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ORIGINAL ARTICLE

Effects of Combination of Intrathecal Fentanyl Clonidine with Bupivacaine in Patients for Operative Knee Arthroscopic Procedure

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ABSTRACT

Introduction: The addition of neuraxial fentanyl or clonidine potentiates the effect of local anesthetic and increases the duration of action and quality of intraoperative and postoperative analgesia. We decided to conduct this study to analyze the synergistic effect of clonidine and fentanyl with bupivacaine on the duration of analgesia surgies. The primary aim is to determine the duration of analgesia for a combination of intrathecal clonidine and fentanyl with bupivacaine in knee arthroscopic surgeries.

Materials and methods: We included 100 patients undergoing operative ARTHROSCOPIO procedure and randomly allocated the patients into four different groups of 25 each.
Group S: 15 mg 0.5% hyperbaric bupivacaine with 1.0 mL normal saline (NS).
Group F: 15 mg 0.5% HB with 25 µcg fentanyl citrate and 0.5 mL NS.
Group C: 15 mg 0.5% HB with 75 µcg clonidine and 0.5 mL NS.
Group FC: 15 mg 0.5% HB with 25 µcg fentanyl citrate and 75 µcg clonidine.

All the patients received the spinal dosage of 4 mL.

Results: The duration of spinal analgesia was greatest in group FC (458.4 ± 179.96 minutes, p-value 0.001). The rescue analgesic requirement in 24 hours was significantly less in group FC, and the incidence of side effects was comparable.

Conclusion: The combination of clonidine and fentanyl with bupivacaine intrathecally does augment its sensory, motor, and analgesic action further, and hence it has an additional advantage with similar side effects.

Keywords: Arthroscopic, Bupivacaine, Clonidine fentanyl, Intrathecal, Postoperative analgesia.

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INTRODUCTION

The addition of neuraxial opioid or nonopioid with local anesthetic increases the duration of action and quality of intraoperative and postoperative analgesia.[1] Clonidine is a centrally acting selective partial alpha-2-adrenergic agonist that acts primarily as an antihypertensive drug and induces sedation, decreases anesthetic requirements, improves the perioperative hemodynamic and sympathoadrenal stability, and prolongs the duration of sensory and motor blockade produced by the local anesthetic when used in spinal anesthesia with bupivacaine.[2,3]

Fentanyl citrate is a synthetic opioid agonist used in spinal anesthesia in combination with bupivacaine to potentiate the analgesic effects.[4]

Both of these drugs, when used intrathecally with a local anesthetic agent, potentiated the effects of anesthesia as well as analgesia.[5] Hence, we used these two drugs in combination with bupivacaine intrathecally to assess the synergistic effects.

The primary aim of this study is to determine the duration of analgesia and motor blockade with a combination of clonidine and fentanyl with bupivacaine in operative knee arthroscopic surgeries. The secondary aim is to assess the onset and fixation of sensory and motor blockade, postoperative analgesic requirement, and incidence of adverse effects like hypotension, bradycardia, shivering, nausea, vomiting, and urinary retention in patients undergoing spinal anesthesia in knee arthroscopic procedures.

MATERIALS AND METHODS

This is a prospective, randomized, controlled, and double-blinded study conducted from June 2011 to June 2012 after obtaining hospital ethical clearance.

We included 100 patients and randomly allocated them to four different groups by block randomization, each block containing four patients, one of each group. The allocation to the group was done by chit system that was labeled as S, F, C, and FC, which the recovery nurse picked up once the patient was received in the recovery room preoperatively. The drug was prepared by the investigator, and spinal anesthesia was given and monitored by an anesthesiologist not involved in the study.

Group S received 15 mg of 0.5% hyperbaric bupivacaine with 1.0 mL of normal saline. Group F received 15 mg of 0.5% hyperbaric bupivacaine with 25 µcg fentanyl citrate and 0.5 mL of normal saline. Group C received 15 mg of 0.5% hyperbaric bupivacaine with 75 µcg clonidine and 0.5 mL normal saline. Group FC received 15 mg of 0.5% hyperbaric bupivacaine with 25 µcg fentanyl citrate and 75 µcg clonidine.

