European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 07, 2022

Clinical profile of patients undergoing spinal Anesthesia with intrathecal bupivacaine with clonidine and intrathecal bupivacaine with fentanyl

1st Author: Dr. Nidhi Kumari, Assistant Professor, Department of Anesthesia and Intensive care unit, NC Medical College and Hospital, Israna, Panipat, Haryana-132107.

2nd Author: Dr. Taqui Fakhri, Assistant Professor, Department of Anesthesia and Intensive care unit, NC Medical College and Hospital, Israna, Panipat, Haryana-132107.

3rd Author: Dr. Neha, Associate Professor, Department of Anesthesia and Intensive care unit, NC Medical College and Hospital, Israna, Panipat, Haryana-132107.

4th Author: Dr. Pulkit Sharma, Postgraduate, Department of Anesthesia and Intensive care unit, NC Medical College and Hospital, Israna, Panipat, Haryana-132107.

Corresponding Author: Dr. Neha, Associate Professor, Department of Anesthesia and Intensive care unit, NC Medical College and Hospital, Israna, Panipat, Haryana-132107.

Abstract:

Objective: Adjuvants prolong the action of intrathecal local anesthetic agents. They have shown to have significant analgesic effects in the postoperative period much after the regression of the sensory and motor blockade. Our objective of the current study was to compare the hemodynamic profile and adverse effects (nausea, pruritus, sedation and respiratory depression) in two groups of adult patients undergoing infra-umbilical and lower limb surgery under spinal anesthesia using either intrathecal clonidine or intrathecal fentanyl as an adjuvant to intrathecal bupivacaine (0.5% heavy).

Materials and Methods: It was a prospective randomized study in which eighty patients posted for lower limb orthopedic surgery were divided into two groups of forty each. Group A – Received intrathecal hyperbaric bupivacaine (2.5 ml) +50 μg clonidine (diluted to 0.5 ml). Group B – Received intrathecal hyperbaric bupivacaine (2.5 ml) + fentanyl 25 μg (diluted to 0.5 ml). Duration of postoperative analgesia, sensory and motor block characteristics, hemodynamic parameters, and side effects were recorded and analyzed.

Results: Both the groups were comparable in demographic data, hemodynamic parameters, but the duration of sensory and motor blockade and duration of analgesia was significantly longer in Clonidine group when compared with the Fentanyl group, with a mild increase in sedation score.

Conclusion: Addition of 50 µg clonidine to intrathecal bupivacaine offers longer duration of postoperative analgesia than 25 µg of fentanyl but with higher sedation. Both the drugs offer similar surgical conditions and prolongs postoperative analgesia (clonidine more than

fentanyl), so we suggest fentanyl as better choice when sedation is not desirable and clonidine is recommended where sedation is acceptable.

Keywords: Bupivacaine, Clonidine, Fentanyl, Spinal anesthesia.

Introduction

Spinal anesthesia is the most common technique during infra-umbilical surgery. Spinal anesthesia along with the local anesthetic agent displays relatively short duration of action which ultimately limits the type of surgeries to be performed under spinal anesthesia. The shorter action duration also warrants the use of opioids and other drugs to provide post-operative analgesia. [1]

Over the years several studies have worked on different mechanisms to prolong the action of intrathecal local anesthetic agents with the help of adjuvants. Different adjuvants like clonidine, dexmedetomidine, and midazolam, opioids, neostigmine and magnesium sulphate have been studied to prolong the effect of spinal anaesthesia. [2] Additionally, they have been shown to have significant analgesic effects in the postoperative period much after the regression of the sensory and motor blockade thus ensuring post-operative pain relief and allowing early ambulation. Bupivacaine is a popular local anesthetic agent used for spinal anesthesia with duration of action of 60 to 240 minutes. [3] Various drugs have been used in the past as an adjuvant with bupivacaine to increase the efficacy and duration of the neuraxial blockade. [4]

