

Observation on Analgesic Efficacy of Intrathecal Clonidine as an Adjuvant to Hyperbaric Bupivacaine in Patients Undergoing Lower Limb Surgeries

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ABSTRACT

Introduction: Postoperative pain relief can improve functionality, reduce physiological and emotional morbidity and improve quality of life. Neuraxial blocks not only reduce the incidence of venous thrombosis, pulmonary embolism, cardiac complications, bleeding transfusion requirements and respiratory depressions but also provide effective postoperative analgesia. With the addition of opioid additives such as clonidine, ketamine, postsurgical analgesic effect of intrathecally administered bupivacaine can be prolonged. Intrathecal administration of clonidine induces antinociceptive effects in humans. Hence, we evaluated the impact of the additive analgesic effects of clonidine with bupivacaine when given intrathecal in lower limb surgeries in a tertiary care hospital and to compare the results with the use of Bupivacaine alone.

Material and Methods: Sixty cases admitted for lower limb surgery were divided into equal groups I and II. Cases in Group I received intrathecal bupivacaine while those in group II received intrathecal combination of bupivacaine and clonidine. Systematic recording and comparison of the results along with the adverse effects of anaesthesia was done.

Results: There was a significantly higher duration of a pain-free period in cases administered with clonidine as an adjuvant to hyperbaric bupivacaine. Conclusion - Addition of clonidine as an adjuvant to hyperbaric bupivacaine for subarachnoid block prolongs the duration of effective anaesthesia and significantly prolongs the duration of analgesia as compared to plain hyperbaric bupivacaine. The utilization of intrathecal clonidine is not associated with respiratory depression, hypotension, bradycardia and pruritus.

Conclusion: Spinal anaesthesia offers advantages of maintaining steady breathing rate and relaxing only desired muscles. At the same time, it is also accompanied by certain adverse effects like shorter duration of action, increase in patient's anxiety etc.

Keywords: Anaesthesia, Analgesia, Bupivacaine, Clonidine, Combination, Intrathecal

INTRODUCTION

Clonidine, an imidazoline, was originally tested as a vasoconstrictor, acting at peripheral α_2 receptors. During clinical trials as a topical nasal decongestant, clonidine was found to cause hypotension, sedation and bradycardia. Dr. August Bier carried out the first spinal anaesthesia in 1899 and his anaesthetic technique has become the standard practice for lower extremity and abdominal surgery worldwide.¹ Nowadays, the most commonly used drugs for spinal anaesthesia are local anaesthetics. However, limited duration of action is the major drawback of single injection administered via spinal route. In clinical practice, a number of adjuvant has been added to intrathecal local anaesthetics for supplementation of

intra-operative anaesthesia and postoperative analgesia.² In 1976, Midazolam was the first water-soluble benzodiazepine (BZP) to be clinically used and was synthesized by Walsar et al. and also was the first BZP that was used in anaesthetic field.^{3,4} Diazepam and midazolam are the frequently used BZP during surgical procedures along with flumazenil, which is commonly employed BZP antagonist. It is due to the 7 member diazepine ring that fuses with the benzene ring in the chemical structure of BZPs, gives BZPs their name. For increasing the pharmacological effect of BZPs, their agonists have a 5-aryl substituent (ring C). Presence of a keto group in the place of ring C and CH₃- group at fourth position in flumazenil differentiates it from BZPs. Therefore, for instantaneous termination of action of BZPs, their antagonist flumazenil can be used.^{5,6} Maintenance of large amount of midazolam in the plasma at a constant rate can be attributed to its lipid-soluble nature.⁷ Older age does not increase the volume of distribution significantly.^{8,9} However, in obese patients, the volume of distribution is increased and the elimination half time is prolonged while the clearance remains unchanged.⁸ Elimination half time is independent of the route of administration. Major operations seem to increase the volume of distribution and prolong the elimination half time.⁹ Extrahepatic locations of the body are also involved in the metabolism of midazolam.¹⁰ Reduction in the clearance of the drug in the plasma and prolongation of clearance half life has been observed in patients with liver disorder in comparison with healthy individuals. However, in such cases, no change has been observed in the volume of distribution of the drug.¹¹ Clonidine is well absorbed after administration and its bioavailability is nearly 100%. There is a good correlation between plasma concentrations of clonidine and its pharmacological effects.¹² The study was aimed to evaluate the impact of the additive analgesic effects of clonidine with bupivacaine when given intrathecal in lower limb surgeries in a tertiary care hospital and to compare the results with the use of Bupivacaine alone

MATERIAL AND METHODS

After prior approval from the Institutional Ethics Committee (IEC), this randomized study was conducted in the Department of Anaesthesiology of Katihar Medical College. All the subjects

