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Dexmedetomidine Sedation In Lowerlimb Amputation In Diabetic Mellitus Patients. A Prospective , Doubleblind, Randomized Comparative Study

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Abstract
Objective: *The aim of the study was to evaluate the effect of Injection Dexmedetomidine sedation in diabetic patients undergoing lowerlimb amputation under low dose spinal anaesthesia.*
Method: *In this prospective doubleblind, randomized controlled study, a total of 60 patients belonging to ASA II physical status between the age group of 35 to 65 yrs scheduled for elective lowerlimb amputation under low dose spinal anaesthesia were selected. The patients were randomly allocated into one of two groups of thirty patients each.*
Group I received intravenous normal saline (as placebo) 5 minutes before 1ml of plain hyperbaric bupivacaine given intrathecally.
Group II received intravenous Dexmedetomidine 0.5 mcg /kg, 5 minutes before 1ml of plain hyperbaric bupivacaine given intrathecally.
Basic vital parameters were recorded during the surgery. Also ,the sedation score ,blood sugar level, visual analogue score, the post operative first analgesic requirement time were evaluated.
Results: *Moderate sedation score and minimal changes in the blood sugar level from the preoperative values were seen in group II patients. ($p< 0.001$). The VAS score at 60 minutes and 120 minutes after SAB were low in group II patients ($P< 0.001$). Also the time to first analgesic need was delayed in group II patients ($p<0.001$) . Shivering was not observed in group II patients. No incidence of desaturation, hypotension ,bradycardia, nausea, vomiting, pruritus were noted in both the groups.*
Conclusion: *Dexmedetomidine sedation in the dosage of 0.5 mcg/kg in Diabetic patients undergoing lowerlimb amputation under spinal anaesthesia reduce the stress response to surgery by producing conscious sedation ,anxiolysis , adequate glycemic control.and also prolongs the postoperative analgesia with reduced incidence of postoperative shivering.*
Keywords: *Dexmedetomidine, hyperbaric bupivacaine, low dose spinal anaesthesia , diabetic mellitus ,lowerlimb amputation.*

I. Introduction

Spinal anaesthesia is the safe and simple technique for lowerlimb amputation surgeries. Though cardiovascular and respiratory stability is preserved with protective airway reflexes, and rapid postoperative recovery, the patients undergoing amputation may have fear of the procedure , its recall [1] and pain at the puncture site . So adequate sedation during spinal anaesthesia offers anxiolysis, amnesia and analgesia which may be more useful in Diabetic patients as they are already psychologically stressed and they are more amenable to develop stress hyperglycemia _stress Diabetis which is associated with increased mortality and morbidity. Anaesthesia and surgery stress in Diabetic patients will produce hypermetabolic response which increase the glucose production and insulin resistance. The treatment of hyperglycemia with insulin infusion has not given benefits [2]. The hypoglycemia is the undesirable complication of intensive insulin therapy. 1932, Cuthbertson evaluated the metabolic responses of four patients with lowerlimb injuries [3]. The stress response to surgery is the number of hormonal changes initiated by neuronal activation of the hypothamic –pituitary—adrenal axis.[4].The endocrine response to surgery is increased secretion of the catabolic hormones resulting in catabolism of carbohydrate, fat and protein. Blood glucose concentration increase after surgery begins as there is increased hepatic glycogenolysis and gluconeogenesis. The compensatory mechanism is impaired in diabetic patients. The magnitude and the duration of the response is proportional to the surgical injury and the development of the complications such as sepsis. Also there is increase in the cytokine production due to tissue response to surgery.Regional anaesthesia with local anaesthetic agents inhibit the stress response to surgery [4].

Adding sedation to this, increase the patient satisfaction, sense of wellbeing, amnesia for the surgical procedure [5].

Dexmedetomidine , imidazole compound ,the pharmacologically active dextroisomer of medetomidine has specific and selective alpha 2 –adrenoceptor agonism. Being a sedative and analgesic without respiratory depressant property provides intraoperative sedation, reduce the discomfort and also cover up the inadequate block height along with prolonging the postoperative analgesia [6] [7] [8] [9] [10] [11]. Alpha 2 agonist reduces vasomotor centre mediated CNS activation causing sympatholysis , sedation, anxiolysis , and analgesic properties [12] [13]. The sub types of alpha 2 receptors are alpha 2 A,B and C[14]. Analgesic effect is mediated by alpha 2 C and alpha 2 A receptors present in the neurons of superficial dorsal horn in lamina II. On activation , it prevents the release of pro – nociceptive transmitters namely substance P and glutamate and hyperpolarize the spinal interneurons inhabiting the signal transmission [15] [16]. The sedative action is by hyperpolarisation in the locus ceruleus neurons on the pons and lower brainstem –alpha 2 A thereby inhibiting noradrenaline release and inhabiting activity in the descending medullospinal noradrenergic pathway [17] [18]. Alpha 2 B agonism suppresses shivering centrally, causes analgesia, and vasoconstriction in the peripheral arteries. The alpha 2 C receptors are involved in sensory processing, modulation of cognition and locomotor activity. The study was designed to evaluate the effect of IV dexmedetomidine in diabetic patients undergoing lowerlimb amputation under low dose spinal anaesthesia.

