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A COMPARATIVE STUDY OF INTRATHECAL FENTANYL AND CLONIDINE AS ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE IN LOWER LIMB ORTHOPEDIC SURGERIES

Anaesthesiology

Chanda Ram PG Resident, Department Of Anaesthesia, Government Medical College, Kota, Rajasthan, India

Chetan Shukla Senior Professor, Department Of Anaesthesia, Government Medical College, Kota, Rajasthan, India

Manish Singh Chauhan* PG Resident, Department Of Anaesthesia, Government Medical College, Kota, Rajasthan, India *Corresponding Author

ABSTRACT

INTRODUCTION:-Spinal anesthesia-Regional anesthesia, is the most commonly used technique which provides a fast and effective onset of sensory and motor block, excellent muscle relaxation, and prolonged postoperative analgesia. In an attempt to further minimize the effects of local anesthetics and prolong the duration of intraoperative and postoperative analgesia, various adjuvants such as vasoconstrictors, alpha-2 agonists, and opioids have been used. Levobupivacaine is a preferred local anaesthetic due to its longer sensory block, lower cardiac and central nervous system toxicity and shorter motor block. Most commonly used opioid in regional anesthesia is fentanyl citrate which is a μ1 - and μ2 -receptor agonist.

In recent years alpha-2 agonist (Clonidine-commonly used as an adjuvant for postoperative analgesia.) are being extensively evaluated as an alternative to neuraxial opioids, as an adjuvants in regional anaesthesia. As neuraxial opioids may be associated with quite a few side effects, most important-respiratory depression. They can provide pain relief by an opioid independent mechanism. Therefore, the present study is being undertaken to evaluate and compare the effects of clonidine and fentanyl as intrathecal adjuvants to hyperbaric bupivacaine in patients undergoing lower limb orthopedic surgery.

MATERIAL AND METHODS:- The study was conducted in Department of Anesthesiology, Govt. Medical College, Kota from jan.2018 to dec.2018. with Due permission from institutional ethical committee was obtained. This is Hospital based Randomized double blind controlled observational study. This study included 80 Cases of either sex admitted for lower limb orthopedic surgeries. The patients were randomly divided into 2 groups of 40 each.

Fentanyl Group (Group F) received 2 ml of 0.5% hyperbaric bupivacaine + .5ml of (25μg) of fentanyl intrathecally. **Clonidine Group (Group C)** received 2 ml of 0.5% hyperbaric bupivacaine + .5 ml (30 μg) of clonidine (1:2.5 dilution) intrathecally. All data were collected and analysed with the help of suitable statistical parameters.

RESULTS:- The mean duration of sensory block in group-Fentanyl was 199.6±7.3 min and in group-Clonidine was 275.7±11.3 min with a statistically highly significant difference (p-value 0.0001). The mean duration of motor block in group-Fentanyl was 151.7±8.6 min and in group-Clonidine was 225.7±12.7 min with a statistically highly significant difference (p-value 0.0001). In our study Modified Ramsay Sedation Score was significantly higher in group clonidine as compared to group fentanyl and the VAS chart for postoperative pain was significantly lower in group clonidine as compared to group fentanyl.

KEYWORDS

fentanyl, Clonidine, lower limb orthopedic surgeries.

INTRODUCTION

The management of pain is a major aspect of anaesthesia. Today's anesthesiologist is not only involved in the preoperative and intraoperative care of the patients but is also responsible for the postoperative pain relief.[1]

Now-a-days use of regional anesthesia techniques for a number of common surgeries is increasing day by day. Regional anesthesia has many benefits over general anesthesia as it eliminates the pain both intraoperatively and postoperatively, provides excellent muscle relaxation, and reduces intraoperative bleeding.[2]

Spinal anesthesia is the most commonly used technique which provides a fast and effective onset of sensory and motor block, excellent muscle relaxation, and prolonged postoperative analgesia.[3] In an attempt to further minimize the effects of local anesthetics and prolong the duration of intraoperative and postoperative analgesia, various adjuvants such as vasoconstrictors, alpha-2 agonists, and opioids have been used.[4]