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were pre-informed about the study protocol and written consent was taken from them. Sixty adult cases of either sex and between the ages of 20 to 70 years of ASA grade I and II that were admitted in the hospital for lower limb surgeries were included in this study. Data pertaining to age, sex and impending surgery of the patient was documented and each patient was clinically examined. Cases not falling in the age group and cases with diabetes mellitus, hypertension, hypotension, respiratory diseases, cardiac diseases, renal diseases, epilepsy, spinal defects, coagulopathy, increased intracranial tension and sepsis were excluded from the study. Preanaesthetic evaluation was performed. Two groups were formulated with 30 patients in each group giving a total of 60 patients. The groups were I and II. Cases in group I received intrathecal 2.5ml of 0.5% hyperbaric Bupivacaine 12.5mg with 0.4ml of normal saline. Cases in group II received intrathecal 2.5ml of 0.5% hyperbaric Bupivacaine 12.5mg with 0.2ml (30µg) of Clonidine in 0.2 ml normal saline solution. No premedication was administered and spinal block was performed with 25G spinal needle in the L3-L4 intervertebral space in the sitting position. The following parameters were recorded and monitored every two minutes for the first twenty minutes and then every five minutes till the completion of the surgery.

1. Clinical parameters
2. Level of sensory blockade
3. Quality of intraoperative analgesia
4. Motor power
5. Time of two segments regression
6. Side effects

Postoperatively, the cases were monitored within four hours of intrathecal injection or upon complete recovery of the sensory and motor functions whichever of the two was longer. Duration of total analgesia was recorded as the time between onsets of analgesia to that of rescue analgesia. Duration of motor blockade was recorded as the time between onsets to resolution of motor blockade.

STATISTICAL ANALYSIS

All the results were analyzed by SPSS software. Paired ‘t’ was used to assess the level of significance.

RESULTS

Both the groups were comparable to each other in age, weight, gender and type of surgery involved as shown in Table-1 and 2. No significant difference in heart rate and blood pressure was observed. Table 3 and 4 highlights the time required for onset of sensory and motor blockade symptoms (in minutes) respectively. Maximum duration of motor blockade was 150 to 160 minutes for group I patients and was 160 to 170 minutes for group II patients as shown in Table 5. Table 6 shows the level of analgesia which was T₁₀ for group I patients and T₈ for group II patients. The maximum time for two segment sensory regression was 81 to 100 minutes for group I patients and was 120 to 140 minutes for group II patients (Table-7). The maximum duration of analgesia for group I and II patients was 160 to 180 minutes and 220 to 260 minutes respectively as shown in Table-8. Time taken between administration of the drug and onset of motor block was less in Group II. All sixty cases required analgesia during twenty four hours after surgery. However, the total number of oral administrations was significantly less in Group

II. There were no episodes of bradycardia, hypotension, sedation or dizziness in any patients (Table-9). Few patients from each group developed urinary retention and time for the first self voiding was almost similar in both groups. No neurological deficits were detected at discharge.

DISCUSSION

A number of decades have passed since the beginning of clinical use of clonidine. This drug which was originally used as an antihypertensive agent is now used orally, intravenously and even intrathecally. This drug also has intrathecal effects when used as an adjuvant. These beneficial effects have been demonstrated in both adults and children. In recent studies

Age in years	Group I	Group II
21-25	4	2
26-30	2	4
31-35	4	7
36-40	9	6
41-45	5	3
46-50	6	8
Total	30	30

Table-1: Age distribution of participants in this study

Weight in kilograms	Group I	Group II
46-50	0	0
51-55	12	11
56-60	15	13
61-65	2	3
66-70	0	3
71-75	1	0
Total	30	30

Table-2: Weight distribution of participants in this study

Time in minutes	Group I	Group II
3-5	02	14
6-8	20	14
9-11	07	01
12-14	01	01
Total	30	30

Table-3: Duration for onset of sensory blockade in minutes

Time in minutes	Group I	Group II
6-8	00	00
9-11	18	17
12-14	11	12
15-17	01	01
Total	30	30

Table-4: Duration for onset of motor blockade in minutes

Time in minutes	Group I	Group II
111-120	00	00
121-130	01	01
131-140	05	04
141-150	06	05
151-160	09	08
161-170	05	09
171-180	04	03
Total	30	30

Table-5: Duration of motor blockade in minutes

Spinal Level	Group I	Group II
T ₄	00	00
T ₅	00	00
T ₆	00	00
T ₇	04	03
T ₈	09	12
T ₉	06	05
T ₁₀	11	10
Total	30	30