II. Materials and Method

After obtaining institutional ethical committee approval and written informed consent from all the participants ,a prospective ,randomized ,double-blind ,placebo –controlled study was done in South Indian Tertiary Care Referral Hospita.The study population consisted of 60 patients with diabetic mellitus classified as American Society of Anaesthesiologists (ASA) physical status II, between the age group 35 to 65 years and posted for elective lowerlimb amputation under lowdose spinal anaesthesia during the course of the years 2014 and 2015 .Their preoperative blood sugar was ranging between 80 to 150 mg in the entire study group with injection insulin withheld on the day of surgery morning which was continued till the previous day night. The study patients were randomly divided into two groups of thirty each by a computer generated randomization table.The exclusion criteria included patient refusal, known allergy to any of the test drugs, contraindication to spinal anaesthesia, those with hypovolemia, cardiovascular, respiratory, renal, hepatic, coagulation disorder, history of alcohol or drug abuse, use of any opiod or sedative medications in the week prior to surgery. All patients had preanaesthetic evaluation and airway assessment the day prior to surgery.A detailed examination of the cardiovascular, respiratory and central nervous system was done with preoperative routine investigations .The patients were advised to fast the night prior to surgery and received tablet Ranitidine 150 mg orally on the previous night and the day of surgery. A study anaesthetist (person A) prepared the study drugs. Person B monitored the heart rate, mean arterial pressure, SpO2, sensory level, visual analogue scale, blood sugar level, level of sedation (Ramsay Sedation Scale) intraoperatively, and the time for first analgesic requirement. Person C was responsible for study drugs administration(intravenous and intrathecal) to the patients. Persons A and C were kept constant throughout the study.Persons B and C were kept unaware of the drug injected to enable double – blinding. After randomization and blinding, patients were allocated into one of the following groups.

Group I patients received 10 ml of normal saline as placebo intravenously over 5 minutes just 5 minutes before intrathecal 0.5% hyperbaric bupivacaine 1 ml.

Group II patients received intravenous dexmedetomidine in the dosage of 0.5 mcg / kg in dilution of 10 ml over 5 minutes just 5 minutes before intrathecal 0.5% hyperbaric bupivacaine 1 ml.

On arrival to operation theatre , baseline vital parameters were monitored with routine non –invasive monitors. All patients were prehydrated with 10 ml /kg normal saline solution before initiation of the subarachnoid block. Thereafter, dexmedetomidine or normal saline were injected for 5 minutes.Five minutes after the injection, at the lateral decubitus position under strict aseptic precautions, spinal anaesthesia was implemented at the level of L3-4 or L4-5 level through midline approach with Quinke type point 25 gauge spinal needle and 1 ml of 0.5% hyperbaric bupivacaine injected intrathecally over 15 seconds after confirmation of free flow of cerebrospinal fluid. After SAB, the patient was returned to supine position. The Level of sensory block was assessed by loss of temperature sensation by alcohol sponge and pin-prick sensation by using a needle in the mid axillary line. Mean arterial pressure, heart rate and oxygen saturation (Sp02) was monitored regularly. The motor block was assessed by Bromage scale. The level of sensory and motor block was checked every 2 min until the maximum level of the block achieved . The heart rate, blood pressures and SpO2 were recorded every 5 min until the end of surgery and every 15 min in the first post- operative hour and

every 30 min for next 3 hrs. Hypotension was defined as more than 25% decrease in the mean arterial pressure and was treated with fluid boluses and injection ephedrine 6mg IV. Bradycardia was defined as heart rate less than 50 beats/min and treated with injection atropine 0.6 mg IV. Hypoxia was defined as oxygen saturation value below 90% and was treated with 100% O2 with oxygen face mask.. Intraoperatively , the level of sedation was evaluated using Ramsay Sedation Score and the blood sugar was measured at 30 min and immediately after the surgery was over. The patints were monitored for any incidence of shivering , nausea, vomiting , hypotension, bradycardia, and respiratory depression . Pain was assessed by Visual Analogue Score at 60 min after SAB (immediately after the surgery was over) and in the subsequent next hour (ie 120 min). We also recorded the first time that the patient asked for analgesia . Total duration of analgesia was defined as the time from administration of SAB until the first complaint of pain.(VAS > 3). Injection diclofenac 75 mg intramuscular was used as rescue analgesic. All parameters were computed through statistical analysis between the two groups by ANOVA test in MATLAB environment.

