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Research Article

A COMPARATIVE STUDY ON EFFICACY OF INTRAVENOUS DEXMEDETOMIDINE VS INTRAVENOUS CLONIDINE TO PROLONG BUPIVACAINE SPINAL ANAESTHESIA

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ABSTRACT
Many techniques and drug regimens, with partial or greater success, have been tried from time to time to eliminate the anxiety component and to prolong the postoperative analgesia during regional anesthesia. α 2 agonists like clonidine, dexmedetomidine are used as adjuvant to local anaesthetics in order to prolong the duration of spinal anaesthesia. They potentiate the effect of local anesthetics and prolong the duration of both motor, sensory spinal blockade and postoperative analgesia. The objective of the study was to compare the duration of sensory and motor block, sedation scores, intra-operative haemodynamic stability of the patients, intraoperative and post operative analgesia and side effects between the groups. In this study time of onset of sensory block (2.58±1.18min) and motor block (3.54+0.45* min), time for attaining highest level of sensory block (11.6±1.9 min) were significantly reduced in dexmedetomidine group compared to clonidine and control groups however there is slight reduction in Duration for motor blockade to reach Modified Bromage scale 3. The Duration for 2 dermatomal Regression of sensory blockade (137.4±10.9 mins), duration of sensory blockade (269.8±20.7min) and duration for motor block regression to Modified Bromage scale 0 (220.7±16.5 mins) prolonged significantly than clonidine and control groups. The heart rate, systolic, diastolic and mean arterial pressures were stable indicating the hemodynamic stability. This concludes that intravenous dexmedetomidine and clonidine prolong the spinal anaesthesia and dexmedetomidine was an effective adjuvant than clonidine for bupivacaine spinal anesthesia.

Keywords: *Dexmedetomidine, Clonidine, Spinal Anaesthesia, Intravenous, Post Operative Analgesia*

INTRODUCTION
Duration of analgesic action of local anaesthetics can be prolonged by mixing them with certain pharmocologic agents called additives or adjuvants. Anaesthetic use of α2 adrenergic receptor agonists has been of considerable and prolonged interest over last 20 years. Clonidine and dexmedetomidine are such type of drugs.

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound commonly used as an adjuvant to local anaesthetics in peripheral nerve blocks where it prolongs the duration of anaesthesia as well analgesia. Dexmeditomidine is a highly selective α2-adrenoreceptor agonist, similar to clonidine. It has been used safely as premedication or as a sedative agent in patients undergoing surgical procedures under regional anesthesia. Dexmedetomidine is used as an adjuvant in epidural, spinal and intravenous regional anaesthesia.

Clonidine is a selective partial agonist for α-2 adrenoreceptors. It is known to increase both sensory and motor block of local anaesthetics and the reduction in the amount or the concentration of local anaesthetic required to produce post operative analgesia. The analgesic effect following its administration is mediated spinally through activation of post synaptic α -2 receptors in substantia gelatinosa of spinal cord (Chiari *et al.,* 1998).

Dexmedetomdine is a more suitable adjuvant to spinal anaesthesia compared to clonidine as it has more sedative and analgesic effects due to its more selective α 2A receptor agonist activity and it has a α2/α1 selectivity ratio which is eight to 10 times higher than that of clonidine. Dexmedetomidine is a highly selective α2‑adrenoreceptor agonist with α2:α1binding ratio of 1620:1 compared to 220:1 for clonidine (Grewal *et al.,* 2011).

Locus coeruleus is among the one having highest densities of α2 receptors which is a predominant noradrenergic nucleus in the brain and an important modulator of vigilance. Activation of α2-adrenoceptor results in hypnotic and sedative effects in this site in the CNS. The locus coeruleus site for the descending medullospinal noradrenergic pathway is an important modulator of nociceptive neurotransmission. In this site, α2-adrenergic and opioidergic systems have common effector mechanisms, which indicates that drugs has a supraspinal site of action (Gertler *et al.*, 2001).
This comparative study is done to evaluate the prolongation of spinal analgesia by the intravenous clonidine and intravenous dexmedetomidine administration after the subarachnoid block, and to assess the hemodynamic changes and the level of sedation on lower abdominal and lower limb surgeries.

