An Observational Comparative Study to Assess the Block Characteristics of Intrathecal Buprenorphine and Clonidine When Added to Bupivacaine for Orthopaedic Lower Limb Surgeries

Antony K. A.¹, Anzer Shah M.²

¹Department of Anaesthesia, Government TD Medical College, Alappuzha, Kerala, India.

²Department of Anaesthesia, Government TD Medical College, Alappuzha, Kerala, India.

ABSTRACT

BACKGROUND

Postoperative analgesia enables faster rehabilitation, improves the patient's level of satisfaction, and reduces hospital stay. Regional anaesthesia is the most common anaesthetic technique used for orthopaedic surgeries across the world. Adjuvants are often administered along with a local anaesthetic during spinal anaesthesia to prolong intraoperative and postoperative analgesia. The main objective of this study was to compare the effect of 60 mcg buprenorphine with that of 30 mcg clonidine when added to 3.2 ml bupivacaine with respect to onset and duration of sensory and motor block, maximum level of sensory block, duration of analgesia, and side effects if any.

METHODS

After obtaining institutional ethical committee clearance, a prospective observational study was conducted among 88 participants undergoing orthopaedic surgery of lower limb. Spinal anaesthesia was given, under aseptic precautions with 0.5% bupivacaine heavy 3.2 ml along with either 60 mcg buprenorphine (0.2 ml) or clonidine 30 mcg (0.2 ml). The buprenorphine receiving patients (n=44) were under group A and the clonidine receiving patients (n=44) were under group B. The heart rate, blood pressure, sensory block level, and duration of analgesia, were recorded.

RESULTS

Analysis of the data shows that the use of clonidine significantly prolonged the duration of analgesia compared to buprenorphine. The incidence of hypotension, bradycardia, nausea and vomiting, etc. were similar in both groups.

CONCLUSIONS

Use of 30 mcg clonidine as an adjuvant in spinal anaesthesia provides significant prolongation of analgesia (mean duration of analgesia 190.5 minutes) compared to 60 mcg buprenorphine (mean duration of analgesia 157.5 minutes) without causing any increased incidence of adverse effects.

KEY WORDS

Spinal Anaesthesia, Adjuvants, Buprenorphine, Clonidine

Corresponding Author:

*Dr. Anzer Shah M,
Assistant Professor,
Manakkakudy, Erumathala P. O.,
Keezhmad, Aluva, Ernakulam-683112,
Kerala, India.
E-mail: anzinbox@gmail.com*

DOI: 10.14260/jemds/2020/328

*Financial or Other Competing Interests:
None.*

How to Cite This Article:

Antony KA, Shah AM. An observational comparative study to assess the block characteristics of intrathecal buprenorphine and clonidine when added to bupivacaine for orthopaedic lower limb surgeries. J. Evolution Med. Dent. Sci. 2020;9(18):1504-1508, DOI: 10.14260/jemds/2020/328

*Submission 25-01-2020,
Peer Review 17-04-2020,
Acceptance 23-04-2020,
Published 04-05-2020.*

BACKGROUND

Postoperative analgesia enables a faster rehabilitation, improves the patient's level of satisfaction, and reduces hospital stay. Post-operative pain influences the quality and duration of recovery time.^[1] Regional anaesthesia is the most common anaesthetic technique used for orthopaedic surgeries across the world. However it can cause hypotension that may be troublesome in cardiac patients. Adjuvants are used to decrease the quantity of local anaesthetic and hence the level of block in order to decrease the hypotension.^[2] They are also often administered along with a local anaesthetic during spinal anaesthesia to prolong intraoperative and postoperative analgesia. There are many adjuvants like fentanyl, morphine, dexmedetomidine, clonidine etc. used along with local analgesic to improve the efficacy of local anaesthetic and to decrease the toxicity.^[3] Opioids are the most frequently used local anaesthetic adjuvants and their use in neuraxial blocks have evolved over the last 50 years.^[4] The opioids potentiate anti-nociception of local anaesthetics by G protein coupled receptor mechanisms by causing hyperpolarisation of the afferent sensory neurons.^[5] The dose, site of injection, lipophilicity and the acid-base milieu of the site of drug deposition determine the extent of efficacy of the block.^[6]