Clonidine is an α_2-adrenergic agonist that is often administered intrathecally in humans. Clonidine has analgesic effect at spinal level mediated by postsynaptic α_2 adrenoreceptors in dorsal horn of spinal cord. Studies in rats have shown that intrathecal clonidine produces side effects like hypotension; bradycardia and sedation. Intrathecal clonidine can decrease sympathetic nervous system activity, renin-angiotensin levels and vasopressin release thereby reducing the tolerance to hemodynamic changes. [5] Addition of clonidine as an adjuvant prolonged the bupivacaine spinal block. However, the marked hemodynamic changes and sedation were observed which may limit the usefulness of intrathecal clonidine. Similarly, when fentanyl was used as an adjuvant, both the incidence and severity of hypotension increased. [6]

Opioids were the first group of drugs to be used as an adjuvant with bupivacaine. Use of opioids resulted in increased duration of analgesia but was associated with undesirable side effects like nausea, vomiting, respiratory depression and sedation. Fentanyl is a short acting lipophilic opioid, which binds to a family of G-protein-linked pre and postsynaptic opioid receptors in Laminae I and II of the dorsal horn of spinal cord. [7] Fentanyl is the most frequently used intrathecal lipophilic opioid and when administered in single dose of 10-30 mcg it has rapid onset and short duration of action (4-6 hrs) with minimal cephalad spread. [8-12]

With this background, the present study was proposed with an aim to compare the hemodynamic profile and adverse effects (nausea, pruritus, sedation and respiratory

depression) in two groups of adult patients undergoing infra-umbilical surgery under spinal anesthesia using either intrathecal clonidine or intrathecal fentanyl as an adjuvant to intrathecal bupivacaine.

Materials and Methods

This is a prospective and randomized study was carried out in Department of Anesthesia, N.C. Medical College and Hospital Israna, Panipat over a period of 1 year.

Inclusion Criteria: Eighty patients of the American Society of Anesthesiologists Classes I or II of either sex and of age 20–60 years of age posted for lower limb orthopedic surgery were randomly divided into two groups (n = 40) using computer-generated program.

Exclusion Criteria: Patients having severe systemic disorders such as diabetes mellitus, hypertension, heart disease, allergy to bupivacaine, spine deformity, increased intracranial pressure, neurological disorders, hemorrhagic diathesis, and infection at the puncture site were excluded from the study.

Group A – Received hyperbaric bupivacaine (2.5 ml) +50 μg clonidine (diluted to 0.5 ml) administered intrathecally. Group B – Received hyperbaric bupivacaine (2.5 ml) + fentanyl 25 μg (diluted to 0.5 ml) administered intrathecally. Total volume of study drug was 3 ml. Preanesthetic checkups were done, and visual analog scale (VAS) was explained to all patients.

All the patients were kept nil orally for 6 hours before surgery. After shifting the patients to Operation Theater, intravenous (IV) cannula was inserted, and preloading was done with Ringer solution (10 ml/kg). Preoperative parameters such as pulse rate, oxygen saturation, and blood pressure were recorded. Under all aseptic precaution, spinal anesthesia was administered at the level of L3–L4 intervertebral space in sitting position using midline approach by 25-gauge Quincke spinal needle. The anesthesiologist who administered anesthesia was blinded to the group allocation.

Pulse rate, respiratory rate, electrocardiogram, SpO_2, and blood pressure were monitored. Pulse rate and blood pressure variations more than 20% of baseline were noted in both groups. Bradycardia and hypotension were treated with IV atropine and ephedrine, respectively. Sensory and motor block was monitored at 2, 4, 6, 8, 10, 15 min, and after that at 15 min interval. Sensory block was tested by pinprick method. The motor block was assessed according to the modified Bromage scale: Bromage 0:

Patients is able to move hip, knee, and ankle and is unable to lift leg against gravity, Bromage 1: Patients is unable to lift leg against gravity but is able to flex knee and ankle, Bromage 2: Patient is unable to flex hip and knee but able to flex ankle, Bromage 3: Patient unable to flex hip, knee, and ankle but is able to move his toes. Bromage scale 4: Complete paralysis. The onset of sensory block was taken from the time of intrathecal injection till loss of pin prick sensation at T10. Duration of sensory block was taken as time from maximum height of

block till regression to Level 1. The onset of motor block was defined as time from intrathecal injection to motor blockade Level 2 in Bromage scale. Duration of motor blockade was taken as time from intrathecal injection till no motor weakness (Bromage 0).

