Chloroprocaine spinal Anaesthesia and the effects of added Clonidine

Authors
Dr Satyen Verma¹, Dr Sarfaraz Ahmad², Dr Akash Gupta³*, Dr Malti Agarwal⁴, Dr Ram Pal Singh⁵, Dr Vigneshwaran Swaminathan⁶

¹Junior Resident, Department of Anaesthesia, RMCH, Bareilly
²Assistant Professor, Department of Anaesthesia, RMCH, Bareilly
³Assistant Professor, Department of Anaesthesia, RMCH, Bareilly
⁴Professor and HOD, Department of Anaesthesia, RMCH, Bareilly
⁵Professor, Department of anaesthesia, RMCH, Bareilly
⁶Junior Resident, Department of Anaesthesia, RMCH, Bareilly

*Corresponding Author
Dr Akash Gupta

Abstract
Background and Aim: 2-Chloroprocaine (C13H19ClN2O2) an ultra-short acting, ester derivative of benzoic acid, is being investigated intrathecally in small doses (30 to 60 mg) and it was find reliable for procedures of short duration. Clonidine (C9H9Cl2N3) an imidazoline derivative, centrally-acting alpha2-adrenergic agonist, improves the quality of spinal bupivacaine and ropivacaine. It has not been studied in combination with 2-CP. So we conducted this study to evaluate effect of adding clonidine to spinal Chloroprocaine.

Methods: In this prospective randomized controlled study, spinal 2-CP (30 mg) with and without clonidine (30 mcg) in 60 adult patients posted for elective surgery of lower abdomen or lower limb. Patients were randomly divided randomly in 2 groups who received intrathecally either chloroprocaine (30mg+0.2 ml saline) or chloroprocaine (30 mg) with clonidine (30 mcg, 0.2ml). Hemodynamic changes, onset and duration of sensory blockade, onset and duration of motor blockade, 2-segment regression time, Peak height for sensory block, time to attain peak height for sensory block were studied in both the groups.

Results: Mean systolic and diastolic blood pressures were significantly more decreased in group of patients who received clonidine with intrathecal chloroprocaine. Duration of sensory block averaged 3.90 ± 1.12 sec and 5.10 ± 1.55 sec without clonidine, time of peak heights of sensory block averaged 7.70 ± 1.56 sec with clonidine and 5.84 ± 1.61 sec without clonidine, duration of sensory blockade averaged 101.00 ± 14.99 min with clonidine and 54.77 ± 7.91 min without clonidine, mean 2-segment regression time was 76.63 ± 15.69 min with clonidine and 40.90 ± 6.99 min without clonidine, onset of motor blockade was averaged 4.40 ± 1.28 sec with clonidine and 6.5 ± 1.20 sec without clonidine, mean duration of motor blockade was 91.80 ± 14.47 min with clonidine and 48.30 ± 8.97 min without clonidine.

Conclusion: We found significantly enhancement in duration of motor and sensory blockade, peak height of sensory anaesthesia and 2 segment regression time by adding clonidine to intrathecal chloroprocaine. No significant adverse effects were seen in the patients while conducting the study. We found Chloroprocaine to be an effective and safe alternative for lower limb and lower abdominal surgeries of short duration.

Keywords: Chloroprocaine, Clonidine, Spinal Anaesthesia, Motor blockade, Sensory blockade.
Introduction