All the patients received the spinal dose of 4 mL volume, and hence normal saline was added.

Patients consenting for inclusion in the study were of physical status American Society of Anesthesiologists grade I and II between the age of 18 and 60 years, height of 150 and 170 cm, and undergoing operative knee arthroscopic surgeries.

Patients refusing consent for inclusion in the study, allergic to local anesthetics, contraindication for regional anesthesia, and on beta-blockers were excluded from the study. Intraoperatively, patients having extremes of hemodynamics, inadequate analgesia, or postspinal anesthesia for more than 20 minutes were excluded from the study.

After securing an intravenous access and after preloading with 500 mL of Ringer lactate, all patients received spinal anesthesia in the sitting position with a 27G spinal needle under all aseptic precautions with the study solution allotted. They were monitored for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), oxygen saturation, the onset, fixation, and duration of sensory action, motor blockade, duration of analgesia, and maximum sensory level by an anesthesiologist not included in this study.

After noting the baseline preoperative parameters, further monitoring was done every 5 minutes after administration of spinal anesthesia for the first 15 minutes and then every 15 minutes till skin sutures were completed.

The perception of tingling in lower limbs was considered as the onset of sensory action. The perception of heaviness in lower limbs was considered as the onset of motor blockade. The time required for fixation of sensory block up to spinal level T 10 was considered as the fixation of sensory action. The fixation of motor block was considered as the time required to achieve a modified Bromage scale of 1.

The sensory level was assessed by pinprick method, pain by visual analogue scale (VAS) of 0 to 10, where 0 is "no pain" and 10 is "worst possible pain," motor blockade by modified Bromage score (Appendix A).

If sensory spinal action or motor blockade was inadequate after 20 minutes of intrathecal injection, the case was excluded.

Appendix A: Modified Bromage scale

1	Complete block (unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knees)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Appendix B: Ramsay sedation score

1	Patient anxious or agitated or both
2	Patient cooperative, oriented, and tranquil
3	Patient response to command only
4	Brisk response to light glabellar tap
5	Sluggish response to light glabellar tap
6	No response

In the case of intraoperative hypotension, SBP < 90 mm Hg was treated with a bolus of 100 mL of Ringer lactate followed by injection ephedrine in aliquots of 6 mg in titrated doses intravenously. The incidence of bradycardia with HR < 45 beats/minute was treated with atropine 0.6 mg intravenous injection. Rescue analgesia was given with paracetamol 1 gm intravenous for pain for VAS score > 4/10.

The incidence of side effects like nausea, vomiting, hypotension, bradycardia, sedation, urinary retention, pruritus, and shivering was noted. The sedation was assessed by Ramsay sedation scale (Appendix B).

Statistical Analysis

Initially, a pilot study was done and the sample size was calculated from 80 patients by considering the difference in the duration of analgesia among groups. With the assumptions of alpha as 0.05, power of 0.85, standard deviation of 107.8 minutes, and maximum difference among the means of four groups as 117.3 minutes, a sample size of 25 was adequate. Hence, we decided to select a study group of 25 per group.

The data were managed in Microsoft Excel spreadsheet. Demographics were described with mean and standard deviation. All the groups were compared using one-way analysis of variance with Tukey's multiple comparison *post hoc* tests to investigate the various parameters like onset and fixation of sensory and motor block, duration of analgesia and motor block, pulse, SBP, DBP, and MAP among the four groups. The data were considered significant with $p < 0.05$. The adverse events were compared using chi-square test, in which $p < 0.01$ was considered statistically significant. All specific graphs were drawn and statistical analysis was done using Minitab16.

RESULTS

No patients were excluded from the study.

Table 1 shows the demographic data for all the groups and they were comparable.

The effect of the study solution is tabulated in Table 2. The duration of onset of sensory and motor blockade was delayed, but fixation of sensory and motor blockade was earlier in the FC group. The duration of analgesia and motor blockade is more in the "FC and C group." The value was significantly greater than in the other groups but comparable with each other.