III. Results

The demographic characteristics of each group were similar and are presented in the following tables and figures. Age ,gender, height , weight and the type of surgeries were comparable between the groups. No statistical differences were observed. Results were expressed as mean and Standard deviation (SD). Analysis of the data between the groups were performed using one way analysis of variance (ANOVA). $P < 0.05$ was considered as statistically significant.

Table 1: Age distribution between the groups

Age	Group1	Group 2
35-45	4	5
45-55	10	8
55-65	16	17

Age Group 1 54.73 ±7.7
Age Group 2 53.7 ± 9

Figure 1: Age distribution between the groups

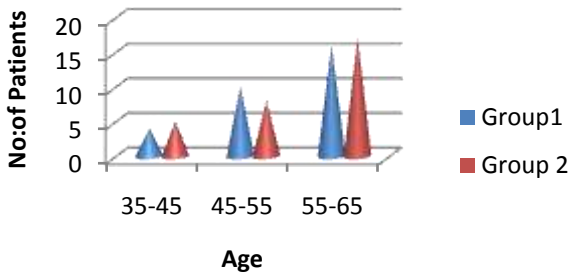


Table 2: Gender distribution between the groups

	Group1	Group 2
Male	26	27
Female	4	3

Figure 2: Gender distribution between the groups

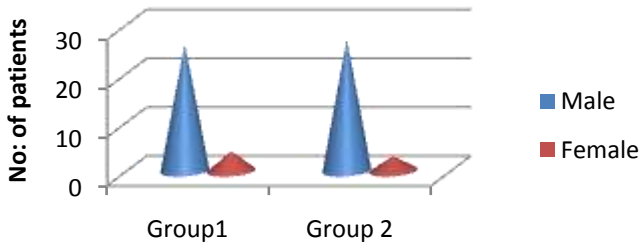


Table 3: Height distribution between the groups

Height (cm)	Group1	Group 2
150-155	5	6
155-160	16	17
160-165	9	7

Height Group 1 158.3 ± 3.3
Height Group 2 157.8 ± 3.5

Figure 3: Height distribution between the groups

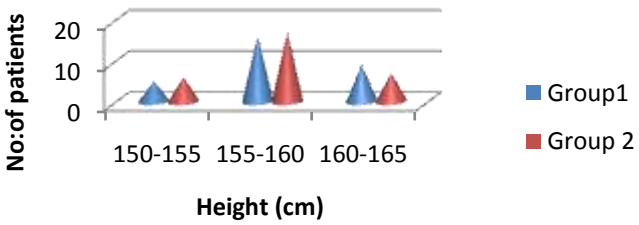


Table 4: Weight distribution between the groups

Weight (Kg)	Group1	Group 2
50-55	8	9
55-60	13	15
60-65	9	6

Weight Group 1 58.3 ±4.2
Weight Group 2 56.5 ± 3.5

Figure 4: Weight distribution between the groups

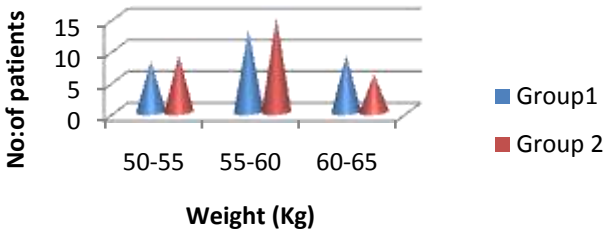
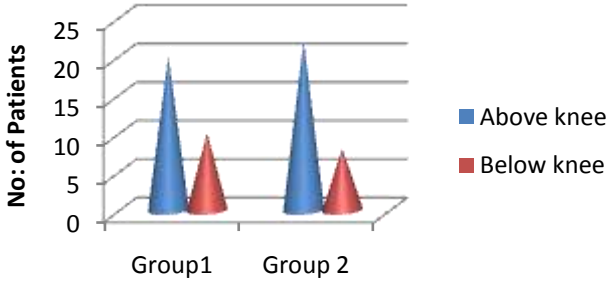