Local anaesthetics (LA) are indispensable in the context of regional anaesthesia and pain management. Local anaesthetics (LA) are a heterogeneous group of compounds which block voltage-gated sodium channels. Sodium channel block is caused by conformational change and the creation of a positive charge in the channel lumen. LA can be divided into short-acting (e.g., chloroprocaine), intermediate-acting (e.g., mepivacaine, lidocaine), and long-acting (e.g., bupivacaine, ropivacaine) compounds. For spinal anaesthesia, the target binding sites are located within the spinal cord (superficial and deep portions) and on the spinal nerve roots in the subarachnoid and epidural spaces. Chloroprocaine being an ultra–short-acting local anesthetic, came in the 1950s. In 1952, Foldes FF first used Chloroprocaine for spinal anaesthesia in 214 patients without neurologic complications. Chloroprocaine is an ultra-short acting, ester derivative of benzoic acid and has been used intrathecally in small doses (30 to 60 mg) and it was reliable for procedures of short duration. Many drugs have been used in spinal anaesthesia as adjuvant to LA. It has been shown that use of adjunct to spinal anaesthetics significantly improves quality and duration of sensory and motor blockade. TNS can occur with modern chloroprocaine preparations, albeit at a considerably lesser rate (0.6%) than lidocaine (14%), so newer preparation of Chloroprocaine is much safer to use for Spinal anaesthesia. Clonidine is an imidazoline derivate and centrally-acting alpha2-adrenergic agonist, with antihypertensive activity. Clonidine was first used in 1984 in epidural blocks. Epidural clonidine in doses of 25-50 μg/h has been found to have beneficial effects in various study populations like spine instrumentation and orthopaedic procedures. After taking clearance from ethical committee, we conducted this study in department of Anaesthesiology, Rohilkhand Medical College, Bareilly. In this study we have evaluated and compared the effect of Chloroprocaine alone and in combination with clonidine in lower limb and lower abdominal surgeries.

Methods

This was a prospective randomized controlled study carried out in patients posted for lower limb and lower abdominal surgeries of different specialities. After taking ethical committee clearance, 60 patients were randomly divided into two groups: Group “A” and “B”. In Group A, for spinal anaesthesia chloroprocaine (30mg + 0.2 ml saline) was used, while in Group B, for spinal anaesthesia chloroprocaine (30 mg) with clonidine (30 mcg, 0.2ml) was used and the drugs was prepared by an anaesthetist not involved in observations. Spinal anaesthesia was performed with all aseptic precautions at the L2-3 inter-vertebral space with the patient sitting, using the midline approach and a 25-gauge spinal needle. After completing spinal injection, patients were placed supine, continued evaluation of sensory (with pin-prick method) and motor blocks for every 2 mins for first 20 mins, then every 5 mins for 40 mins, and then every 15 mins until the sensory block regressed to S1 dermatome and complete motor block regression was done. The level of sensory block was assessed using the loss of pinprick sensation (24-gauge hypodermic needle); whereas motor block by modified Bromage scale. After surgical anaesthesia was achieved, readiness for surgery was defined as loss of pin prick sensation ≥ T10 along with motor blockade to modified Bromage ≥2. Sensory and motor functions during the procedure were observed on the non-operative side. If the patient complained of pain during surgery, supplemental analgesia with 0.02 mg/kg inj Butarphanol IV was administered. We Compared hemodynamic changes, onset and duration of sensory blockade, onset and duration of motor blockade, 2-segment regression time, peak height for sensory block, time to attain peak height for sensory block, to find out if any side effects/ complications like
nausea, vomiting, bradycardia, hypotension and Transient neurologic symptoms.
In our study we described Bradycardia, when heart rate was reduced to less than 50 beats / min and Hypotension was described when systolic blood pressure was reduced to more than 30% of base line.

**Statistical Analysis:** The data from the present study was systematically collected, compiled and statistically analysed. Descriptive & inferential statistical analysis were derived from results on continuous measurements, presented as mean ± SD while results on categorical measurements were presented in numbers (%age). Student t test was used to find the significance of the study parameters on a continuous scale between 2 groups (intergroup analysis).

The p value was determined to evaluate the level of significance, p<0.05 was considered as significant at 5% significance level, while p<0.01, significant at 1% was considered as highly significant. Chi Square/ Fisher’s exact test was used to find the significance of the study parameters on the categorical scale where ever applicable between 2 or more groups.

The statistical data analysis was done by Microsoft Excel 2016 and Microsoft Word 2016 it was used to generate graphs, charts and tables.

