin prick method. Motor block was assessed using the modified bromage score. Vasopressor Inj. Ephedrine 6mg bolus was given for patients who had a fall in MAP of 20% or more. Once the surgery was completed, the motor block was checked every 15 minutes till bromage score of 0 is achieved. Once sensory block regressed to S2 dermatome and modified bromage score of 0, then the patient was attempted to ambulate. If ambulation was successful then patients were made to attempt voiding of urine. If either ambulation or voiding were unsuccessful, then at ten minute intervals repeat attempts were made until the patient succeeded. All data were entered and analysed using SPSS version 24. Mean and standard deviation was derived for all parametric variables and percentage for all frequency variables. Student T test and chi-square test were used for deriving the statistical inference.

Results

The demographic variables among the study subjects were shown in Table 1.

The mean age of the patients in group A was 39.4 years and in group B it was 40.5 years and the male: female ratio was almost similar in both the groups. Mean height and weight and the mean duration of surgery did not show a statistical significant difference between the two groups based on student T test (Table 1).

Table 1: Demographic characteristic among the study subjects

Demographic variable	Group A	Group B	P value
Age (in years)	39.4 ± 11.8	40.5 ± 12.3	0.818
Male : female	27 : 23	28 : 22	0.916*
Weight (kg)	60.4 ± 7.7	64.2 ± 10.7	0.384
Height (cm)	151.8 ± 9.4	152.3 ± 8.7	0.419
Duration of surgery (min)	32.2 ± 4.6	32.4 ± 4.1	0.946

P value derived by using student T test
**-P value derived by using chi-square test*

The sensory and motor block characteristics such as the time for initiation of sensory block, level of sensory block achievement (T10) and the time for maximum sensory and motor block was similar among the patients who received 2-Chloroprocaine alone and 2-Chloroprocaine with fentanyl and no statistical significant difference was observed between the two groups. Time for regression of sensory block, recovery of motor block and time to void urine was comparatively more among group B (2-chloroprocaine with fentanyl) than group A (2-chloroprocaine) and the difference was found to be statistically significant ($p < .05$). The length of stay in post-anesthesia ICU and

Table 2: Comparison of sensory and motor block characteristics between the two groups

Variables	Group A	Group B	P value
Time for sensory block (min)	4.3 ± 0.67	4.5 ± 0.71	0.654
Sensory block level achieved (min)	T 10	T 10	1.00
Time for maximum sensory block (min)	6.3 ± 0.48	6.3 ± 0.47	0.678
Time for maximum motor block (min)	5.7 ± 0.52	5.9 ± 0.61	0.359
Time for regression of sensory block (min)	65.7 ± 2.1	78.1 ± 3.2	< .0001
Time for recovery of motor block (min)	67.3 ± 4.1	69.3 ± 1.8	0.050
Time to ambulate (min)	84.3 ± 1.09	85.4 ± 1.2	0.418
Time to void urine (min)	198.8 ± 21.9	230 ± 30.9	<.001
Length of stay in Post- anesthesia ICU (min)	304.1 ± 26	312.5 ± 18.5	0.076
Patient satisfaction score (out of 10)	8.5 ± 1.3	8.2 ± 1.05	0.181

P value was derived using student T test

the patient satisfaction score did not show a statistical significant difference between the two groups (Table 2).

The heart rate and the mean arterial pressure were measured from the time of inducing the anesthetic agent (basal) until 30 minutes in the interval of 5 minutes. It was observed that both the heart rate and the MAP were found to be slightly high among the patients who received 2-chloroprocaine with fentanyl (group B) compared to patients who had taken 2-chloroprocaine alone (group A) but the difference was not found to be statistically significant ($p > .05$) (p value derived using student T test). So it can be inferred that there was no gross hemodynamic changes between the two groups (Fig 1 and 2).

Similarly the incidence of adverse events such as bradycardia, hypotension, nausea and vomiting were almost equal in both the groups except for the incidence of post-operative urinary retention found to be slightly high among the fentanyl group but it did not show a statistical significant difference between the two groups (Table 3).