Duration of analgesia was defined as time from intrathecal injection till administration of first rescue analgesic. Any side effects such as nausea, vomiting, pain, shivering, pruritus, sedation, hypotension, bradycardia, and respiratory discomfort were noted. Patients were assessed for degree of sedation, and scoring was done with Campbell sedation score as: 1: Wide awake, 2: Awake and comfortable, 3: Drowsy and difficult to arouse, and 4: Not arousable. Postoperatively, the pain score was recorded by using VAS between 0 and 10 (0 = no pain, 10 = severe pain). Injection paracetamol (1 gm) was given intravenously as rescue analgesic when VAS was >5. Time of administering the first dose of rescue analgesia was noted.

Statistical Analysis

Interpretation of the data was carried out and analyzed using statistical package for social sciences (SPSS version 25). Data was represented as mean ± standard deviation for continuous data and frequency (percentage) or median (range) for nonparametric (categorical) data. The two groups were compared using analysis of variance. Student's t-test was used to test the null hypothesis that the mean of the two groups is same at 5% level of significance. The proportion of adverse effects was compared using Chi-square test. $P < 0.05$ was considered statistically significant. $P < 0.001$ was considered highly statistically significant.

Results

Table 1: Demographic characteristics of the study population

Parameters	**Group A: Clonidine**	**Group B: Fentanyl**	**p - value**
Age (years)	40.14 ± 10.16	38.16 ± 10.12	0.13
Height (cms)	60.22 ± 2.16	60.1 ± 2.28	0.23
Weight (kgs)	60.23 ± 5.35	59.08 ± 6.07	0.28
Duration of Surgery (mins.)	100 ± 14.39	101.2 ± 13.17	0.40
Male: Female	25:20	28:17	
ASA PS Grade I: II	23:22	25:20	
SBP (mm Hg)	120.23 ± 5.45	120.37 ± 6.61	0.30
DBP (mm Hg)	75.27 ± 7.84	75.16 ± 5.88	0.81
MAP (mm Hg)	90.22 ± 5.41	90.3 ± 4.31	0.76
HR (bpm)	80.32 ± 8.70	80.28 ± 8.06	0.04

Table 2: Comparison of different block characteristics

Block characteristics	**Group A: Clonidine**	**Group B: Fentanyl**	**p - value**
Onset of sensory block	5.43 ± 1.11	5.35 ± 0.46	0.39
Onset of motor block	8.34 ± 1.13	8.41 ± 1.01	0.48
Time to reach peak sensory level	9.17 ± 0.37	9.11 ± 0.37	0.45
The duration of sensory block	119.34 ± 7.86	92.07 ± 4.80	0.00
Duration of motor block	201.36 ± 9.46	190.42 ± 8.56	0.00
Duration of spinal anesthesia	235.58 ± 14.68	210.3 ± 5.62	0.00
Time when first rescue analgesia was given	390.41 ± 22.14	250.4 ± 13.16	0.00

In table 2, 'Clonidine' has a mean onset time of sensory block of 5.43 minutes whereas the 'Fentanyl' has an onset time of 5.35 minutes. The difference in mean is of 0.08 minute which is insignificant at 5% level of significance with a p-value of 0.39.

Clonidine has mean onset of motor block 8.34 minutes whereas the 'Fentanyl' has onset of 8.41 minutes. The difference in mean is of -0.07 minutes which is not significant at 5% level of significance with a p-value of 0.48. The difference is both low and statistically insignificant.