**Results**
In our study, in comparison between both the groups, mean heart rate was significantly more decreased in group of patients who received clonidine with intrathecal chlorprocaine. In group A there was no incidence of clinically significant bradycardia in any patient while in group B, bradycardia was seen in 2 patients (6.6%), out of which one patient was given 0.5 mg injection Atropine to treat bradycardia. Rest 3 patients recovered without any intervention. In our study mean systolic and diastolic blood pressures were decreased from base line in both the groups after spinal anaesthesia. In comparison between both the groups mean systolic and diastolic blood pressures were significantly more decreased in group of patients who received clonidine with intrathecal chlorprocaine. In patients of group A, there was not clinically significant reduction in blood pressure after spinal anaesthesia while in patients of group B hypotension was seen in 10% of patients in our study. Which was treated with boluses 200ml – 250 ml of iv fluid and only 1 patient required vasoactive agent injection Mephentermin in the dose of 6mg, once. In the present study, we found that mean time of onset of sensory analgesia was less in group of patients who received Chloroprocaine with clonidine. The mean time taken to achieve highest level of sensory analgesia was significantly more in group of patients who received Chloroprocaine with clonidine. The mean time for two segment sensory regression in was significantly more in group of patients who received Chloroprocaine with clonidine. In the present study mean time taken for sensory regression to L1 was significantly more in group of patients who received Chloroprocaine with clonidine. The mean time of total duration of motor block was significantly more in group of patients who received Chloroprocaine with clonidine. We found significantly enhancement in duration of motor and sensory blockade, peak height of sensory anaesthesia and 2 segment regression time by adding clonidine to intrathecal chlorprocaine. No significant adverse effects were seen in the patients while conducting the study.
Table 1: Comparison of Age, Weight and Gender in Between Group A and Group B

|               | GROUP A       | GROUP B       | t-value | p-value |
|---------------|---------------|---------------|---------|---------|
| AGE           | 42.40 ± 12.29 | 45.27 ± 13.85 | 0.848   | 0.400#  |
| SEX           |               |               |         |         |
| MALE          | 21(70%)       | 26(86.7%)     |         |         |
| FEMALE        | 9(30%)        | 4(13.7%)      | 2.455   | 0.117#  |
| WEIGHT        | 70.77 ± 6.64  | 68.50 ± 6.08  | 1.381   | 0.1726# |

# statistically not significant

Graph 1: HEART RATE

Graph 2: Mean Systolic Blood Pressure
Table-2 Comparison of Mean Onset of Sensory Block, Time of Peak Height For Sensory Block, Duration of Sensory Block and 2-Segment Regression time in between Group A and Group B.

|                      | GROUP A       | GROUP B       | t-Value | p-Value |
|----------------------|---------------|---------------|---------|---------|
| Onset of sensory blockade | 5.10 ± 1.55   | 3.90 ± 1.12   | 3.437   | <0.001* |
| Time of Peak height for sensory block | 5.84 ± 1.61   | 7.70 ± 1.56   | 4.544   | <0.001* |
| Duration of sensory block | 54.77 ± 7.91  | 101.00 ± 14.99 | 14.94   | <0.001* |
| 2-segment regression time | 40.90 ± 6.99  | 76.63 ± 15.69 | 11.444  | <0.001* |

*statistically significant.

Table-3 Comparison of Mean Onset of Motor Block at Different Time Interval in Between Group A and Group B.

|                      | GROUP A       | GROUP B       | t-Value | p-Value |
|----------------------|---------------|---------------|---------|---------|
| Onset of motor blockade | 6.5 ± 1.20    | 4.40 ± 1.28   | 6.556   | <0.001* |
| Duration of motor block | 48.30 ± 8.97  | 91.80 ± 14.47 | 13.99   | <0.001* |

*statistically significant.
Table-4 Comparison of Peak Height for Sensory Block in Between Group A and Group B.

| Peak height for sensory block | GROUP A | GROUP B | X² -value | P -value |
|-------------------------------|---------|---------|-----------|---------|
| number                        | %       | number  | %         |         |
| T6                            | 0       | 8       | 26.7      | 10.58   | 0.014*  |
| T8                            | 18      | 16      | 53.3      |         |         |
| T9                            | 1       | 0       | 0.0       |         |         |
| T10                           | 11      | 6       | 20.0      |         |         |
| TOTAL                         | 30      | 30      | 100.0     |         |         |

*statistically significant.

