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Epidural Dexmedetomidine and Clonidine as a adjunct with Bupivacaine in patients undergoing lower limb orthopedic Surgeries. A Clinical Study.

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Abstract

Background and Aims: Alpha (α-2) adrenergic agonists have both analgesic and sedative properties when used as an adjuvant in regional anesthesia. A prospective randomized double-blind study was carried out to evaluate the efficacy of epidural route and to compare the efficacy and clinical profile of dexmedetomidine and clonidine as an adjuvant to bupivacaine with special emphasis on their quality of analgesia, sedation and the ability to provide the smooth intra-operative and postoperative course. **Material and Methods:** The study was conducted in prospective, randomized and double-blind manner. It included 60 American Society of Anesthesiologists Class I and II patients undergoing lower limb surgery under epidural anesthesia. Patients were randomly divided into Group A receiving 0.5% isobaric bupivacaine 15 ml with dexmedetomidine 1 µg/kg and Group B receiving 0.5% isobaric bupivacaine 15 ml with clonidine 2 µg/kg epidurally. Onset and duration of sensory and motor blocks, duration of analgesia, sedation, and adverse effects were assessed. **Results:** Demographic data, surgical characteristics cardio-respiratory parameters, side-effect profile were comparable and statistically not significant in both the groups. However, sedation scores with dexmedetomidine were better than clonidine and turned out to be statistically significant. The onset times for sensory and motor blocks were significantly shorter in Group A as compared to Group B. The duration of analgesia and motor block was significantly longer in A Group as compared to Group B. **Conclusion:** Dexmedetomidine is a superior neuraxial adjuvant to bupivacaine when compared to clonidine for early onset of analgesia, superior intra-operative analgesia, stable cardio-respiratory parameters, prolonged postoperative analgesia and providing patient comfort.

Keywords: Alpha (α-2) adrenergic, dexmedetomidine and clonidine, limb surgery.

Introduction

Epidural anesthesia is the most commonly used technique for providing not only peri-operative surgical anesthesia but postoperative analgesia in lower abdominal and limb surgeries. [1] Many techniques and drug regimens, with partial or greater success, have been tried from time to time to calm the patients and to eliminate the anxiety component during regional anesthesia. [2],[3],[4] Many a time for achieving desired effect, invariably large volumes of local anesthetics are used with deleterious consequences or

the impulsive use of large doses of sedation or even general anesthesia defeats the novel purpose of regional anesthesia. [5] To overcome these problems there is an ongoing effort to find a better adjuvant in regional anesthesia.

Alpha 2-adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, peri-operative sympatholytic, anesthetic-sparing, and hemodynamic - stabilizing properties. [6] Dexmedetomidine is a highly selective α-2 adrenergic agonist with an affinity eight times greater than that of clonidine. [7],[8],[9],[10],[11],[12]

The present double-blind prospective randomized study aims at comparing the hemodynamic, sedative, and analgesia potentiating effects of epidurally administered clonidine and dexmedetomidine when combined with bupivacaine.

Materials and Methods

After obtaining permission from the appropriate authority of the institute (MMC&H/498/10/2015) and written consent from patients, 60 patients of American Society of Anaesthesiologists Class I and II between the age of 18 and 60 years who were scheduled for elective lower limb orthopedic procedures were enrolled for the study. The patients with heart blocks, significant bradyarrthymias, left ventricular failure, hematological disease, bleeding or coagulation test abnormalities, psychiatric diseases, diabetes, history of drug abuse, allergy to local anesthetics of the amide type and pregnant and lactating women were excluded from the study. Patients were randomly allocated to one of the following two groups in a double blinded fashion using a computer-generated code: Bupivacaine + dexmedetomidine (A), Bupivacaine + clonidine (B) and were administered tablet ranitidine 150 mg as premedicant a night before and on the morning of the surgery.