Buprenorphine has also been used in intrathecal (75-150 µg) and epidural routes (150-300 µg) with reasonable efficacy.^[7] Additionally, it has also shown good efficacy when used in a dose of 0.3 mg as an adjuvant to peripheral nerve blocks. Alpha 2 adrenoreceptor antagonists (Clonidine, Dexmedetomidine) are one of the most widely used class of local anaesthetic adjuvants which give satisfactory effect in neuraxial and peripheral blocks. Clonidine is an imidazole derivative with selective partial agonist properties which inhibits nociceptive impulses by activation of post junctional alpha-2 adrenoreceptor in the dorsal horn of spinal cord.^[8] In neuraxial blocks, it has a local effect on blockage of sympathetic outflow while in peripheral nerve blocks it prolongs duration of analgesia by hyperpolarisation of cyclic nucleotide gated cation channels.^[9] Co-administration of clonidine and local anaesthetics epidurally has been used in abdominal surgeries, total knee replacement surgeries,^[10] labour analgesia, chronic pain and cancer pain treatment. Alpha2-adrenoceptors are located on primary afferents of both peripheral and spinal nerve endings, on the superficial laminae of the spinal cord, and within several brainstem nuclei implicating analgesic action at peripheral, spinal, and brainstem sites in animals.^[11] But evidence supports only a spinal action of clonidine in producing analgesia in humans. Clonidine also produces a minor degree of nerve conduction blockade (C-fibers) at high concentrations,^[12] and hence the enhancement of peripheral nerve block when added to local anaesthetics.

The main objective of this study was to compare the effect of 60 mcg buprenorphine vs 30 mcg clonidine when added to 3.2 ml bupivacaine with respect to onset and duration of sensory and motor block, maximum level of sensory block, duration of analgesia, and side effects if any.

Rationale of the Study

Clonidine and buprenorphine are frequently used along with bupivacaine in spinal anaesthesia. But the studies comparing the block characteristics of these two drugs in equal volume of 0.2 ml are limited in number. Hence, we conducted a new study comparing these two drugs.

Objectives

1. To compare the efficacy of intrathecal clonidine 30 mcg vs intrathecal buprenorphine 60 mcg as adjuvant to bupivacaine in prolonging the duration of analgesia as assessed by the visual analogue scale after lower limb orthopaedic surgeries
2. To compare the incidence of side effects like hypotension, bradycardia, nausea and vomiting.

Hypothesis

Equal volume of two potent spinal adjuvants buprenorphine and clonidine can prolong the analgesia.

Inclusion Criteria

Age group 18-65 yrs. Patients presenting for thyroidectomy surgery American Society of anaesthesiology (ASA) class I & II.

Exclusion Criteria

- Hypertensive patients controlled with multiple drugs.
- Morbidly obese patients- BMI >35.
- GA or epidural given in addition to spinal block.
- Patients having coagulation abnormalities.
- Patients having major cardiovascular, respiratory or renal disease.

METHODS

After obtaining institutional ethical committee clearance, the Study was conducted as a prospective observational one conducted in the orthopaedic operation theatres of Govt. TD Medical College, Vandanam, Alappuzha.

Sample size

Sample size was estimated by using the difference in the meantime of sensory regression between clonidine group and buprenorphine group from the study Major Vishal Arora et al as 209 ± 33.8 min and 183.2 ± 46.8 min. using these values at 95% Confidence limit and 80% power sample size of 40 was obtained in each group by using the formula

$$\frac{s2SD^2(Z_{\frac{\alpha}{2}} + Z_{\beta})^2}{d^2}$$

SD- Standard deviation from previous study

$Z_{\alpha/2} = Z_{1.96} = 2/0.05$ from Z table at type 1 error of

5% = 1.96 $Z_{\beta} = Z_{0.842} = 0.2$ from Z table at 80% power

D= effect size= difference between mean value

With 10% non-response sample size of $40 + 4 \approx 44$ cases will be included in each group.

Methodology

After getting approval from the institutional ethical committee, participants were recruited for this study. Patients were educated about the study using patient information sheet. Informed written consent was taken from all patients in their mother tongue. The patients were given Tab. Ranitidine 150 mg and Tab. Metoclopramide 10 mg PO on the night before surgery and at 6 am on the morning of surgery. Patients were kept nil per oral for 8 hours prior to surgery. Upon arrival in the operating room ECG, noninvasive blood pressure monitor, and pulse oximeter were connected and basal heart rate and BP were recorded. Intravenous access with 18 G cannula in forearm was obtained and intravenous fluid 0.9% NS was started. All patients were premedicated with IV Midazolam 1 mg.