Table-6: Level of analgesia

Time in minutes	Group I	Group II
41-60	02	00
61-80	10	01
81-100	13	01
101-120	03	06
121-140	01	19
141-160	00	02
161-180	01	01
181-200	00	00
Total	30	30

Table-7: Time for two segment sensory regression

Time in minutes	Group I	Group II
121-140	02	00
141-160	08	00
161-180	10	00
181-200	10	02
201-220	00	02
221-240	00	13
241-260	00	13
261-280	00	00
281-300	00	00
Total	30	30

Table-8: Duration of analgesia

Spinal Level	Group I	Group II
Hypotension	01	02
Nausea	02	01
Shivering	02	03
Heavy headedness	02	01
Pruritus	00	00

Table-9: Post-operative side effects

clonidine has been demonstrated to be an effective sedative and analgesic and to reduce the amount of anaesthetic agents required. When compared to clonidine, midazolam exerts its impact by modulating the brain's inhibitory neurotransmitter; \hat{I}^3 - amino butyric acid (GABA). GABA receptors are of two type, out of which BZPs are a component of BZP-GABAA receptor complex.^{12,13} Chloride ions gating gets initiated after the activation of GABAA receptors which results in resistance of GABAA receptors to neuronal excitation.¹⁴ Midazolam exerts its anxiolytic effect by acting on mammillary body and by elevating the glycine inhibitory neurotransmitters. Increased effect of GABA on the motor circuit of brain by midazolam and alterations in the glycine receptors in the spinal cord attributes to its anti-convulsant properties and muscle-relaxant properties respectively.⁴ Apart from these effects, its action by affecting the

opiate receptors has also been well known.¹⁵ Spinal anaesthesia is the most commonly used regional anaesthetic technique. Local anaesthetic although provide adequate anaesthesia, they act for a comparatively shorter duration of time. To overcome this short coming, various additives like intrathecal opioids, have been tried since past few decades to increase the duration of action of anaesthetic solutions.¹⁶⁻¹⁸ The advantages of these adjuvant opioids in providing post-operative anaesthesia are well documented in the literature. However, certain dose-dependent adverse effects have been seen with these opioids such as vomiting, nausea, pruritis, sedation etc.¹⁹ For the management of both acute and chronic and also cancer pain, midazolam has been routinely used via intrathecal route.²⁰⁻²³ The first practical demonstration of midazolam's effect in relieving somatic pain was done by Goodchild and Noble.²⁰ Midazolam facts as a n agonist at the BZP binding sites of GABA-A receptors which forms the rationale for its intrathecal use. With midazolam occupying the receptor sites, an increase in activity of GABA is observed. Stabilization of trans-membrane potential at/near the vicinity of resting potential is the function performed by activated GABA receptors.²⁴ BZP when administered intrathecally spine-mediated analgesia. Processing and stimulation of nociceptive and thermoceptive actions are carried by binding sites of GABA receptors which are most abundantly located in the dorsal root nerve portion with peak amount present in lamina II of nerve cells. The present knowledge and results validates the safe analgesic effect of BZP molecules emphasizing on the absence of prominent irreversible adverse effects.²⁵ Addition of preservative free midazolam to hyperbaric bupivacaine for spinal anaesthesia enhances the duration of anaesthetic effect as compared to plane Bupivacaine without any major adverse effects such as pruritis, respiratory depression etc. Clonidine when administered intrathecally decreases the incidence of postoperative nausea vomiting (PONV). Moreover, intrathecal clonidine does not have any clinically significant effect on perioperative hemodynamic. A small diluted dose of preservative free intrathecal clonidine appears to have few systemic side effects and is free of short term neurotoxicity. Clonidine is a selective partial agonist for $\hat{I}^{\pm 2}$ adrenoreceptors. Its analgesic effect is mediated spinally through activation of post-synaptic $\hat{I}^{\pm 2}$ receptors in substantia gelatinosa of spinal cord. Intrathecal clonidine when combined with local anaesthetic significantly potentiates the intensity and duration of motor blockade due to the fact that $\hat{I}^{\pm 2}$ adrenoreceptor agonists induce cellular modification in the ventral horn of spinal cord and facilitate the local anaesthetic action and prolongation in sensory block can be due to vasoconstrictive effect of clonidine.²⁶

CONCLUSION

Maintenance of spontaneous breath apart from relaxation of muscles required to be relaxed during surgery are the most significant advantages of the spinal anaesthesia. At the same time, it has certain disadvantages also like shorter duration of action, increase in patient's anxiety etc. In brief, intrathecal preservative free clonidine appears safe and has clinically acceptable analgesic properties.

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