Clonidine has a mean time to reach the peak sensory level of 9.17 minutes whereas the 'Fentanyl' has the mean time of 9.11 minutes. The difference in mean is of 0.06 minutes which is insignificant at 5% level of significance with a p-value of 0.45.

Clonidine has mean duration of sensory block 119.34 minutes whereas the 'Fentanyl' has duration of 92.07 minutes. The difference in mean is of 27.27 minutes which is significant at 5% level of significance with a p-value of 0.00.

Clonidine has a mean duration of motor block 201.36 minutes whereas the 'Fentanyl' has duration of 190.42 minutes. The difference in mean is of 10.94 minutes which is significant at 5% level of significance with a p-value of 0.00.

Clonidine has a mean duration of spinal anesthesia 235.58 minutes whereas the 'Fentanyl' has duration of 210.3 minutes. The difference in mean is of 25.28 minutes which is significant at 5% level of significance with a p-value of 0.00.

Clonidine dose has a mean time of 390.41 minutes when the first rescue analgesia was given whereas the 'Fentanyl' dose has duration of 250.4 minutes. The difference in mean is of 140.01 minutes which is significant at 5% level of significance with a p- value of 0.00.

Table 3: Comparison of sedation score

	Group A: Clonidine	Group B: Fentanyl	p - value
Sedation Score at intra-operative 30 mins	1.09 ± 0.21	1.02 ± 0.14	0.01
Sedation Score at intra-operative 60 mins	1.44 ± 0.16	1.02 ± 0.14	0.00
Sedation Score at intra-operative 90 mins	1.46 ± 0.23	1.00 ± 0.11	0.00
Sedation Score at intra-operative 120 mins	1.47 ± 0.22	1.00 ± 0.09	0.00
Sedation Score at post-operative 120 mins	1.44 ± 0.02	1 ± 0.00	0.00
Sedation Score at post-operative 240 mins	1.22 ± 0.02	1 ± 0.00	0.00
Sedation Score at post-operative 360 mins	1 ± 0.00	1 ± 0.00	-

Table 4: Comparison of heart rate at different time intervals between groups

Time interval	Group A: Clonidine	Group B: Fentanyl	**Significance of difference**
	Mean±SD	Mean±SD	**P value**
Baseline	79.31	82.53	0.064
5 min	76.25	79.42	<0.001
10 min	69.53	75.64	<0.001
20 min	66.26	73.62	<0.001
40 min	62.54	70.84	<0.001
60 min	62.63	70.13	<0.001
90 min	60.65	69.58	<0.001

Table 4: Comparison of two groups for side effects.

Complication	Group A: Clonidine		Group B: Fentanyl		**Significance of difference**
	No.	**%**	**No.**	**%**	**P value**
Hypotension	3	6.6	4	8. 8	0.412
Bradycardia	2	4.4	1	2.2	0.523
Nausea	0	0	3	6.6	-
Pruritus	0	0	4	8.8	-

Discussion

Clonidine is a selective partial agonist for alpha-2-adrenoreceptors. It is known to potentiate both sensory and motor block of local anesthetics. [13] The possible mechanisms involved in potentiating spinal block include: Suppression of the activity of wide dynamic range neurons and release of substance P, norepinephrine and acetylcholine in spinal cord dorsal horn and direct inhibition of impulse conduction in Aδ and especially C fibers, possibly by increasing potassium conductance. Clonidine, thus complements the action of local anesthetics in stabilizing neurons and accounts for enhancement of effect of local anesthetics and opioids by modulating the transmission of painful stimuli thereby preventing the state of central sensitization.