The patients were positioned in either sitting or lateral position. Under strict asepsis precautions spinal anaesthesia was given at the L3-L4 intervertebral space using 25G spinal needle. The group A (n=44) received 3.2 ml 0.5% heavy bupivacaine and 60 mcg (0.2 ml) buprenorphine and the group B (n=44) received 3.2 ml 0.5% heavy bupivacaine and 30 mcg clonidine (0.2 ml).

Patients were made supine after the spinal injection and were closely monitored. The level of anaesthesia at the end of 5 minutes was assessed by cold spirited cotton. The patients were then positioned according to the orthopedic surgery and surgery was allowed to continue. Any adverse effects like hypotension, bradycardia, nausea and vomiting were recorded. Any incidence of hypotension defined as more than 20% fall of MAP was treated with Inj. Mephentermine 6 mg IV. Heart rate less than 50 was taken as bradycardia and was treated with Inj. Atropine 0.6 mg IV. Perioperative nausea and vomiting were treated with Inj. Ondansetron 4 mg IV. After the surgery the patient was shifted to the post-operative recovery room, and monitoring is continued. The end point of analgesia was taken as the time at which the patient requested for further analgesic. The patient after moving the toes were taken as recovered from spinal anaesthesia and were shifted to high dependency unit for 24 hours for monitoring.

Statistical Analysis

Data collected will be entered a Microsoft excel data sheet and will be analysed using SPSS 22 version software. Categorical data will be represented in the form of frequencies and proportions. Chi-square will be the test of significance. Continuous data will be represented as mean standard deviation. Independent t test will be the test of significance to identify the mean difference between the two groups. p value <0.05 will be considered statistically significant. All statistical and analyses were carried out using the software Statistical Package for the Social Sciences (SPSS) Statistics version 19.0.0 with the help of a professional statistician. Data was expressed in its frequency and percentage as well as mean and standard deviation.

RESULTS

Group A- Buprenorphine.

Group B- Clonidine.

Time	Group B			Group A			t	p
	Mean (bpm)	SD	N	Mean (bpm)	SD	N		
Base line	71.3	9.6	44	70.6	6.9	44	0.35	0.724
0-5 mt	66.3	8.3	44	71.5	10.0	44	2.31*	0.024
5-10 mt	65.0	6.8	44	72.6	10.5	44	3.51**	0.001
10-15 mt	67.6	7.2	44	73.6	9.5	44	2.91**	0.005
15-20 mt	68.2	7.9	44	73.8	8.4	44	2.79**	0.007
20-30 mt	69.0	7.4	44	73.8	7.8	44	2.55*	0.013
30-end of surgery	69.1	7.5	44	72.6	8.0	44	1.85	0.069
Till 3h post op	69.1	8.0	44	72.8	8.8	44	1.77	0.082

Table 1. Distribution of Heart Rate in the Group

*: Significant at 0.05 level **: Significant at 0.01 level, The base line heart rate was comparable in both groups (p value 0.724). The heart rate after the injection of the drugs was significantly different for the first 30 minutes with higher heart rate for the buprenorphine group. The difference in heart rate was negligible after 30 minutes. (p value >0.05)

Time	Group A			Group B			t	p
	Mean (mmHg)	SD	N	Mean (mmHg)	SD	N		
Base line	98.9	10.7	44	99.9	10.0	44	0.38	0.705
0-5 mt	98.1	18.0	44	86.7	11.2	44	2.81**	0.007
5-10 mt	90.4	12.5	44	76.4	12.0	44	4.67**	0.000
10-15 mt	92.8	11.5	44	78.4	11.8	44	5.03**	0.000
15-20 mt	92.9	10.7	44	80.8	15.4	44	3.41**	0.001
20-30 mt	94.4	11.9	44	86.4	11.4	44	2.09*	0.040
30-end of surgery	97.8	11.5	44	100.1	12.7	44	1.57	0.122
Till 3h post op	106.6	14.0	44	107.5	15.2	44	0.25	0.801

Table 2. Distribution of Blood Pressure in the Group

*: Significant at 0.05 level **: Significant at 0.01 level. The base line blood pressure was comparable in both the groups (p value 0.705> 0.05). Blood pressure was significantly lower among clonidine group than buprenorphine group from 0- 30 minutes after injection. (p value < 0.05). After 30 minutes both groups did not significantly differ (p value >0.05).