Levobupivacaine is a preferred local anaesthetic due to its longer sensory block, lower cardiac and central nervous system toxicity and shorter motor block. It produces localized anesthesia by blocking the transmission of action potential in sensory, motor and sympathetic nerve fibers, by inhibiting the passage of sodium through voltage sensitive ion channels in the neuronal membrane.[2] The duration of action of levobupivacaine is dose dependent and it was found that 10 mg is the minimum dose for effective sensory and motor block in spinal anesthesia.[5] Intrathecal opioids as an adjuvant to low dose local anesthetics, produces a synergistic effect by acting directly on the opioid receptors in the spinal cord.[6]

Almost all opioids have been used as adjuvants intrathecally. Most commonly used opioid in regional anesthesia is fentanyl citrate which is a μ1 - and μ2 -receptor agonist. It is a highly potent drug because of its high lipophilicity with minimal cephalad spread making it the least likely of all the intrathecal opioids to cause delayed respiratory depression [7]. Furthermore, it is reported that a single administration of an opioid may also induce a long lasting increase of threshold pain sensitivity, leading to delayed hyperalgesia [3]. However, pruritus, nausea, vomiting, respiratory depression, and urinary retention are other common side effects for which search for ideal nonopioid adjuvants goes on.[2]

In recent years alpha-2 agonist are being extensively evaluated as an alternative to neuraxial opioids, as an adjuvants in regional anaesthesia. As neuraxial opioids may be associated with quite a few side effects, such as respiratory depression, nausea, urinary retention and pruritis. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis.[8,9] The faster onset of action of local anaesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into postoperative period, dose sparing action of local anaesthetics and stable cardiovascular parameters make these agents a very effective adjuvant in regional anaesthesia. [10]

They can provide pain relief by an opioid independent mechanism as it directly stimulates pre- and postsynaptic alpha-2 adrenoceptors in the dorsal horn grey matter of the spinal cord, thereby inhibiting the release of nociceptive neurotransmitters.[11] α_2-adrenergic agonists have both analgesic and sedative properties, when used as adjuvants to regional anaesthesia. α_2 agonists also carry the unique advantage of providing analgesia and sedation without causing significant respiratory depression.

Clonidine is an alpha-2 adrenergic agonist that has a variety of

different actions including antihypertensive effects as well as the ability to potentiate the effects of local anaesthetics. Clonidine is a potent, short acting, synthetic, lipophilic spinal analgesic. It has been commonly used as an adjuvant for postoperative analgesia.

Therefore, the present study is being undertaken to evaluate and compare the effects of clonidine and fentanyl as intrathecal adjuvants to hyperbaric bupivacaine in patients undergoing lower limb orthopedic surgery.

MATERIALAND METHOD

Study Area : The study was conducted in Department of Anesthesiology, Govt. Medical College, Kota from jan.2018 to dec.2018. with Due permission from institutional ethical committee was obtained.

Study Design : Hospital based Randomized double blind controlled observational study

Sample Size : Sample size was calculated 39 subjects for each of the 2 groups at α error 0.05 and Power 80% assuming minimal detectable difference in mean time to first analgesic request with fentanyl, clonidine group to be 50 minutes with SD of 70 minutes so for the study purpose 40 cases was taken in each group.

Sampling Technique: Simple random technique through chit in box method.

Study Universe: Cases undergoing lower limb orthopedic surgeries like tibia nailing, tbw patella,femer nailing etc. (Duration 60-90 min).

Study Groups : The study was conducted in following two groups of patients. Each group consist of 40 patients (n =40/group).

Fentanyl Group (Group F) :Patients receive 2 ml of 0.5% hyperbaric bupivacaine + .5ml of (25µg) of fentanyl intrathecally.

Clonidine Group (Group C) : Patients receive 2 ml of 0.5% hyperbaric bupivacaine + .5 ml (30 µg) of clonidine (1:2.5 dilution) intrathecally.

Pre-anaesthetic assessment:

- Standard protocol was followed for Pre-anaesthetic assessment of patients.

Blinding and Randomization :

This trial is so planned that neither the doctor nor the patient was aware of the groups and the drug used. Randomization is a statistical procedure by which the participants were allocated into 2 different groups. In this study randomization was done by chit in box method. A total of 80 chits (40 per group) were made, each chit mentioning a particularly study group.

PROCEDURE:

Informed written consent was obtained after complete explanation about the study protocol and the procedure. Spinal anaesthesia was performed at L3-L4 interspace with the standard protocol. Postoperatively the pain score was recorded by using Visual Analogue Pain Scale (VAS) between 0 and 10 (0 = no pain , 10 = worst pain)

Total duration of analgesia : Time from intrathecal drug administration to patient's first demand of rescue analgesia (ON VAS 3)

Visual analogue score – Postoperatively, the pain was assessed by using visual analog pain scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain). It was assessed at every 30 min.