Discussion

2-Chloroprocaine is a recently reintroduced anesthetic agent for day care procedures after being initially withdrawn from the market because of its tendency in causing neurotoxicity. Recent studies had highlighted that addition of opioids with local anaesthetics would prolong the analgesia effect

Fig 1: Comparison of heart rate between two groups after induction of anaesthesia

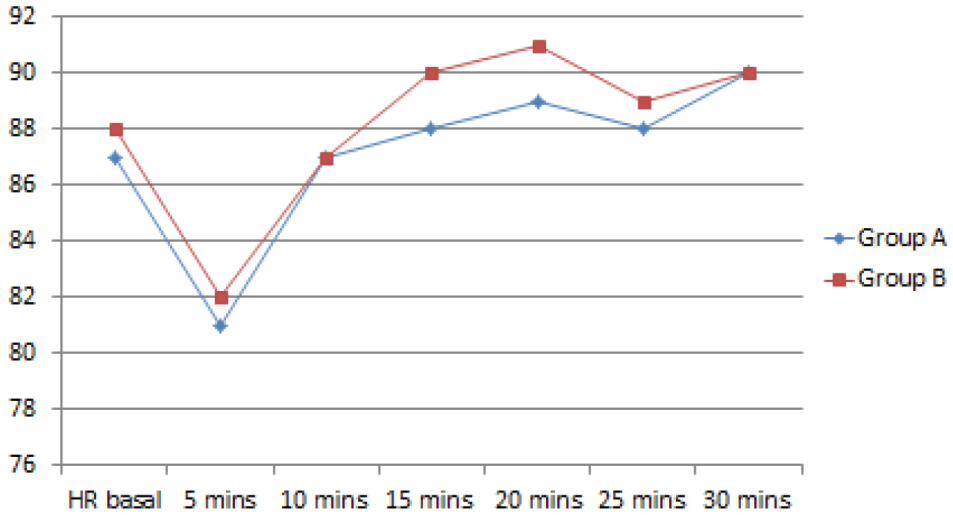

Fig 2: Comparison of Mean arterial pressure between two groups after induction of anaesthesia

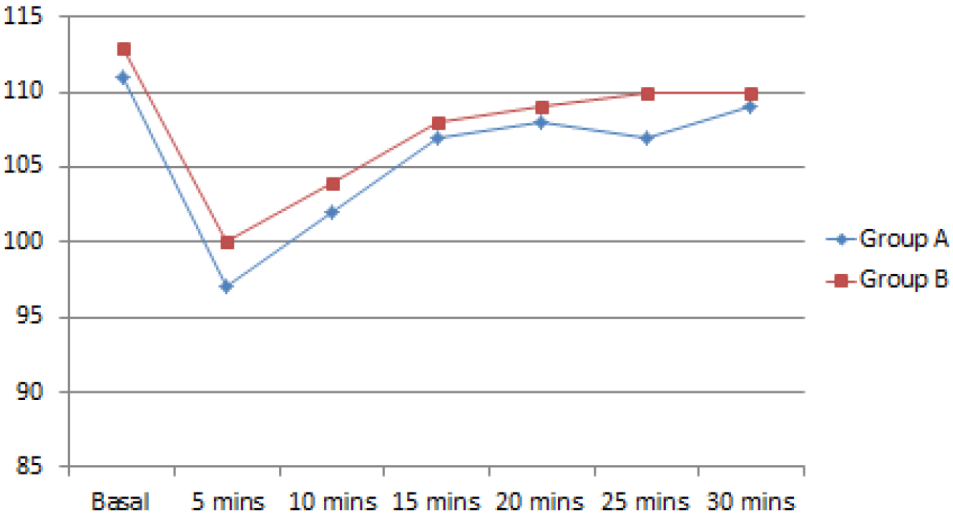

Table 3: Incidence of side effects between the two groups

Side effect	Group A (n=50)	Group B (n=50)	P value
Bradycardia	1 (2%)	2 (4%)	0.384
Hypotension	2 (4%)	2 (4%)	1.00
Nausea	1 (2%)	2 (4%)	0.384
Vomiting	1 (2%)	1 (2%)	1.00
Pruritis	0	1 (2%)	0.219
Post-operative urinary retention	0	2 (4%)	0.183

P value derived using Chi-square test

when administered intrathecally. Among the various opioids which is currently in market fentanyl is the most commonly used which when given along with local anesthetic agent increases the sensory analgesia without prolonging the recovery of spinal anesthesia[13,14]. Fentanyl acts by stimulating μ receptor and it was the first among the fentanyl family of opioids and later sufentanil, alfentanil, and remifentanil were included in that family. Studies had shown that analgesia may occur within 1 to 2 minutes after intravenous administration of fentanyl and its action lasts for 2–4 hours[15,16]. Similar to morphine fentanyl produces central nervous system actions such as fatigue, sedation, nausea, vomiting, dizziness, respiratory depression and bradycardia which are all dose dependant[17].