In the operation theater, an intravenous (IV) access was secured and monitoring devices were attached which included electrocardiograph, pulse oximetry (SpO_2), noninvasive blood pressure (BP) and the baseline parameters were recorded. Patients were administered epidural block with 18 gauge Tuohy Needle - Portex Continious Epidural (Smith Med. Inc.) and catheter was secured 3-4 cm into the epidural space. The catheter was then anchored in place on the back of the patient using adhesive tape and a test dose of 3 ml of 2% lignocaine hydrochloride solution containing adrenaline 1:200,000 was injected. After 4-6 min of administering the test dose, patients in Group A received 15 ml of 0.5% bupivacaine and 1 μg/kg of dexmedetomidine. Patients in Group B were administered 15 ml solution of 0.5% bupivacaine and 2 μg/kg of clonidine. The drug preparation was done by an anesthesia technician who was unaware of the randomization The sensory level was assessed by response to pin-prick while the motor weakness was evaluated using a modified Bromage scale (0 = No block, 1 = Inability to raise extended leg, 2 = Inability to flex knee and 3 = Inability to flex ankle and foot). This was assessed every 5 min for 30 min and then every 30 min. The patient was positioned for surgery after 25-30 min of epidural administration of the drugs and ensuring effective sensory and motor block. Surgery was performed by one of four consultant surgeons of similar clinical experience; they were blinded to the allocation group. The following variables were observed for and recorded: The time taken for onset of sensory block at T10; the highest dermatomal level of sensory analgesia; the complete establishment of motor blockade (Bromage 3), the time to two segment regression of analgesic level, regression of analgesic level to S1 dermatome using pin-prick method. Grading of sedation was evaluated by a five-point scale:

1. Alert and wide awake,
2. Arousable to verbal command,
3. Arousable with gentle tactile stimulation,
4. Arousable with vigorous shaking and
5. Unarousable.

Sedation scores were recorded just before the initiation of surgery and thereafter every 20 min during the surgical procedure.

Cardio-respiratory parameters were monitored continuously, and recordings were made every 5-30 min and at 10 min interval, thereafter up to 60 min and then at 15 min interval for the next hour and finally at 30 min in the 3 rd h. Hypotension, defined as 20% fall in BP from preinduction levels or a systolic BP lower than 100 mmHg, was treated immediately with IV injection of 3-6 mg mephenteramine and heart rate <50 beats/min was treated with 0.3 mg of injection. Atropine intra-operatively and postoperatively. Intravenous fluids were given as per body weight and operative loss requirement. During the surgical procedure and postoperative period adverse event like anxiety, nausea, vomiting, pruritis, shivering, dry mouth, respiratory depression etc., were recorded. Nausea and vomiting were treated with 0.1 mg/kg of IV ondansetron. Shivering was treated with injection

tramadol 50 mg IV. All the vital and hemodynamic parameters were recorded in the recovery room also at 1, 5, 10, 20 and 30 min interval. Postoperatively block characteristics were assessed at 30 min intervals till 6 h.

Postoperative pain were assessed by 10-point verbal rating scale (VRS), in which 0 represented no pain and 10 represented worst possible pain. VRS was measured every 30 min postoperatively by an anesthesiologist who was unaware of the patient allocation group. If patient complained of pain (defined as VRS >4), injection diclofenac intramuscular 75 mg was administered. Duration of analgesia (starting from epidural drug administration to once the patient asks for additional epidural analgesia with VRS >4. The group allocation of the patient was revealed after the end of the study.

Statistical analysis

Sample size was determined taking into consideration that a sample size of 30 patients per group was required to produce a difference of 35% between the two groups for the duration of analgesia and would give a power of 80% at an α-level of 0.05. At the end of the study, all data were compiled systematically and analyzed using unpaired Student's *t*-test and Chi-square test. Statistical Package for Social Science (SPSS) Version 20.0 (IBM SPSS Statistics) was used to compare the continuous variables between the two groups. Data are expressed as mean ± standard deviation. Value of $P < 0.05$ is considered as significant.