Graphs 1A to C shows the hemodynamics intraoperatively. Our statistical analysis revealed a significant reduction in DBP at 60 minutes for groups C and S and groups F and C, p-values being 0.006; at 90 minutes for groups C and S; and at 105 minutes for groups F and C, p-values being 0.021 and 0.043 respectively. Similarly, reduction in MAP at 45 minutes for group C compared with group S was significant, with p-value being 0.028. But the reduction in pulse, SBP, DBP, and MBP was comparable in all groups at all other times.

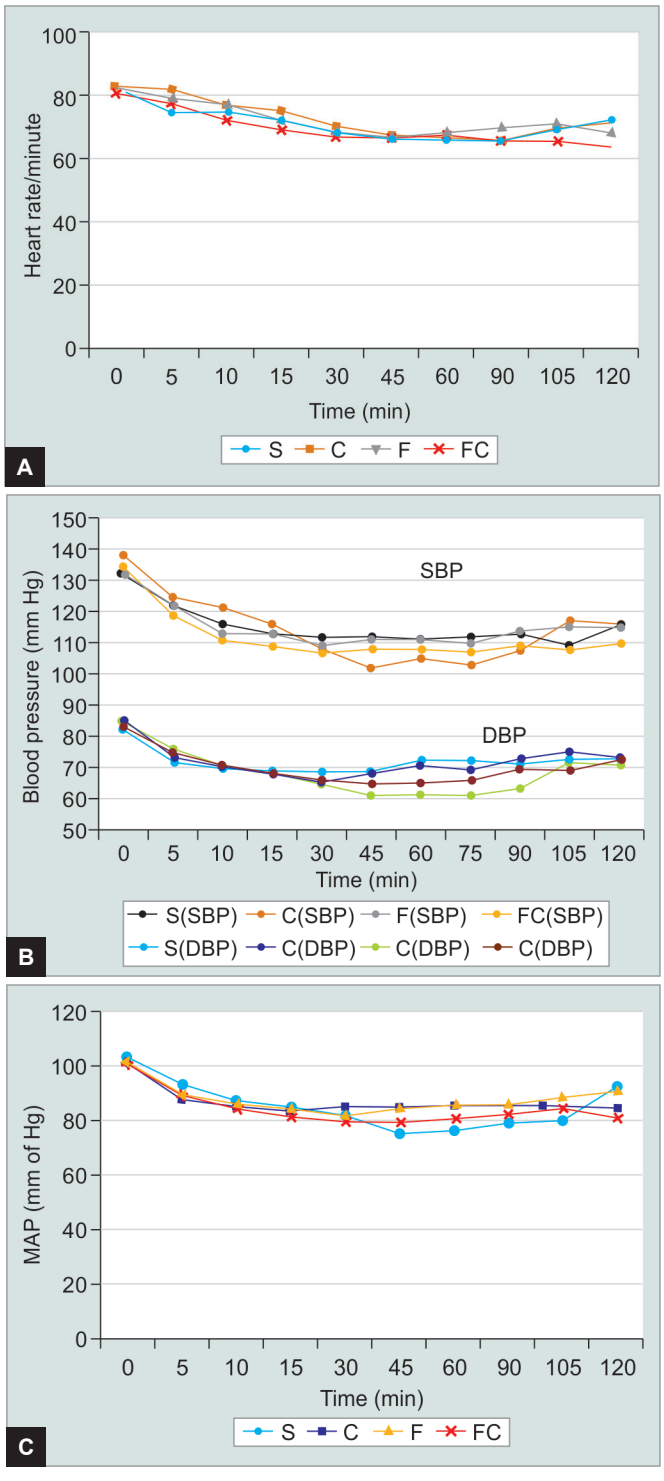
In our study, there was a significant reduction of DBP between 45 and 60 minutes and MAP between 60 and 105 minutes in FC and C groups as compared with group S postspinal anesthesia, but when we compared FC and C groups, the results were comparable.

Table 3 shows the incidence of side effects, which is comparable in all the groups.