Visual analog pain scale (VAS)

Score	Criteria		
0	No pain	1,2,3	Mild pain
4,5,6	Moderate pain	7,8,9	Severe pain
10	Worst imaginable pain		

Patients were allowed to receive rescue analgesics on VAS score of3 intravenous Diclofenac 75mg was given as rescue analgesic. This time from intrathecal injection to first administration of rescue analgesic (total duration of analgesia) was noted. This was the end point of our study. Patient were monitored for 24 hrs for any adverse effects.

The incidence of adverse effects such as nausea, vomiting, shivering, respiratory depression, sedation and hypotension was recorded.

End point of study – Motor and sensory block recover completely.

Post operative sedation level is measured by using FOUR POINT

SEDATION SCALE

Score	Degree of Sedation
1	Eyes open spontaneously
2.	Eyes open to speech
3.	Eyes open when shake
4.	Unresponsive

OUTCOME VARIABLES

1. Mean time in onset of sensory block.
2. Mean time in onset of motor block.
3. Mean duration of sensory block
4. Mean duration of motor block.
5. Mean duration of analgesia
6. Median VAS Score.
7. Proportion of cases with complications.

OUTCOME ANALYSIS

- For significance in difference in mean time i.e. outcome variable 1 to 5 → ANOVA test of significance.
- For significance in difference in median VAS Score i.e. outcome variable 6 → Kruskal Wallis test of significance.
- For significance in difference in proportion of cases i.e. outcome variable 7 → Chi – Square test of significance.
- For significance cut off values are as follows →p> 0.05 = not significant p < 0.05 = significantp = 0.05 = just significant p < 0.001 = highly significant.

RESULTS:

Table: 1 Duration of sensory block (mins)

Duration of sensory block	Mean	SD	P-value	Remarks
GROUP -FENTANYL	199.6	7.3	0.0001	Significant
GROUP-CLONIDINE	275.7	11.3		

Here, mean duration of sensory block in group-Fentanyl was 199.6±7.3 min and in group-Clonidine was 275.7±11.3 min with a statistically highly significant difference (p-value 0.0001).

Table: 2 Duration of motor block (mins)

Duration of motor block (mins)	Mean	SD	P-value	Remarks
GROUP -FENTANYL	151.7	8.6	0.0001	Significant
GROUP-CLONIDINE	225.7	12.7		

The mean duration of motor block in group-Fentanyl was 151.7±8.6 min and in group-Clonidine was 225.7±12.7 min with a statistically highly significant difference (p-value 0.0001).

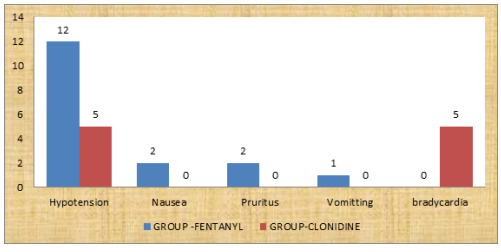

Fig: 1 side effects

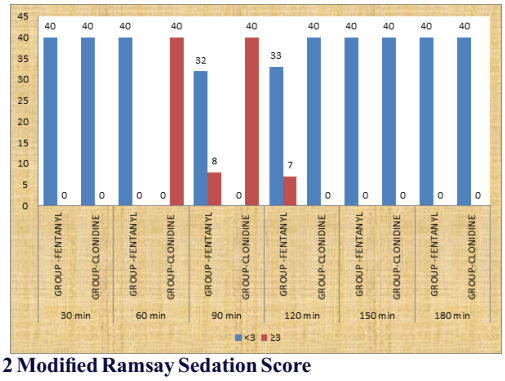

Fig: 2 Modified Ramsay Sedation Score

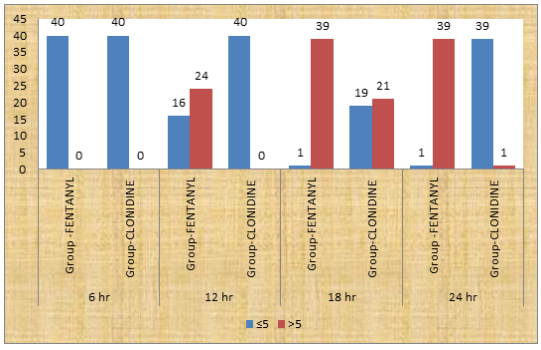

Fig: 3 Visual Analogue Scales

DISCUSSION:

Clonidine is a selective partial agonist for α2 adrenergic receptors. It is more potent after neuraxial than systemic administration indicating spinal site of action and favoring neuraxial administration. It provides effective and long lasting post-operative analgesia. . Intrathecal α2 agonists are found to have antinociceptive action for both somatic and visceral pain.