In the present study, both the groups were comparable with respect to age, sex, height, weight, ASA physical status and the duration of surgery as no statistical difference was observed between the two groups and so there was no need of exclusion of study subjects. This was almost similar to the studies done by Baskara etal and Mulroy etal[18,19].

Changes in heart rate and Mean arterial pressure from the time of induction of anesthesia over a period of 30 minutes were almost similar in both the groups in our study, and it proves that addition of fentanyl to 2-Chloroprocaine do not have any major impact in the hemodynamic system. Studies done earlier had also proven the same.

In our study the mean time for the onset of sensory block, level of sensory block achieved (T10) and the time taken for maximum sensory and motor block was found to be more or less similar in the group which received 2-Chloroprocaine and the group that received fentanyl with 2-Chloroprocaine. So it was proven that addition of fentanyl did not alter the onset of sensory and motor block. The mean time for the onset of sensory block and the achievement of maximum sensory block was 4.3–4.5 mins and 6.3 mins respectively and it was similar to the studies done by Camponovo *et al.* and Baskara et al[20,18]. Similarly the time for maximum motor blockade was 5.7–5.9 mins and it was in par with the study reported by Lacasse et al[21].

In the present study the time for regression of sensory block between group A and group B (65.7 mins vs 78.1 mins), which showed that the group which received fentanyl had a longer time for sensory block regression and it was found to be statistically significant and similarly time for recovery of motor blockade was high among group B compared to group A (69.3 vs 67.3 mins) and was found to be statistically significant and the results were almost similar to the study done by Jacob A et al[22]. Another study conducted by Singariya Geeta et al showed that the mean duration of sensory block was prolonged in group CF (2-Chloroprocaine with fentanyl) in comparison to group CS (2-Chloroprocaine with normal saline), 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, $P < 0.0001$)[23]. A similar study done by Vath, Julie S et al showed that peak block with fentanyl averaged T5 (T3-T7) and without fentanyl T9 (L1-T4) ($p < .005$). The time taken for regression to L1 was 78 ± 7 mins in fentanyl group and it was 53 ± 19 mins without fentanyl ($p < .05$). Complete regression of block occurred at 104 ± 7 mins

with fentanyl and 95 ± 9 mins without fentanyl ($p < .05$)[24]. A similar type of results was also quoted in a meta-analysis study conducted by Retter S etal[25]. In the present study the time for ambulation among the two groups (84.3 vs 85.4 mins) and the time to void urine (198.8 vs 230 mins) was significantly higher among the group which received fentanyl and it was in par with the studies done by Jayaprakash Siddaiah et al and Baskara et al[24,18]. In our study the length of stay in the post-anaesthesia ICU and the patient's satisfaction score did not show statistical significant difference between the two groups. The incidence of hemodynamic side effects such as hypotension and bradycardia did not show any difference between the two groups and similarly the incidence of nausea and vomiting was also seen in equal numbers in both the groups, whereas the incidence the post-operative urinary retention was found to be slightly higher in the fentanyl group and it was similar to the studies done earlier.

The major limitation of the current study, it was not a completely blinded study**.** Although this limitation was identified much before enrolling the patients, we found no better alternative but it was minimized by having the same blinded observer responsible for collecting all data during the entire study.

Conclusion

The addition of intrathecal fentanyl to 2-Chloroprocaine in spinal anaesthesia significantly prolongs the regression of sensory and motor block without a prolonging the duration of post- anaesthesia ICU stay. Fentanyl addition to 2-CP did not show a significant change in the patient satisfaction score and in the occurrence of adverse events with a stable hemodynamic system. We conclude that the addition of fentayl to 2-Chloroprocaine has a significant synergistic effect in prolonging postoperative analgesia without prolonging the time for ambulation.

References

1. Gangadhar S B, Gopal T M, Sathyabhama, Paramesh K S. Rapid emergence of day-care anaesthesia: A review. Indian J Anaesth 2012; 56:336–41.

2. C. Arzola, P. M. Wieczorek, Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis, BJA: British Journal of Anaesthesia, Volume 107, Issue 3, September 2011, Pages 308–318, https://doi.org/10.1093/bja/aer200.

3. Pollock JE. Transient neurologic symptoms: etiology, risk factors, and management. Reg Anesth Pain Med. 2002; 27:581–6.

4. Hejtmanek M.R. and Pollock J.E. Chloroprocaine for spinal anesthesia: a retrospective analysis. Acta Anaesthesiologica Scandinavica. 2011; 55: 267–272 https://doi.org/10.1111/j.1399-6576.2010.02371.x.

5. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine. Anesth Analg. 1980; 59:452–4.

6. Rahimzadeh P, Faiz SHR, Imani F, Derakhshan P, Amniati S. Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. BMC Anesthesiol. 2018 Jun 6; 18(1):62. doi: 10.1186/s12871-018-0531-7.

7. Mahendru V, Tewari A, Katyal S, Grewal A, Singh MR, Katyal R. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery: A double blind controlled study. J Anaesthesiol Clin Pharmacol. 2013 Oct; 29(4):496–502. doi: 10.4103/0970-9185.119151.

8. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. J Anaesthesiol Clin Pharmacol. 2011 Jul; 27(3):339–43. doi: 10.4103/0970-9185.83678.

9. 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, randomised, controlled trial. Acta Anaesthesiol Scand 2014; 58:560–6.

10. Kouri ME, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with lidocaine in volunteers. Anesthesia & Analgesia. 2004 Jan 1; 98(1):75–80.

11. Casati A, Danelli G, Berti M, Fioro A, Fanelli A, Benassi C et al. Intrathecal 2- chloroprocaine for lower limb outpatient surgery: a prospective, randomized, double-blind, clinical evaluation. Anesthesia & Analgesia. 2006 Jul 1; 103(1):234–8.

12. Safari F, Aminnejad R, Mohajerani SA, Farivar F, Mottaghi K, Safdari H. Intrathecal Dexmedetomidine and Fentanyl as Adjuvant to Bupivacaine on Duration of Spinal Block in Addicted Patients. Anesth Pain Med. 2016 Jan 31; 6(1):e26714. doi: 10.5812/aapm.26714.

13. Förster JG, Rosenberg PH. Revival of old local anesthetics for spinal anesthesia in ambulatory surgery. Curr Opin Anaesthesiol. 2011; 24:633–7.

14. Ravindran RS, Bond VK, Tasch MD, Gupta CD, Luerssen TG. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine. Anesth Analg. 1980; 59:447–51.

15. Bailey PL, Stanley TH: Intravenous opioid anesthetics, in Miller RD (ed): Anesthesia, 4th ed. Philadelphia, PA, Churchill Livingston, 1994; Chapter 12.

16. Stanley TH: The history of opioid use in anesthetic delivery, in Eger EI II, Saidman LJ, Westhorpe RN (eds): The Wondrous Story of Anesthesia. New York, Springer, 2014; Chapter 48.

17. Rauch R, Reynolds L, Geach J, Bull J, Stearns L, Scherlis M, Parikh N, Dillaka L: Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: A randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2012; 28:859–870.

18. Bhaskara B, Prabhakar SA, Rangadhamaiah R. Intrathecal 1% 2-chloroprocaine with fentanyl in comparison with ropivacaine (0.5%) with fentanyl in day care perianal surgery: Prospective randomized comparative study. Anesth Essays Res. 2019; 13:471–5.

19. Mulroy MF, Salinas FV, Larkin KL, Polissar NL. Ambulatory surgery patients may be discharged before voiding after short-acting spinal and epidural anesthesia. Anesthesiology 2002; 97:315–9.

20. 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.

21. Lacasse MA, Roy JD, Forget J, Vandenbroucke F, Seal RF, Beaulieu D, et al. Comparison of bupivacaine and 2-chloroprocaine for spinal anesthesia for outpatient surgery: A double-blind randomized trial. Can J Anesth. 2011; 58:384–91.

22. Jacob A, Kopp S, Bacon D. The History of Anaesthesia In: Barash P, Cullen B, Stoelting R, Cahalan M, Stock M, Ortega R editors Clinical Anaesthesia 7th Edition Philadelphia Lippincott 2013; p 15–18.

23. Singariya, Geeta, Choudhary, Kusum, Kamal, Manoj, Bihani, Pooja, Pahuja, Himani, Saini Pradeep. Comparison of analgesic efficacy of intrathecal 1% 2-chloroprocaine with or without fentanyl in elective caesarean section. A prospective, double-blind, randomised study. Indian Journal of Anaesthesia. February 2021; Volume 65, Issue 2, p 102–107.

24. Vath, Julie S. MD; Kopacz, Dan J. MD Spinal 2-Chloroprocaine: The Effect of Added Fentanyl, Anesthesia & Analgesia: January 2004; Volume 98, Issue 1, p 89–94.

25. 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.