DISCUSSION

Intrathecal opioids are lipophilic and act on the pre- and postsynaptic primary afferent neurons and modulate the C and A delta fibers.[1] They have a synergistic effect with local anesthetic, thereby potentiating their action. Alpha-2-adrenergic agonist also enhances analgesia from intraspinal opioids.[2]

Intrathecal clonidine is a partial agonist at alpha-2-adrenoceptors that inhibits the nociceptive impulses by activating postjunctional alpha-2-adrenoceptors in the dorsal horn of the spinal cord. It also has a local effect on sympathetic nerves of the spinal cord and thus delays the clearance of the drugs and enhances the duration of



Graphs 1A to C: Hemodynamic parameters: (A) Heart rate; (B) SBP and DBP; and (C) MAP

Table 1: Demographic data of the study

Demographics	*Group S*	*Group C*	*Group F*	*Group FC*
Age (Years)	31.4 ± 12.41	39.04 ± 12.63	35.08 ± 10.75	32.96 ± 11.83
Sex Male/Female	21/4	15/10	20/5	19/6
Height	160.4 ± 5.47	159.96 ± 5.21	157.96 ± 21.94	157.76 ± 19.09
Weight	70.6 ± 9.86	67.84 ± 9.24	72.4 ± 9.34	75.52 ± 22.63
Duration of surgery in minutes	97.8 ± 27.19	97.4 ± 26.58	102 ± 25.61	106.2 ± 21.61

Table 2: Motor, sensory and the analgesic effect of the study solution

Sensory, Motor & Analgesic Effects	*Group S*	*Group C*	*Group F*	*Group FC*
Onset of sensory action in secs	38.4 ± 18.80	41.4 ± 18.79	45.8 ± 30.97	61.2 ± 29.2
Onset of motor action in secs	57.8 ± 38.6	65.4 ± 58.11	69.8 ± 45.74	91 ± 51.05
Fixation of sensory level in secs	336.2 ± 173.66	184.2 ± 73.29	295.5 ± 122.95	375.6 ± 153.43
Fixation of motor action in secs	482.6 ± 226.44	298 ± 150.49	377.2 ± 140.55	445.6 ± 179.02
Duration of analgesia in mins	306.2 ± 124.26	411 ± 110.53	367.4 ± 89.79	458.4 ± 179.96
Duration of motor block in mins	237.2 ± 90.02	319 ± 121.14	260.8 ± 99.8	296.4 ± 117.26
No. of doses of rescue analgesic required in 24 hrs	2.04 ± 0.2	1.36 ± 0.48	1.76 ± 0.59	1.08 ± 0.57

Table 3: Incidence of side effects

Side effects	*Group S*	*Group C*	*Group F*	*Group FC*
Nausea	1	1	Nil	Nil
Vomiting	1	1	1	Nil
Hypotension	Nil	1	1	1
Bradycardia	Nil	1	1	1
Urinary retention	Nil	1	Nil	1
Pruritus	Nil	Nil	Nil	Nil
Sedation	Nil	Nil	Nil	Nil
Shivering	Nil	Nil	Nil	Nil

action.[2] It enhances both sensory and motor blockade of local anesthetic by blocking conduction of C and A delta fibers,[6,7] increases potassium conductance in neurons,[8] and intensifies conduction block of local anesthetics.[6]

Strebel et al[9] analyzed the effect of four different dosages of clonidine with local anesthetic and concluded that 150 µcg of clonidine with bupivacaine was an effective dose for intrathecal use with minimal adverse effects. The addition of clonidine intrathecally or epidurally leads to dose-dependent increase in the duration of anesthesia and analgesia.[9-11] It causes a reduction in the requirement of opioids.[11,12] There is an additive effect of intrathecal opioids with alpha-adrenergic agonists,[13,14] and thus the dose of both agents should be reduced. With the addition of opioids, the effective dosage of clonidine further reduces to 75 to 100 µcg, beyond which incidence of side effects, such as hypotension and sedation, increases.[2] Considering the synergistic effect of opioids and clonidine with local anesthetics,[14] we decided to limit the dosage of clonidine to 75 µcg.

We decided to carry out this study to evaluate whether the combination of clonidine fentanyl further potentiates the muscle relaxation and analgesia with a conventional dose of bupivacaine postarthroscopic surgeries and whether we can use this combination for other long-standing orthopedic surgeries.