Fentanyl is a lipophilic μ receptor agonist opiod. Intrathecally It exerts its effect by combining with opioid receptor in the dorsal horn of spinal cord and may have a supraspinal spread and action.

In our study, we compared intrathecal clonidine and fentanyl in terms of safety and efficacy, and to compare the efficacy, we used the effective analgesia duration measured in minutes for requirement of rescue analgesia.

In present study mean duration of sensory block in group-Fentanyl was 199.6±7.3 min and in group-Clonidine was 275.7±11.3 min with a statistically highly significant difference (p-value 0.0001). (**Table -1**)

The mean duration of motor block in group-Fentanyl was 151.7±8.6 min and in group-Clonidine was 225.7±12.7 min with a statistically highly significant difference (p-value 0.0001).). (**Table-2**)

In consistent with these Routray et al found that duration of sensory block in Group C was 250.52 ± 18.41 min compared to 205.16 ± 19.55 min in Group F which was statistically significant ($P < 0.001$). Duration of motor block was 190.19 ± 26.11 min in Group C in comparison to 171.31 ± 24.58 min in Group F which was statistically significant ($P < 0.001$)[12]

Mehandru et al found that duration of sensory and motor block in group BC and BF were comparable with no statistical differences between these two groups[13]. Srinivasagam et al found that there was significant difference in duration of sensory and motor block. The mean duration of sensory block was 174.33±23.44 min in Fentanyl group and 306.67±60.47 min in Clonidine group[14]. Tilkar*et al*. conducted a prospective study to differentiate between the effects of fentanyl versus clonidine when added to intrathecal bupivacaine in spinal anesthesia. They concluded that addition of intrathecal clonidine to hyperbaric bupivacaine was more advantageous than fentanyl with special regard to its analgesic properties [15].

In our study majority of patients had hypotension (30%) followed by nausea (5%), pruritus (5%) and vomiting (2.5%) in fentanyl group as compared to clonidine group in which 12.5% had hypotension and bradycardia as side effects. (**Figure-1**)

In consistent with this study by Routrayet al[12] found that hypotension and bradycardia was associated with clonidine. Tilkaret al[15] observed that the incidence of bradycardia and sedation was significantly higher in the group- clonidine. Chiari et al [16] observed that Clinical efficacy of Intrathecal Clonidine to relieve visceral pain in well-established but Clonidine is also associated with few side effects like bradycardia, hypotension and dry mouth.

In our study, Modified Ramsay Sedation Score was significantly higher in group clonidine as compared to group fentanyl. **(Figure: 2)**

In consistent with this Srinivasagametal [14] found that Sedation score in group BC was higher than in group BF. Mahendru et al. [13] found that No significant difference was observed in the sedation scores with patients in two groups having score of 1.

In our study, the VAS chart for postoperative pain was significantly lower in group clonidine as compared to group fentanyl. **(Figure: 3)**

This was supported by the study of Jain et al.[17] who found that pain score remained 0 in clonidine + bupivacaine group as compared to 0.5% bupivacaine alone group. VAS scores for pain were also least in the 75 μg clonidine group in the study carried out by Grandheet al.[18]. Al-Ghanem et al observed that Intrathecal α2 agonists are found to have antinociceptive action for both somatic and visceral pain.[19].

CONCLUSION:

We concluded that intrathecal clonidine when added to bupivacaine in spinal anesthesia provides prolonged duration of postoperative analgesia than fentanyl but with higher degree of sedation. Fentanyl may be recommended as a better option when sedation is not desirable.

CONFLICT OF INTEREST: there is no conflict of interest between authors.

ABBREVIATION:

ASA	American Society of Anaesthesiologists
VAS	Visual Analog Pain Scale

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