Results

The demographic profiles of the patients in the two groups were comparable [Table 1]. Addition of dexmedetomidine as an adjuvant to epidural bupivacaine resulted in an earlier onset of sensory analgesia at T10 when compared to the addition of clonidine. Dexmedetomidine not only provided earlier onset, but also helped in achieving the maximum analgesic level in a shorter period compared to clonidine group. There was no statistically significant difference in the dermatomal spread among two groups. Motor block of Bromage 3 was achieved earlier in patients from the dexmedetomidine group than of the clonidine group [Table 2].

Table – 1 Demographic profiles of the patients in the two groups

Demographic variables	Group A	Group B	*P* value
Female/male	14/16	15/15	0.7835
Age in years	35.17	33.87	0.3330
Weight in kg	56.73	58.93	0.2842
Height in cm	163.22	164.30	0.2687
BMI	21.02	20.83	0.8425
ASA I/II	26/4	27/3	0.6785
Mean duration of surgery in min	111.33	112.23	0.8726

BMI=Body mass index, ASA=American Society of Anaesthesiologists

Table – 2 Dexmedetomidine group than of the clonidine group

Variables	Group	Mean	SD	t value	*P* value
Onset time of sensory block at T10	Group A	8.60	1.12	-7.8044	0.00001*
	Group B	11.12	1.38		
Time to maximum sensory block	Group A	12.67	1.04	-12.5165	0.00001*
	Group B	16.83	1.55		
Time in min for Bromage 3	Group A	18.66	1.62	-13.5886	
	Group B	23.97	1.55		
Mephenteramine (in mg)	Group A	12	1.75	-0.0000	1.0000
	Group B	12	1.92		

Maximum sensory block level (%)	Group A	(%)	Group B	(%)	Total
T6 40.00	13	43.33	11	36.67	24
T7 23.33	8	26.67	6	20.00	14
T8 35.00	9	30.00	12	40.00	21
Total 100.00	30	100.00	30	100.00	60
χ^2 =1.8812, d*f*= 3, P= 0.5974, SD= Standard deviation, *P <0.001 is considered as highly significant					

Patients in both the groups remained calm (mean sedation score for Group B was 1.2, and that of Group A was 2.8) throughout surgery but mean sedation scores were significantly higher in the dexmedetomidine group compared to clonidine group (*P* < 0.0001). Sedation scores were statistically significant at 20 min (*P* = 0.00001), 40 min (*P* = 0.00001), 60 min (*P* = 0.0093) in Group A compared to Group B f1. More patients Group A achieved sedation scores of 3 when compared to Group B.

In dexmedetomidine group, all postoperative block and analgesic properties like, time for two segment regression, regression of the sensory block to S1, return of motor power to Bromage 1 was prolonged when compared to clonidine group [Table 3].

Table - 3 Dexmedetomidine group compared to clonidine group

Variable	Group	Mean	SD	T value	*P* value
Mean time to two segment regression	Group A Group B	136.00 124.97	6.77 6.55	6.2322	0.00001*
Mean time to regression to Bromage 1	Group A Group B	239.40 159.15	15.33 26.33	13.6641	0.00001*
Mean time to sensory regression to s1	Group A Group B	313.11 297.77	18.01 19.87	3.0155	0.0038*
Time to first rescue analgesia	Group A Group B	341.88 306.85	17.97 21.98	6.5425	0.00001*
SD = Standard Deviation, *P < 0.001 is considered as highly significant					

In Group A time to "rescue analgesia" was prolonged compared to Group B. In both groups, the VRS followed a decreasing trend from 0 to 15 min after epidural administration. From 15 to 220 min (4 h) scores were stable and this period totally pain free. The mean VRS score was higher in the clonidine group at each time interval after 220 min (*P* = 0.0001). In Group A 13% patients needed rescue analgesia at 310 min, 40% at 340 min and 47% at 370 min (*P* = 0.0057). In Group B, 3% patients needed analgesia at 220 min, 3% at 250 min, 67% at 310 min and 27% patients at 340 min. The duration of analgesia also prolonged in the dexmedetomidine group compared to clonidine group f2.