Benhamou et al[15] studied the effect of the combination of fentanyl and clonidine with hyperbaric bupivacaine for cesarean section on 78 patients. He compared intrathecal bupivacaine alone or combined with 75 µcg clonidine or with clonidine 75 µcg and fentanyl 12.5 µcg. He concluded that addition of only clonidine improved the spinal analgesia, but clonidine fentanyl combination further increased the analgesia. In his study, the pain scores were 23 ± 7 mm with bupivacaine, 17 ± 6 mm with bupivacaine clonidine, and 2 ± 1 mm with bupivacaine clonidine and fentanyl. Similarly, Chopra and Talwar[16] studied the combination of low doses of intrathecal fentanyl 15 µcg and clonidine 30 µcg with hyperbaric bupivacaine 12.5 mg for analgesia in gynecologic surgeries and concluded that analgesia was prolonged from 176 ± 40.8 minutes in BF, 323 ± 99.5 minutes in BC, and 426 ± 152 minutes in BCF. Similarly, Hadil and Hamid[17] used low-dose clonidine for anal surgery on 60 patients and concluded that addition of clonidine to fentanyl effectively increased the duration of spinal analgesia, decreased postoperative pain with minimal risk of hypotension and sedation.

Similarly, Kothari et al[18] studied the effect of 50 µcg clonidine on two different doses of 0.5% hyperbaric bupivacaine 10 and 8 mg with plain 12.5 mg of 0.5% hyperbaric bupivacaine for cesarean section. They evaluated that with the addition of clonidine, the dose of bupivacaine could be reduced and produced adequate analgesia, motor paralysis, and prolongs the duration of postoperative analgesia. De Kock et al[19] studied the effect of small doses (15, 45, and 75 µcg) of intrathecal clonidine on a small dose of intrathecal ropivacaine 8 mg. They concluded that low-dose clonidine of 15 µcg potentiates the action of sensory block and did not affect the motor blockade of low-dose ropivacaine, thus improving the quality of intraoperative analgesia without compromising early mobilization. But when 75 µcg was added, it increased the sensory action, motor blockade, and the time required for ambulation compared with 15 µcg clonidine. They used 8 mg of ropivacaine, which when used alone did not have both adequate muscle relaxation and analgesia in 9 out of 30 patients.

Demographic data and the duration of surgery are comparable in our study.

The duration of spinal analgesia was greatest in group FC (458.4 ± 179.96 minutes), 411 ± 110.53 minutes in group C, 367.4 ± 89.79 minutes in group F, and the least (306.2 ± 124.26 minutes) in group S. The results are

statistically significant between groups FC and S and groups C and S, with the p-value 0.0001. These findings are similar to those of Benhamou et al,[15] who found that in the BCF group, spread of sensory block was increased and the duration of analgesia was 215 ± 79 minutes, which was significantly greater than that of the other groups. It was also similar to the findings of Chopra and Talwar,[16] who had found that the duration of sensory block (221 minutes) and analgesia (426 minutes) were effectively higher in group BCF as compared with BC and BF groups. Our findings also coincided with the findings of Hadil and Hamid[17] who had found the total duration of analgesia to be 324.6 ± 55.4 minutes in clonidine fentanyl group as compared with clonidine, fentanyl, and bupivacaine groups, when used in anal surgeries.

The duration of motor action was highest in group C (319 ± 121.14 minutes), group FC (296.4 ± 121.14 minutes), group F (260.8 ± 99.8 minutes) followed by group S (237.2 ± 90.02 minutes). The results are statistically significant between groups C and S, p-value being 0.041. Since the duration is greatest in groups containing clonidine, this may not be a favorable factor for day care surgeries. In the study conducted by Benhamau et al,[15] the duration of motor action for group B was 158 minutes, group BC was 172 minutes, and group BCF was 162 minutes. Similarly, in the study conducted by Chopra and Talwar,[16] the duration was 166 minutes in group B, 206 minutes in group BC, and 254 minutes in group BCF. These findings were similar to the findings in our study.

Table 2 shows the motor, sensory, and the analgesia effect of the study population.

The onset of sensory action was earliest in group S (38.4 ± 18.8 seconds) and a maximum of 61.2 ± 29.2 seconds in group FC. The results were statistically significant between group S and group FC, p-value being 0.027. Similarly, the onset of motor action was earliest in group S (57.8 ± 38.6 seconds) and longest in group FC (91 ± 51.05 seconds), p-value being 0.103, and the results are statistically comparable.