Clonidine has been used intrathecally in different doses. The dose of clonidine used in the present study corresponds to that of van Tuijl *et al*. [14] who administered intrathecal clonidine in a dose of 75 mcg/kg. The results of our study demonstrates that that the addition of clonidine in doses of 50 µg to bupivacaine (2.5 ml) and 2 µg to bupivacaine (2.5 ml) plus fentanyl (12.5 µg) truncates the time of onset of sensory and motor block. Similar results were observed by Gecaj -Gashi *et al*. [15] who reported shorter onset of sensory and motor block in patients receiving intrathecal clonidine. Grace *et al*., [16] however observed prolonged time to onset of motor block in pethidine-clonidine group which is in contrast to the results of our study. The difference in the result could be due to the fact that higher doses of pethidine 0.75 mg/kg were used in this study. It is possible that the higher dose of intrathecal pethidine could mask the effect of intrathecal clonidine.

We also observed significant prolongation of the duration of motor block in the groups A and B. Singh *et al*. [17] and Benhamou *et al*. [18] also reported significant prolongation of motor block when clonidine was used as an adjuvant for intrathecal use. The time of duration of motor block was similar in the group A and B. Similar results were reported by Nazareth *et al*. [19] who obtained corresponding duration of motor block in the intrathecal clonidine group and in a group where combination of intrathecal clonidine and fentanyl were administered.

Postoperatively, lower VAS scores were observed for 12 h and significantly reduced cumulative 24 h supplemental analgesic consumption was noted in groups receiving intrathecal clonidine, indicating good postoperative analgesic effect. The results of our study was comparable to those of Merivirta *et al*., [20] where addition of clonidine intrathecally resulted in significantly reduced VAS scores and significant reduction in postoperative analgesic consumption.

Intrathecal clonidine has been reported to result in intraoperative hypotension. However, we observed stable hemodynamics among all the groups without any incidence of respiratory depression. This could be explained by adequate preloading which was performed in all the patients prior to subarachnoid block. In addition, the dose used in our study was small, and the mean level of anesthesia achieved was $T_{8\text{-}9}$. [21] Our results are similar to those of Singh *et al*. [17] who observed no significant difference in HR and blood pressure in patients receiving 50 µg and 75 mcg of clonidine intrathecally undergoing cesarean section. Similarly, Nazareth *et al*. also reported stable hemodynamic parameters in the groups receiving intrathecal clonidine and fentanyl combination. [19] However, Dobrydnjov *et al*. [22] reported significant decreases in patients receiving clonidine and fentanyl intrathecally. The difference could be explained by the fact that they used 3.5 ml of hyperbaric bupivacaine and clonidine as compared to the present study, accounting for higher level of sensory blockade achieved and thus explaining hypotension.

Patients in groups A and B were sedated as evidenced by higher sedation scores. However, sedation never exceeded grade 2 and did not cause any problems in any of the patients. Nazareth *et al*. also reported mild to moderate degree of sedation in the clonidine groups. [19]

Clonidine is known to cause sedation, and this hypnotic response is believed to be mediated via locus coeruleus where alpha-2-adrenergic receptors are abundant. [23]

A potential limitation of our study design relates to small sample size. Secondly, we did not attempt dose-response effect by using various doses of clonidine. Recently, there are few studies which report beneficial effects of using 30 or even 15 mcg of intrathecal clonidine with minimal adverse effects. Possibly, further reducing the dose of clonidine could have elucidated dose-response relationship. [24]

Conclusion

Addition of 50 µg clonidine to intrathecal bupivacaine offers longer duration of postoperative analgesia than 25 µg of fentanyl but with higher sedation. Both the drugs offer similar surgical conditions and prolongs postoperative analgesia (clonidine more than fentanyl), so we suggest fentanyl as better choice when sedation is not desirable and clonidine is recommended where sedation is acceptable.