Table-5 Comparison of Mean Onset of Side Effect In Between Group A and Group B.

| Side Effect     | Group A | Group B |
|-----------------|---------|---------|
| TNS             | 0       | 0       |
| Hypotension     | 0       | 3       |
| Bradycardia     | 0       | 2       |
| PONV            | 1       | 3       |
| Respiratory Depression | 0 | 0 |
| Pruritus        | 0       | 0       |
| Shivering       | 0       | 4       |

Discussion

Day Care Surgeries are the latest trend in practice to reduce hospital stay and cost burden. The patients do not wish to lose work. They prefer to resume their day today activities at the earliest. A faster recovery for the patients not only benefits the patients but also reduces the burden from the already overburdened health care services in our country.

Our study showed that intrathecal 30 mg preservative free chloroprocaine produces adequate sensory and motor anaesthesia for short duration procedure of lower abdomen and lower limb and that the addition of 30 mcg clonidine to intrathecal chloroprocaine prolongs both quality and duration of sensory and motor blockade. Casati A et al 6 evaluated the dose-response relationship of 2-Chloroprocaine for lower limb outpatient procedure and concluded that chloroprocaine provided adequate spinal anaesthesia for outpatient procedures lasting 45–60 min. Förster JG et al7 also found similar results and stated Chloroprocaine as an appealing option for spinal anaesthesia.

In studies adding 15 mcg of clonidine with bupivacaine8 and ropivacaine9 showed increased block height compared with each drug alone. Spinal clonidine has been shown to improve the quality of spinal anesthesia, but in doses of 1–2 mcg/kg, significant systemic side effects were seen, including sedation, hypotension, and bradycardia 10,11,12. Recent studies have evaluated the effects of clonidine in doses as small as 15 mcg and have found it to be effective and without these unwanted side effects 8,9. Kouri ME et al13 on Chloroprocaine has shown mild hemodynamic changes and none of patient needed vasoactive agents. Casati A et al14, Dobrynjov I et al15 and Gonter et al15 also found similar results.. In other studies done by Siddaiah et al16, Teunkens A et al17, Lacasse MA et al18, on Chloroprocaine and they did not find significant bradycardia in patients. In our study the mean systolic and diastolic blood pressure was significantly more decreased in patients of group B than group A. In the studies done by Kouri et al13, Casati et al19 and Gonter et al15 on Chloroprocaine have shown mild blood pressure changes with none of patient needed vasoactive agents.

The study conducted by Lacasse MA et al18, Siddaiah et al16 and Camponovo et al21 on Chloroprocaine found incidence of hypotension 8%, 12%, 4.5% respectively. We found significant early onset of sensory blockade in group of patients who received clonidine to spinal chloroprocaine. Similar results to our study were...
found by Chetty DK et al\textsuperscript{22} Dissimilar results with this study were seen by Agarwal et al\textsuperscript{23} and Davis BR et al\textsuperscript{2}. There was significant difference in Peak height for sensory block in between group A and Group B (p=0.014). We found that peak height of sensory block attained was higher in group of patients who received Chloroprocaine with clonidine. Our results were similar with the study done by De Kock M et al\textsuperscript{24}, Agarwal et al\textsuperscript{23} and Dobrydnjov I et al\textsuperscript{25}. Although in their study Davis BR et al\textsuperscript{2} didn’t find any significant change in peak height of sensory block.