Group	Mean (min)	SD	N	t	p
Group B	190.5	9.2	44	9.79**	0.000
Group A	157.5	17.0	44		

Table 3. Distribution of Time for 1st Request for Further Analgesia

**: Significant at 0.01 level
The mean duration for the first pain to appear for clonidine group was 190.5 min and that of buprenorphine group was 157.5 min. The time required was significantly longer for clonidine group (p value 0.000< 0.05).

Group	Mean (min)	SD	N	t	p
B	186.4	33.6	33	15.47**	0.000
A	81.8	19.4	33		

Table 4. Distribution of Time for Receding to Sensory Level to T10

**: Significant at 0.01 level

The mean duration for receding to T₁₀ level for the clonidine group was 186.4 min and that of buprenorphine group was 81.8 min. The time required was significantly longer for clonidine group (p value 0.000< 0.05).

Nausea & Vomiting	Group A		Group B		p#
	Count	Percent	Count	Percent	
No	43	97.0	44	100.0	1.00
Yes	1	3.0	0	0.0	

Table 5. Comparison of Nausea & Vomiting

#: Fisher's Exact Test.
One patient among buprenorphine group developed nausea and vomiting but it was statistically not significant. (p value 1.00> 0.05)

DISCUSSION

Effective pain control is essential for optimum care of patients in the perioperative period. However, despite advances in the knowledge of pathophysiology of pain, the pharmacology of

analgesics and the development of more effective techniques, patients continue to experience considerable pain after surgery. One disadvantage with spinal anaesthesia using local anaesthetics alone is that analgesia ends with the regression of the block, which means that there is an early post-operative need for analgesia post-operative pain, apart from causing discomfort has other deleterious effects involving mainly the cardio-respiratory system. In recent years various adjuvants are being added to spinal anaesthesia for prolonging the analgesia and motor block. Fentanyl, buprenorphine, clonidine, dexmedetomidine etc. are frequently used.

Clonidine is a partial agonist for alpha 2 adrenergic receptors.^[13] It is more potent after neuraxial administration than systemic administration indicating spinal site of action. Buprenorphine is a partial agonist opioid,^[14] which increases the sensory block without much alteration in hemodynamic parameters. Numerous studies had been done comparing intrathecal clonidine-bupivacaine mixture vs plain bupivacaine and intrathecal buprenorphine -bupivacaine mixture vs plain bupivacaine. However, there are only few studies comparing both clonidine -bupivacaine and buprenorphine-bupivacaine. Mixture. Systematic review of randomized trials by Nadia Elia et al showed significant prolongation of sensory and motor block in intrathecal clonidine local anaesthetic combination,^[15] Benhamou et al showed that adding clonidine to intrathecal bupivacaine increased duration of analgesia in caesarean patients.^[16]

BS Sethi, Mary Samuel et al studied the efficacy of analgesic effects of low dose intrathecal clonidine as an adjuvant and found that it significantly increased duration of spinal block without much side effects.^[17] Arvinder Pal Singh, Ravinder Kaur et al studied intrathecal buprenorphine as an adjuvant and found that it significantly increased duration of analgesia without causing an increase in duration of motor blockade.^[6] Sunil Dixit in his study concluded that intrathecal buprenorphine is a suitable drug for postoperative analgesia after caesarean section with no effect on neonatal Apgar scores.^[18] Rashmi Dubey, Roseline Zohra Ali et al studied the effect of intrathecal buprenorphine for infraumbilical abdominal surgeries and lower limb surgeries and found superior efficacy for buprenorphine group than control group.^[19] Borse Y.M et al showed prolongation of postoperative analgesia in orthopaedic procedures by intrathecal buprenorphine.^[20]

So, from the present study intrathecal clonidine was found to be a safe alternative to buprenorphine in equal volume (0.2 ml) for use in spinal anaesthesia along with local anaesthetic 0.5% heavy bupivacaine.

As the number of studies comparing equal volume of these two adjuvants are less in number more studies should be undertaken for conclusively proving the superiority of one over the other.