MATERIALS AND METHODS

The clinical study was conducted on 150 patients at the Mamatha General Hospital, Khammam, Telangana state, India during the period July 2014 to June 2015 by obtaining approval from institutional ethical committee. Adult patients scheduled for elective surgeries of the lower abdomen and lower extremities were taken in to the study. Only adults belonging to ASA grade I was included. Patients with neurological disorders, anaemia, and hypertension, cardiac and respiratory disorders were eliminated from this study. After a thorough clinical examination and relevant laboratory investigations of all patients, an informed, valid, written consent was obtained, both for conduct of study as well as administration of spinal anaesthesia.
A total of 150 ASA Grade I adults for elective surgeries of lower abdomen and lower extremities under spinal analgesia were divided into 3 groups each consisting of 50 patients. All patients were kept nil by mouth from midnight before surgery and tablet diazepam 5mg was administered at bed time the day before surgery. The patients were re-examined, assessed and weighed pre-operatively on the day of surgery. Intravenous access was established with a 23G intravenous access and preloading was done with 15 ml/kg Lactated Ringer's solution 30 minutes before procedure. Anaesthesia machine and accessories were checked and drugs, including emergency drugs like atropine were kept ready. Also monitoring equipments like pulseoximeter, non invasive blood pressure (NIBP) and electrocardiogram (ECG) monitors were checked and applied to each patient on arrival to the operating room and baseline parameters were recorded. Under strict aseptic conditions, with the patient in the sitting position, a lumbar puncture was performed at L3-L4 intervertebral space. After ensuring free flow of CSF, subarachnoid block was performed with 3 ml of 0.5% hyperbaric bupivacaine. All patients of individuals were given Intrathecal Bupivacaine 15mg.
Group A: These group patients received slow intravenous clonidine 1 μg /kg, 15min before spinal analgesia followed by maintenance dose of 0.5 μg/kg/hr till the end of surgery.
Group B: patients received a loading dose of 1μg/kg of dexmedetomidine intravenously by infusion pump over 10 mins followed by maintenance dose of 0.5 μg/kg/hr till the end of surgery.
Group C: control group received an equivalent amount of 0.9% normal saline.
After the various treatments, the above groups were monitored regularly for baseline reading of pulse rate, blood pressure, arterial oxygen saturation (SPO2), respiratory rate were recorded.

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Data was analyzed by Ftest, ANOVA and post hoc test with Turkeys test. Significance is assessed at 5 % level of significance. P value <0.05 was considered significant.

RESULTS AND DISCUSSION

Spinal anesthesia was successful in all the patients. The demographic profiles of the patients among the groups were comparable with regards to age, sex, and weight and body mass index. The distribution of vital data and mean duration of surgery was comparable among the groups. The age and sex distribution was given in table 1 and the surgical procedures performed in the different groups were given in table 2.

I. Assessment of Sensory blockade

Sensory blockade was assessed for every 2 mins for the first 10 mins and thereafter every 15 mins during surgery and post operatively. All the durations were calculated considering the time of spinal injection as time 0. Sensory blockade was checked with an alcohol swab in mid axillary line and the time taken for the highest level of sensory blockade, two dermatomal regression from the maximum level and regression to S1 level was noted.

A) Onset of sensory blockade: The onset of sensory blockade was determined by applying pinprick for every 30sec interval after the completion of injection of the drug in CSF. The onset of analgesia in control group was 5.02+1.03 min, clonidine group was 4.02 ± 1.06 min where as in the Dexmedetomidine group was 2.58 ± 1.18 min. The difference in onset of analgesia between was found to be significant (p.>0.005). Similar results have been observed by Whizar-Lugo *et al.,* (2007), Kaya *et al.,* (2010) and Reddy *et al.,* (2013).

B) Highest level of sensory block [dorsal]: The median highest level of sensory black was T4 and mean time to reach it was in control group 15.2+1.45 min, clonidine group11.9+2.1 and dexmedetomidine group 11.6±1.9 mins. Dexmedetomidine and clonidine treated patients maintained higher sensory block without significant difference compared to control group. Similar results have been observed by Whizar-Lugo *et al.,* (2007), Kaya *et al.,* (2010) and Reddy *et al.,* (2013).