Time taken for highest level of sensory analgesia was statistically significant in both the group and the time needed was more in patients who received clonidine as an adjuvant to Chloroprocaine intrathecally. Our observations were same as found by Agarwal et al\textsuperscript{23} as time to achieve peak height was statistically more in group of patients who received 15 mcg Clonidine as an adjuvant to spinal block. In spite of this our findings were different than the observations found by Singh G et al\textsuperscript{26}. In our study, time for 2 segment regression was statistically higher in group of patients who got spinal anaesthesia with Chloroprocaine along with Clonidine. Our observations were concurrent with study done by Agarwal et al\textsuperscript{23} as time to two segment sensory regression was statistically more in group of patients who received 30mcg Clonidine as an adjuvant to spinal block. Same results were found by Dobrydnjov I et al\textsuperscript{25} although our observations were dissimilar to the study done by Davis BR et al\textsuperscript{2} on Intrathecal 30mg Chloroprocaine alone and with 15 mcg Clonidine. In the present study duration of sensory blockade was statistically significant (p<0.001) and different among the groups, it was prolonged in the group who received Chloroprocaine with Clonidine intrathecally. Our observations were similar to the studies done by Davis BR et al\textsuperscript{2}, Kanazi GE et al\textsuperscript{27} and Singh G et a\textsuperscript{26}. Time for onset of motor block was the mean time of onset of motor blockade with modified Bromage grade 3. In our study we found significant less time required for onset of motor blockade in group of patients who received intrathecally Chloroprocaine with Clonidine. Our result was same with the observations found by Kanazi GE et al\textsuperscript{27} although our results were different to study done by Singh G et al\textsuperscript{26}. In our study we found more mean time of total duration of motor block in group of patients who received clonidine as an adjuvant to intrathecal chloroprocaine. Our results were similar with the results observed in study done by Davis BR et al\textsuperscript{2}, Dobrydnjov I et al\textsuperscript{25} and Singh G et al\textsuperscript{26} they observed significant increase in duration of motor block by using Clonidine as an adjuvant to intrathecal Bupivacaine.

No adverse effects were seen in the patients while conducting the study.

**Side Effects**

In our study incidence of post-operative nausea and vomiting was seen in 1 patient (3.3%) in group A and in 3 patients (10%) of group B which may be due to more incidence of hypotension in patients of group B. None of patient from group A had shivering while 4 patients (13.3%) of group B developed shivering. None of our patient gave complaint of pruritis. In our study there was no incidence of transient neurologic symptoms. None of our patients gave complaint of pruritis or Respiratory depression in either group.

**Conclusion**

We concluded that low-dose clonidine increases the duration and potentiates the quality of both sensory and motor blockade when used as an adjuvant to chloroprocaine spinal anesthesia. Up to low dose of 30 μg, the unwanted side effects seen with the traditional larger doses were not observed. The duration of sensory and motor blockade was shorter in Chloroprocaine and better suited for elective short duration surgery. Peak Sensory Block achieved was higher with CP with Clonidine group and the slower regression of the block, made it a good choice for elective lower limb surgery. This makes it a suitable combination for outpatient anesthesia.
References
1. Miller R, Cohen N, Eriksson L, Fleisher L, Wiener-Kronish J, Young W. Miller's anesthesia. 8th ed. 2015. p. 1688
2. Davis BR, Kopacz DJ. Spinal 2-chloroprocaine: the effect of added clonidine. Anesthesia & Analgesia. 2005 Feb 1;100(2):559-65.
3. Foldes FF, McNall PG. 2-Chloroprocaine: a new local anesthetic agent. Anesthesiology: The Journal of the American Society of Anesthesiologists. 1952 May 1;13(3):287-96.
4. Miller R, Cohen N, Eriksson L, Fleisher L, Wiener-Kronish J, Young W. Miller's anesthesia. 8th ed. 2015. p. 1696
5. Rockemann MG, Seeling W, Brinkmann A, Goertz AW, Hauber N, Junge J, Georgieff M. Analgesic and hemodynamic effects of epidural clonidine, clonidine/morphine, and morphine after pancreatic surgery--a double-blind study. Anesthesia & Analgesia. 1995 May 1;80(5):869-74.
6. Casati A, Fanelli G, Danelli G, Berti M, Ghisi D, Brivio M, Putzu M et al. Spinal anesthesia with lidocaine or preservative-free 2-chloroprocaine for outpatient knee arthroscopy: a prospective, randomized, double-blind comparison. Anesthesia & Analgesia. 2007 Apr 1;104(4):959-64.
7. Förster JG. Short-acting spinal anesthesia in the ambulatory setting. Current Opinion in Anesthesiology. 2014 Dec 1;27(6):597-604.
8. Dobrydnjov I, Axelsson K, Thorn S-E, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesth Analg 2003;96:1496–503.
9. De Kock M, Gautier P, Fanard L, et al. Intrathecal ropivacaine and clonidine for ambulatory knee arthroscopy. Anesthesiology 2001;94:574–8.
10. Dobrydnjov I, Samarutel J. Enhancement of intrathecal lidocaine by addition of local and systemic clonidine. Acta Anaesthesiol Scand 1999;43:556–62.
11. Niemi L. Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anaesthesiol Scand 1994;38:724–8.
12. Bonnet F, Brun Buisson V, Francois Y, et al. Effects of oral an subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth Pain Med 1990;15:211–4.
13. Kouri ME, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with lidocaine in volunteers. Anesthesia & Analgesia. 2004 Jan 1;98(1):75-80.
14. 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.
15. Dobrydnjov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, Gupta A. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesthesia & Analgesia. 2003 May 1;96(5):1496-503.
16. Gonter AF, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with procaine in volunteers. Anesthesia & Analgesia. 2005 Feb 1;100(2):573-9.
17. Siddaiah J, Pujari VS, Madalu AS, Bevinaguddaiah Y, Parate LH. A comparative study on the effect of addition of intrathecal buprenorphine to 2-chloroprocaine spinal anesthesia in short duration surgeries. Journal of Anaesthesiology, Clinical Pharmacology. 2019 Oct;35(4):533-9.
18. Teunkens A, Vermeulen K, Van Gerven E, Fieuws S, Van de Velde M, Rex S. Comparison of 2-chloroprocaine, bupivacaine, and lidocaine for spinal anesthesia in patients undergoing knee arthroscopy in an outpatient setting: a double-blind randomized controlled trial. Regional Anesthesia & Pain Medicine. 2016 Sep 1;41(5):576-83.