References

1. Dhumal P, Gunjal V, Kurhekar V. Synergistic effect of intrathecal fentanyl and bupivacaine combination for cesarean section. IJPBR. 2013; 4(1):50-6.
2. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. *Indian J Anesth.* 2007;51:415.
3. Joshi SA, Khadke VV, Subhedar RD, Patil AW, Motghare VM. Comparative evaluation of intrathecal midazolam and low dose clonidine: efficacy, safety and duration of analgesia. A randomized, double blind, prospective clinical trial. Ind J Pharmacol. 2012; 44(3):357-61.
4. Karnawat R, Chhabra S, Mohammed S, Paliwal B. Comparison of Effect of Epidural Bupivacaine, Epidural Bupivacaine Plus Fentanyl and Epidural Bupivacaine Plus Clonidine on Postoperative Analgesia after Hip Surgery. J Anesth Clin Res. 2013; 4:373.
5. Asghar AM, Samina I, Muhammad S, Asiyah A. A double-blind randomized control trial to compare the effect of varying doses of intrathecal fentanyl on clinical efficacy and side effects in parturients undergoing cesarean section. J Anaesthesiol Clin Pharmacol. 2018; 34(2):221-6.
6. Chopra P, Talwar V. Low dose intrathecal clonidine and fentanyl added to hyperbaric bupivacaine prolongs analgesia in gynecological surgery. J Anaesthesiol Clin Pharmacol. 2014; 30(2):233-7.
7. Mahendru V, Tewari A, Katyal S, Grewal A, Singh R, 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; 29(4):496-502.
8. Sun S, Wang J, Bao N, ChenY, Wang J. Comparison of dexmedetomidine and fentanyl as local anesthetic adjuvants in spinal anesthesia: a systematic review and meta-analysis of randomized controlled trials. Drug Des Devel Ther. 2017; 11:3413-24.

9. 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 J Anaes. 2014; 8(2):209-14.
10. Sivevski AG, Karadjova D, Ivanov E, Kartalov A. Neuraxial Anesthesia in the Geriatric Patient. Frontiers in medicine. 2018; 5:254.
11. Santamaria C, Woodruff A, Yang R, Kohane, D. Drug delivery systems for prolonged duration local anesthesia. Materials Today. 2017; 20(1):22-31.
12. Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RS. Clinical aspects of acute post-operative pain management & its assessment. J Adv Pharm Technol Res. 2010; 1(2):97-108.
13. Singh RB, Chopra N, Choubey S, Tripathi RK, Prabhakar, Mishra A. Role of Clonidine as adjuvant to intrathecal bupivacaine in patients undergoing lower abdominal surgery: A randomized control study. Anesth Essays Res. 2014 Sep-Dec;8(3):307-12.
14. Van Tuijl I, van Klei WA, van der Werff DB, et al. 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; 97:365-70.
15. Gecaj-Gashi A, Terziqi H, Pervorfi T, Kryeziu A. Intrathecal clonidine added to small-dose bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery. Can Urol Assoc J 2012; 6:25-9.
16. Grace D, Bunting H, Milligan KR. Postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement. Anesth Analg. 1995; 80(1):86–91.
17. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Saudi J Anaesth. 2013; 7:283- 90.
18. Benhamou D, Thorin D, Brichant JF. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesth Analg. 1998; 87(3):609–613.
19. Nazareth M, Ghoshal P, Namshikar V, Gaude Y. Addition of intrathecal fentanyl to bupivacaine clonidine mixture effect on quality of subarachnoid block and postoperative analgesia. Anesth Essays Res. 2013; 7(1):76-82.
20. Merivirta R, Kuusniemi K, Jaakkola P, Pihlajamäki K, Pitkänen M. Unilateral spinal anaesthesia for outpatient surgery: A comparison between hyperbaric bupivacaine and bupivacaine-clonidine combination. Acta Anaesthesiol Scand 2009; 53:788-93.
21. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: A dose-response study. Anesth Analg 2004; 99:1231-8.
22. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmström B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: A double-blind, randomized and placebo-controlled study. Acta Anaesthesiol Scand 2005; 49:538-45.

23. Idowu OA, Sanusi AA, Eyelade OR. Effects of intrathecally administered fentanyl on duration of analgesia in patients undergoing spinal anesthesia for elective caesarean section. Afr J Med Med Sci 2011; 40:213-9.
24. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. Minerva Anestesiol 2014; 80:96-112.