C) Time for sensory regression of two dermatomes: The time was 137.4 ± 10.9 mins in the dexmedetomidine group which was longer than the clonidine (124.32 ± 15.01 min) and control group (102.8+14.8 min). There exists a significant difference between groups. Significant prolongation in mean time for two dermatomal regression of sensory blockade was also reported by Tekin *et al.,* (2007), Elcıcek *et al.,* (2010) and Hong *et al.,* (2012) in their studies.

*D) Duration of sensory blockade***:** The duration of sensory blockade was defined by the time interval between the onsets of sensory analgesia to the two segment regression. The duration of sensory analgesia was 269.8±20.7 min in the Dexmedetomidine group, 196.1± 5.9 min in the clonidine group whereas169.2+12.1min in control. There was a significant difference between the duration of sensory analgesia. Significant prolongation in mean duration of sensory blockade in dexmedetomidine group was also reported by Al Mustafa *et al.,* (2007).

II. Assessment of motor blockade

Motor blockade was assessed by Modified Bromage Scale (Bromage, 1965). Time taken for motor blockade to reach Modified Bromage Scale 3 and regression of motor blockade to Modified Bromage Scale 0 was noted.

A) *Time of onset of motor block:* Time was reduced by dexmedetomidine (3.54 ± 0.45 min) when compared with clonidine (4.26 ± 1.39 min) and control groups (4.59+1.26 min).

B) *Duration for motor blockade to reach Modified Bromage scale 3:* Time was reduced by dexmedetomidine (4.21 ± 1.52 min) when compared with clonidine (4.57 ± 1.02 min) and control groups (5.54+1.9 min).

C) Duration for motor block regression to Modified Bromage scale 0: Time was prolonged by dexmedetomidine (220.7±16.5 min) when compared with clonidine (192.4+17.53min) and control groups (131.5+10.5 min).

The mechanism of motor block produced by α2‑agonist is unclear but there is some evidence that clonidine results in direct inhibition of impulse conduction in the large, myelinated A‑α fibers. The 50% effective concentration (EC50%) measured to block motor fibers is approximately 4‑folds that of small, unmyelinated C fibers. This could explain the less prolonged motor block compared with sensory block, as conduction of motor nerve fibers were less inhibited than sensory nerve fibers at the same concentration of clonidine (Al-Metwalli *et al.,* 2008).

The regression time to reach the modified Bromage Scale 0 was significantly prolonged in dexmedetomidine group compared to clonidine group (Whizar-Lugo *et al.,* 2007; Reddy *et al.,* 2013) Elcıcek *et al.,* (2010) and Hong *et al.,* (2012) also found that complete resolution of motor blockade was significantly prolonged in dexmedetomidine group. But contrary to all the above studies. Kaya *et al.,*

(2010) reported no significant prolongation in the duration of motor block in dexmedetomidine group compared to control group.

Table 1: Age and sex distribution

Group	Sex		Age groups			
	Male	Female	21-30	31-40	41-50	51-60
Group A	24	26	14	14	14	8
Group B	19	31	15	16	15	4
Group C	23	27	16	15	13	6

Table 2: List of surgical procedures

S. No	Surgical procedure	Group A	Group B	Group C
1	Herniorrhaphy	5	6	7
2	Eversion of sac	10	4	4
3	Haemorrhoidectomy	5	4	5
4	Fistulectomy	5	5	6
5	Orthopaedicprocedures	15	27	21
6	Split skin grafting of lower limb	10	4	8

Table 3: Comparison of sensory and motor blockade in different groups

	Control	Clonidine	Dexmedetomidine
Highest level of sensory block[dorsal]	T5-T8	T 4-T6	T 3 –T5
Time of onset of sensory block	5.02+1.03	4.02+1.06	2.58±1.18*
Time for attaining highest level of sensory block	15.2+1.45	11.9+2.1	11.6±1.9 mins
Duration for 2 dermatomal Regression of sensory blockade	102.8+14.8	124.32±15.01	137.4±10.9 mins
Duration of sensory blockade	169.2+12.1	196.1+5.9	269.8±20.7 mins*
Time of onset of motor block	4.59+1.26	4.26+1.39	3.54+0.45*min
Duration for motor blockade to reach Modified Bromage scale 3	5.54+1.9	4.57+1.02	4.21±1.52 mins
Duration for motor block regression to Modified Bromage scale 0	131.5+10.5	192.4+17.53	220.7±16.5 mins
Time of first request of analgesic (min)	145.56+15.32*	192.41±38.42	242.51±22.32