19. Lacasse MA, Roy JD, Forget J, Vandenbroucke F, Seal RF et al. Comparison of bupivacaine and 2-chloroprocaine for spinal anesthesia for outpatient surgery: a double-blind randomized trial. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2011 Apr 1;58(4):384-91.

20. 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.

21. Camponovo C, Wulf H, Ghisi D, Fanelli A, Riva T, Cristina D, Vassiliou T, Leschka K, Fanelli G. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: a prospective, observer-blinded, randomised, controlled trial. Acta Anaesthesiologica Scandinavica. 2014 May;58(5):560-6.

22. Agarwal D, Chopra M, Mohta M, Sethi AK. Clonidine as an adjuvant to hyperbaric bupivacaine for spinal anesthesia in elderly patients undergoing lower limb orthopedic surgeries. Saudi journal of anaesthesia. 2014 Apr;8(2):209-14.

23. Agarwal D, Chopra M, Mohta M, Sethi AK. Clonidine as an adjuvant to hyperbaric bupivacaine for spinal anesthesia in elderly patients undergoing lower limb orthopedic surgeries. Saudi journal of anaesthesia. 2014 Apr;8(2):209-14.

24. De Kock M, Gautier P, Fanard L, Hody JL, Lavand’homme P. Intrathecal Ropivacaine and Clonidine for Ambulatory Knee Arthroscopy A Dose–Response Study. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2001 Apr 1;94(4):574-8.

25. Dobrynjnov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, Gupta A. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesthesia & Analgesia. 2003 May 1;96(5):1496-503.

26. Singh G, Aulakh GS, Aulakh NK, Singh RM, Bose A, Katayal S, Aulakh BS. Effect of intrathecal clonidine versus fentanyl on bupivacaine spinal block in transurethral resection of prostate surgeries. Anesthesia, essays and researches. 2016 Jan;10(1):65-70.

27. Kanazi GE, Aouad MT, Jabbour- Khoury SI, Al Jazzar MD, Alameddine MM, Al- Yaman R, Bulbul M, Baraka AS. Effect of low- dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta anaesthesiologica Scandinavica. 2006 Feb;50(2):222-7.