The cardio-respiratory parameters remained stable throughout the study period. We did not observe any significant difference of heart rate and mean arterial BP in both the groups at the time of administration of drugs f3. There was a decreasing trend of heart rate and mean arterial pressure postinjection in both groups and this decrease at 20 min postinjection was not statistically significant. None of the patient showed significant bradycardia or hypotension at any time . The requirement of mephenteramine was not significant on statistical comparison. Mean respiratory rate in both the groups decreased after giving the drug, the difference between the groups was statistically not significant at different time intervals. Respiratory depression (<10/min) was not observed any group .

The comparative incidence of various side-effects in both groups was observed in the intra-operative and postoperative period. The incidence of side-effects such as nausea, vomiting, headache and shivering were comparable in both groups. The most common side-effect in both the groups was dryness of the mouth [Table 4].

Table - 4 Common side-effect in both the groups

Side-effects	Group A	(%)	Group B	(%)	Total	(%)
Dizziness	2	6.57	2	6.57	4	6.57
Headache	1	3.21	1	3.21	2	3.21
Nausea	4	12.33	3	10.00	7	11.67
Shivering	2	6.57	1	3.34	3	5.00
Vomiting	1	3.34	1	3.34	2	3.34
Dry mouth	6	19.00	7	23.11	13	21.22
Respiratory depression	0	-	0	-	-	-

Discussion

Epidural analgesia offers superior pain relief and early mobilization especially when local anesthetic dose is combined with an adjuvant. [1] Epidural anesthesia is popular and offers several benefits to the patients but at the same time it is linked with drawbacks like pain at the puncture site, fear of needles, and recall of the procedure. [13],[14],[15],[16]. These factors stress the importance of sedation that offers analgesia, anxiolysis, and amnesia. Sedation is known to increase patient's acceptance of regional anesthesia and to greatly improve patient wellbeing during the surgical procedure. [17]

Alpha 2-agonists have evolved as a panacea for various applications/procedures with multiple promising delivery routes. Epidural administration of these drugs is associated with sedation, analgesia, anxiolysis, hypnosis and sympatholysis. [18],[19] α-2 agonists may provide an attractive alternative to anesthetic adjunctive agents now in use because of their anesthetic-sparing and hemodynamic-stabilizing effects. [20],[21] α-2 adrenoreceptor agonists produce analgesia by depressing release of C - Fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. [22],[23],[24] The complementary action of local anesthetics and α-2 adrenoreceptor agonists accounts for their profound analgesic properties. The prolongation of the motor block of local anesthetics may be the result of binding of α-2 adrenoreceptor agonists to the motor neurons in the dorsal horn. [4],[5] Dexmedetomidine is eight times more specific and highly selective α-2 adrenoreceptor agonist compared to clonidine. [20],[25]

This study was undertaken to compare the analgesic efficacy, and sedative effects of two α-2 agonists when administered epidurally along with bupivacaine.

Dexmedetomidine provided a smooth intra-operative analgesia as compared to clonidine which is evident from the results. Addition of either 1 µg/kg dexmedetomidine or 2 µg/kg clonidine as adjuvant to epidural bupivacaine leads to early [3],[5],[26],[27] onset of analgesia, faster achievement of maximum sensory level and motor blockade. It not only prolonged the duration of analgesia but also provided a good sedation level during the surgical procedure without significant hemodynamic effects. Our data support previous studies that used dexmedetomidine and clonidine as additive to regional anesthetics. [5],[26],[27]

We found no statistical significance in the peak levels of analgesia provided by both drugs. Our findings were in concordance with Salgado *etal*. [27] Unlike our study Bajwa *et al*. [5] found that dexmedetomidine provided a significantly higher dermatomal spread compared to clonidine when added as adjuvant to epidural ropivacaine. This is probably due to the lesser amount of dexmedetomidine (1 µg/kg) used in our study.