The fixation of sensory level at T8 was earliest in group C (184.2 ± 78 seconds), group F (295.5 ± 122.95 seconds), group S (336.2 ± 173.66 seconds), and group FC (375.6 ± 153.43 seconds). The results are statistically significant between groups C and S and group C and F and FC, p-value being 0.0001. The fixation of motor action was earliest in group C (298 ± 150.49 seconds), group F (377.2 ± 140.55 seconds), group FC (445.6 ± 179.05 seconds), and group S (482.6 ± 226.44 seconds). The results are statistically significant between groups FC and C and groups S and C, p-value being 0.005. Although the sensory and motor effects started late, the maximum effect was achieved earlier in the group containing only clonidine but not fentanyl clonidine. Similarly, Chopra and Talwar[16] demonstrated earlier sensory action when clonidine was added to bupivacaine.

In our study, there was a significant reduction of DBP between 45 and 60 minutes and MAP between 60 and 105 minutes in groups FC and C compared with group S postspinal anesthesia but when we compared groups FC and C, the results were comparable. Strebel et al[9] in their study compared different doses of intrathecal clonidine and demonstrated a reduction in the MAP and a significant decrease in DBP. But there was no difference in the number of patients with MAP reduced >30% and in the maximal decrease of MAP in spite of increasing dosage of clonidine in the groups. Similarly, Grace et al[20] in their study demonstrated hemodynamic stability with larger dosages of intrathecal clonidine 150 µcg with 0.5 mg morphine, relative cardiovascular stability with 75 to 100 µcg clonidine with 0.5 mg morphine, and a significant decrease in the MAP with 75 µcg clonidine with 0.5 mg morphine in hip arthroplasties. Similarly, when clonidine was used for labor analgesia, the incidence of hypotensive effects was higher, probably due to combined effect of clonidine and opioids.[21,22]

The number of doses of rescue analgesics in 24 hours was significantly less in group FC (1.08 ± 0.57), group C (1.36 ± 0.48), group F (1.76 ± 0.59), and group S (2.06 ± 0.2). The difference was significant between groups S and C; S and FC; F and C; and F and FC, p-value being 0.0001.

Similarly, Hadil and Hamid[17] concluded that rescue analgesia was less with clonidine fentanyl bupivacaine group in 24 hours. Sites et al[11] also demonstrated a reduction in requirement of morphine in the first 24 hours after cesarean section in clonidine fentanyl group. On the contrary, Van Tuijl et al[23] assessed the requirement of morphine in postcesarean section who received intrathecal clonidine and concluded that it effectively increased the duration of spinal analgesia but not the requirement of morphine in 24 hours, which is contradictory to our results.

The incidence of side effects is comparable in all groups. The incidence of hypotension and bradycardia is the same in all groups except group S. The incidence of nausea and vomiting was seen in groups S and C, the results being comparable. Nazareth et al[5] studied bupivacaine fentanyl clonidine combination intrathecally for orthopedic cases and found that the incidence of sedation and pruritus was significantly more frequent in the BCF group. The incidence of pruritus and sedation increased considerably in the BCF group in the study conducted by Benhamou et al.[15] There was no incidence of pruritus and sedation in our study. The incidence of sedation was found to be highest in group BC followed by group BCF and least in group BF in the study conducted by Chopra and Talwar.[16]

CONCLUSION

Thus, we conclude from our study that the addition of clonidine and fentanyl improves the duration of analgesia and motor blockade. It can be further increased if a higher dosage of local anesthetic is used. It also reduces the requirement of analgesic in the postoperative period.

The limitation of our study is that we should have titrated the dose of local anesthetic considering the synergistic effect of clonidine, fentanyl, and bupivacaine to facilitate early mobilization and thus early discharge from the hospital.