CONCLUSIONS

Use of intrathecal clonidine 30 mcg- 0.2 ml as adjuvant to local anaesthetic bupivacaine in subarachnoid block is a safe practice. Use of 30 mcg clonidine as an adjuvant in spinal

anaesthesia provides significant prolongation of analgesia (mean duration of analgesia 190.5 minutes) compared to 60 mcg buprenorphine (mean duration of analgesia 157.5 minutes) without causing any increased incidence of adverse effects.

REFERENCES

- [1] Tan M, Law LS, Gan TJ. Optimizing pain management to facilitate enhanced recovery after surgery pathways. *Can J anaesthesia* 2015;62(2):203-18.
- [2] Fanelli G, Casati A, Aldegheri G, et al. Cardiovascular effects of two different regional anaesthetic techniques for unilateral leg surgery. *Acta anaesthesiol Scand* 1998;42(1):80-4.
- [3] Anderson CTM. Adjuvants in regional and neuraxial anaesthesia: an update. In *Pediatric anaesthesiology*. March 14-17, 2013. Las Vegas, NV. Society for Pediatric anaesthesia and the American Academy of Pediatrics Section on anaesthesiology and Pain Medicine. <http://www2.pedsanesthesia.org>
- [4] Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *anaesthesiology* 1979;50(2):149-51.
- [5] Stein C, Millan MJ, Shippenberg TS, et al. Peripheral opioid receptors mediating antinociception in inflammation. Evidence for involvement of mu, delta and kappa receptors. *J Pharmacol Exp Ther* 1989;248(3):1269-75.
- [6] Candido KD, Winnie AP, Ghaleb AH, et al. Buprenorphine added to the local anaesthetic for axillary brachial plexus block prolongs postoperative analgesia. *Reg anaesth Pain Med* 2002;27(2):162-7.
- [7] Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anaesthesia. A clinical review of clonidine (1984-1995). *anaesthesiology* 1996;85(3):655-74.
- [8] Tamsen A, Gordh T. Epidural clonidine produces analgesia. *Lancet* 1984;324(8396):231-2.
- [9] Gupta S, Raval D, Patel M, et al. Addition of epidural clonidine enhances postoperative analgesia: a double-blind study in total knee-replacement surgeries. *Anaesthesia Essay Res* 2010;4(2):70-4.
- [10] Förster JG, Rosenberg PH. Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. *Br J anaesth* 2004;93(5):670-7.
- [11] Gaumann DM, Brunet PC, Jirounek P. Hyperpolarizing afterpotentials in C fibers and local anaesthetic effects of clonidine and lidocaine. *Pharmacology* 1994;48(1):21-9.
- [12] Isaac L. Clonidine in the central nervous system: site and mechanism of hypotensive action. *Journal of Cardiovascular Pharmacology* 1980;(2 Suppl 1):S5-19.
- [13] Walsh SL, Preston KL, Stützer ML, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology and Therapeutics* 1994;55(5):569-80.
- [14] Elia N, Culebras X, Mazza C, et al. Clonidine as an adjuvant to intrathecal local anaesthetics for surgery: systematic review of randomized trials. *Regional anaesthesia and Pain Medicine* 2008;33(2):159-67.

- [15] Benhamou D, Thorin D, Brichant JF, et al. et al. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. *anaesthesia & Analgesia* 1998;87(3):609-13.
- [16] Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. *Ind J Anaesth* 2007;51(5):415-9.
- [17] Singh AP, Kaur R, Gupta R. Intrathecal buprenorphine versus fentanyl as adjuvant to 0.75% ropivacaine in lower limb surgeries. *Journal of anaesthesia and Clinical Pharmacology* 2016;32(2):229-33.
- [18] Dixit S. Post-operative analgesia after caesarean section: an experience with intrathecal buprenorphine. *Ind J Anaesth* 2007;51(6):515-8.
- [19] Rashmi D, Roseline ZA, Nishant B, et al. Comparative study on post-operative pain relief by intrathecal buprenorphine hydrochloride with control group. *International Journal of Advances in Medicine* 2016;3(4):880-7.
- [20] Borse YM, Thorat SA, Dighe JP, et al. A comparative study of intrathecal bupivacaine and bupivacaine with buprenorphine for post-operative analgesia in orthopaedic surgeries. *J Indian Journal of Clinical Anaesthesia* 2015;2(2):92-6.