Table 4: Intra and post operative complications

	Control	Clonidine	Dexmedetomidine
Hypotension	5	3	5
Bradycardia	1	2	5
Sedation	1	1	17
Nausea and vomiting	2	2	1

III. Sedation Evaluation

The level of sedation was evaluated both intraoperatively and post operatively every 15 mins using Ramsay Level of Sedation Scale till the patient is discharged from PACU

Ramsay sedation score

Scale Level of sedation

1 -Patient anxious, agitated, or restless
2- Patient cooperative, oriented, and tranquil alert
3- Patient responds to commands
4 -Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5 -Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6 -Asleep, no response

Mean sedation scores were significantly higher in the dexmedetomidine group ($P < 0.0001$). Patients with sedation scores greater than three were 54% in dexmedetomidine group, 21% in clonidine group and 9% in the placebo group. The sedation produced by dexmedetomidine differs from other sedatives, as patients easily aroused (Reddy *et al.,* 2013).

IV. Post operative analgesia (from onset of analgesia to the rescue analgesia)

Numbers of patients requiring supplemental analgesia (1 μg/kg body weight of Fentanyl) intra operatively were noted. Time for first request for postoperative analgesic (duration of analgesia) was noted. Patients were given 20 mg/kg (maximum upto 1.2gm) IV paracetamol initially when the patient complained of pain. Diclofenac 75 mg IM was given if patient still complained of pain even after30 mins after paracetamol infusion. Tramadol 50 mgslow IV was given if patient still complained of pain even at 30 mins after diclofenac administration. Following surgery, the patients were interrogated at different intervals for Post operative pain relief. Magills classification was used to determine the degree of pain relief. The duration of analgesia (from onset of analgesia to the rescue analgesia) in cloidne group was 382.54±6.53 min and the duration in Dexmedetomidine group was 432.45±8.31min. There exists a significant difference between duration of postoperative analgesia. Dexmedetomidine also increased the time to first request for post operative analgesia (242.51±22.32min) compared with clonidine (192.41±38.42min) and placebo (145.56+15.32min). Comparison of mean times in sensory and motor blockade in different groups was given in table 3. In our study, time of first request for analgesic was significantly prolonged in the dexmedetomidine group than clonidine and control groups. This could be attributed to the mechanism of action of dexmedetomidine which differs from clonidine in being eight to ten times more selective to α2‑adrenoceptors especially forα2A and α2C subtype of this receptor (Feld *et al.,* 2006).

V. Intra and Post Operative Complications

The complications in different groups were given in table 4. All the above haemodynamic disturbances are not required any therapeutic intervention. All the disturbances were recovered with infusion of crystalloid solution. The sedation in groups is grade 1 that is drowsiness and the patients complained of nausea after were treated. Bradycardia, hypotension, nausea and vomiting were not statistically significant among the groups. Dexmedetomidine has been used intravenously in doses ranging from 0.1 to 10 μg/kg/h but higher doses have been associated with a significant incidence of bradycardia and hypotension (Grant *et al.,* 2004).

The hemodynamic stability was assessed by heart rate, systolic, diastolic and means arterial pressures. When we observed the trend of mean heartrates in the dexmedetomidine group appears to be lower than that of clonidine and control groups, but there is no significant difference among the groups except at 5 mins after spinal anesthesia where the mean heart rate was significantly lower ($P = 0.0299$). Mean heart rates of both the groups were above 70/min indicating the hemodynamic stability in dexmedetomidine and clonidine groups at given doses. The trend of MAP, showed no significant difference in MAP among the groups before administration of premedication but both dexmedetomidine and clonidine group had a significantly lower MAP after premedication. These hemodynamic changes were due to decrease in central sympathetic outflow.

Conclusion

Intravenous dexmedetomidine resulted in an early onset action of bupivacaine, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the postoperative period and stable cardiovascular parameters there by making dexmedetomidine an effective adjuvant than clonidine for bupivacaine spinal anesthesia.

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