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REFERENCES

1. Saxena AK, Arava SK. Current concepts in neuraxial administration of opioids and non-opioids: an overview and future perspectives. Indian J Anaesth 2004;48(1):13-24.
2. Eisenach JC, De Kock M, Klimscha W. Alpha-2 adrenergic agonists for regional anesthesia - A clinical review of clonidine (1984-1995). Anesthesiology 1996 Sep;85(3):655-674.
3. Jain PN, Gehdoo RP, Priya V, Sheila M. A prospective study of intrathecal clonidine for postoperative pain relief. Indpain 2003;17(2):12-14.
4. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for caesarean section. BMC Anesthesiol [Internet]. 2005 [cited 17 May 2005];5:5. Available from: http://www.biomedcentral.com/1471-2253/5/5
5. Nazareth M, Ghoshal P, Namshikar V, Gaude Y. Addition of intrathecal fentanyl to bupivacaine clonidine mixture effect on quality of sub arachnoid block and postoperative analgesia. Anaesth Essays Res 2013 Jan-Apr;7(1):76-82.
6. Butterworth JF, Strichartz GR. The alpha 2 adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers. Anaesth Analg 1993 Feb;76(2):295-301.
7. Gaumann DM, Brunet PC, Jirounek P. Clonidine enhances the effect of lidocaine on C- fiber action potential. Anaesth Analg 1992 May;74(5):719-725.
8. Andrade R, Aghajanian GK. Opiate and alpha 2-adrenoreceptor induced hyperpolarizations of locus ceruleus neurons in brain slices: reversal by cyclic adenosine 3′:5′-monophosphate analogues. J Neurosci 1985 Sep;5(9):2359-2364.
9. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: a dose-response study. Anaesth Analg 2004 Oct;99(4):1231-1238.
10. Capogna G, Celleno D, Zangrillo A, Constantino P, Foresta S. Addition of clonidine to epidural morphine enhances postoperative analgesia after Cesarean section. Reg Anaesth 1995 Jan-Feb;20(1):57-61.
11. Sites BD, Beach M, Biggs R, Rohan C, Wiley C, Rassias A, Gregory J, Fanciullo G. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty. Anaesth Analg 2003 Apr;96(4):1083-1088.
12. Eisenach JC, D'Angelo R, Taylor C, Hood DD. An isobolographic study of epidural clonidine and fentanyl after cesarean section. Anaesth Analg 1994 Aug;79(2):285-290.
13. Ossipov MH, Harris S, Lloyd P, Messineo E, Lin BS, Bagley J. Antinociceptive interaction between opioids and medetomidine: systemic additivity and spinal synergy. Anesthesiology 1990 Dec;73(6):1227-1235.
14. Yaksh TL, Reddy SVR. Studies in primate on the analgetic effects associated with intrathecal action of opiates, alpha-adrenergic agonists, and baclofen. Anesthesiology 1981 Jun;54(6):451-467.
15. Benhamou D, Thorin D, Brichant JF. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during Cesarean section. Anaesth Analg 1998 Sep;87(3):609-613.
16. Chopra P, Talwar V. Low dose intrathecal clonidine, and fentanyl added to hyperbaric bupivacaine prolongs analgesia in gynaecological surgery. J Anesthesiol Clin Pharmacol 2014 Apr;30(2):233-237.
17. Hadil M, Hamid A. Combined low-dose clonidine with fentanyl as an adjuvant to spinal bupivacaine 0.5% for anal surgery. Ains Shams J Anesthesiol 2009;2:35-39.
18. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth 2011 Jan;5(1):31-35.
19. 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 2001 Apr;94(4):574-578.
20. Grace D, Bunting H, Milligan KR, Fee JP. Postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement. Anaesth Analg 1995 Jan;80(1):86-91.
21. Sia AT. Optimal dose of intrathecal clonidine added to sufentanil plus bupivacaine for labour analgesia. Can J Anaesth 2000 Sep;47(9):875-880.
22. Paech MJ, Banks SL, Gurrin LC. A randomized double-blinded trial of subarachnoid bupivacaine and fentanyl, with or without clonidine, for combined spinal/epidural analgesia during labor. Anaesth Analg 2002 Nov;95(5):1396-1401.
23. Van Tuijl I, Van Klei WA, van der Werff DBM, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section. A randomized controlled trial. Br J Anaesth 2006 Sep;97(3):365-370.