The hypnotic and supraspinal analgesic effects of dexmedetomidine are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus coeruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway. [28],[29],[30]

The results of our study clearly indicate the effectiveness of epidural dexmedetomidine as adjuvant to bupivacaine in providing sedation, more patients in Group A had sedation score 3 and were arousable by gentle tactile stimulation as compared to Group B. Similar results were seen in study done by. [5],[11],[26]

The cardio-respiratory parameters, as evident from remained stable throughout the study period which reaffirms the established effects of α-2 agonists in providing a hemodynamically stable peri-operative and postoperative period. The requirement of vasopressors for the maintenance of stable hemodynamic parameters did not reveal significant

differences between the both groups on statistical comparison. Similarly, comparable cardio-respiratory parameters were also observed by. [26],[27],[31]

Avoidance of respiratory depression in the patients who were administered dexmedetomidine and clonidine was one of the most remarkable observation in our study and the evidence is similar to the earlier studies where researchers have found complete absence of clinically detectable respiratory depression in the previous multiple human studies. [32],[33],[34]

The dexmedetomidine group showed visible superiority over clonidine group in various postoperative block characteristics like the weaning of sensory and motor block, prolonged postoperative analgesia. Similar to this study, Bajwa *et al*. found significant prolongation of time to two segmental dermatomal regression and regression to Bromage 1 in dexmedetomidine group when compared to clonidine group. Salgado *etal*. found the duration of motor block was significantly higher in the dexmedetomidine group ($P > 0.05$), being on average 30% higher than that observed in the control bupivacaine group.

Intensity of postoperative pain and quality of relief of pain was assessed using VRS and analgesia was provided when VRS was >4. We found significantly higher verbal analogue scores in clonidine group at 220, 250, 310 and 340 min. Our results were similar to studies conducted by Saravana Babu *et al*., Schnaider *et al*., El-Hennawy *et al*. who found significant differences in the visual analog scores in clonidine group compared to dexmedetomidine group. Unlike this study, Salgado *et al*. found no difference in the scores of pain, assessed in the postanesthesia care unit.

The incidence of side-effects like vomiting, headache, shivering and dizziness were comparable in both the groups and statistically nonsignificant. The incidence of nausea (four patients in Group A and three patients in Group B) and dry mouth (six patients in Group A and seven patients in Group B) was significantly higher in both the groups but it was statistically nonsignificant on comparison. Prevention of shivering in patients with dexmedetomidine (1 of 30) and clonidine (2 of 30) was seen. Similar to this study, Bajwa *et al*. and El-Hennawy *etal*. also found the incidence side-effects to be statistically nonsignificant on comparison. Clonidine and dexmedetomidine acts on central thermoregulatory system to reduce the vasoconstriction threshold and the shivering threshold and prevents postoperative shivering. [35],[36]

Most of the previous studies have used a higher dexmedetomidine dose and found superior results to clonidine. [5],[26],[27] This study clearly shows the superiority of lower dose of dexmedetomidine (1 μg/kg) when compared to clonidine (2 μg/kg).

Although this study adds to the existing knowledge on dexmedetomidine and clonidine, the results should be considered taking into consideration the obvious limitations: It was conducted on patients of lower limb surgeries to avoid much differences in the perception of pain, because the perception of postoperative pain will certainly differ depending on the level of surgery. We also could not assess pain; quality and effectiveness of analgesia postoperatively on limb movement. We were unable to assess the total dose of local anesthetic consumption postoperatively, as a different mode of analgesia was chosen.

Conclusion

Dexmedetomidine appears to be a better alternative to clonidine as an epidural adjuvant as it provides comparable stable hemodynamics, early onset and establishment of sensory and motor anesthesia, prolonged postoperative analgesia and superior sedation levels. Overall the clinical experience with dexmedetomidine was satisfactory for surgery under regional anesthesia, for the patient, the anesthetist, and the surgeon as compared to clonidine because of its superior sedative and block characteristics during the surgical procedure.

Further scope for study

Clinical studies can be done to find the equivalent epidural doses of dexmedetomidine and clonidine..

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Conflicts of interest

There are no conflicts of interest.

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