Table 5: Type of surgery

Type of surgery	Group1	Group 2
Above knee	20	22
Below knee	10	8

Figure 5: Type of surgery

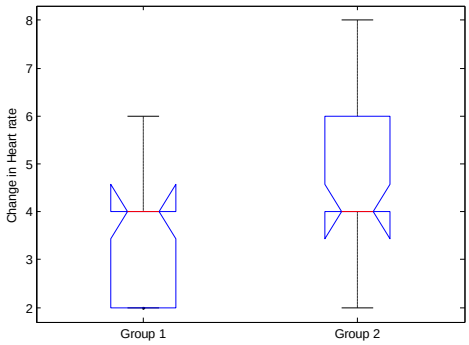


Basal haemodynamic variables were comparable between the groups. Intraoperatively, there was a clinically and statistically decrease in heart rate in Group II patients compared to Group I patients (p value0.003). But no incidence of bradycardia was noted in both the groups.
The baseline heart rate and the lowest heart rate achieved during the study period were recorded. The maximum change in the heart rate (Δ HR Max) from the baseline was then derived and the mean and the standard deviation of Δ HR Max calculated in Group I and II. The comparison was shown in Table 6 and figure 6.

Table 6 Maximum change in the heart rate (Δ HR Max)

Heart rate	Group	Mean ± SD
	Group1	3.6±1.2
	Group 2	4.7±1.8

Figure 6: Inter –group comparison of maximum change in the heart rate



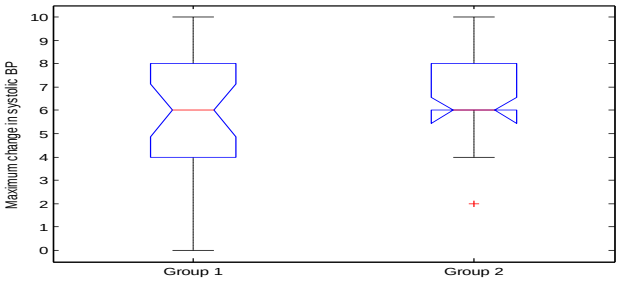
p value 0.003 (P<0.01)

No incidence of desaturation was noted in both the groups. The baseline systolic blood pressure and the lowest systolic blood pressure achieved during the study period were recorded. Maximum change in the systolic blood pressure (Δ SBP max) from the baseline was then derived. The mean and the standard deviation of ΔSBP max calculated in the group I and group II. Inter –group comparison of Δ SBP max revealed no statistical difference between the groups. (p value 0.5) (Table 7)

Table 7: Maximum change in systolic blood pressure from the base line (Δ SBP max)

Δ SBP max (mm Hg)	Group	Mean ± SD
	Group1	5.9±2.6
	Group 2	6.2±1.6

Figure 7: Inter –group comparison of Δ SBP



p value 0.5

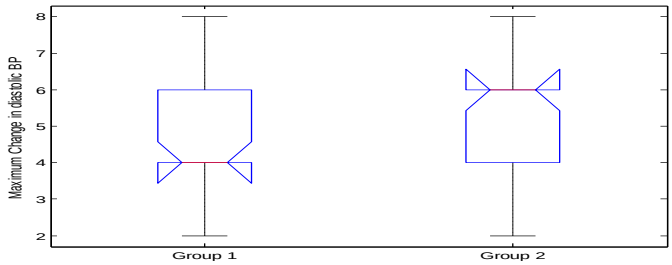
The base line diastolic blood pressure and the lowest diastolic blood pressure achieved during the study period were recorded. Maximum change in the diastolic blood pressure (Δ DBP max) from the baseline was then derived. The mean and the standard deviation of ΔDBP max calculated in the group

I and group II. Table 6 Inter-group comparison of Δ DBP max revealed no statistical difference between the groups.(P 0.3).

Table 8: Maximum change in diastolic blood pressure from the base line (Δ DBP max)

	Group	Mean ± SD
Δ DBP max (mm Hg)	Group1	4.7±1.8
	Group 2	5.1±1.5

Figure 8: Inter –group comparison of Δ DBP



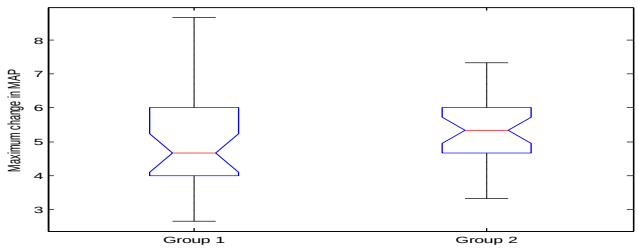
p value 0

The baseline mean arterial pressure and the lowest mean arterial pressure achieved during the study period were recorded. Maximum change in the mean arterial pressure (Δ MAP max) from the baseline was then derived. The mean and the standard deviation of (ΔMAP max) in group I and group II were calculated and intergroup comparison is shown in the table 9 (p value 0.2)

Table 9: Maximum change in MAP from the base line (Δ MAP max)

	Group	Mean ± SD
Δ MAP max (mm Hg)	Group1	5.1±1.5
	Group 2	5.4±1.1

Figure 9: Inter –group comparison of Δ MAP



p value 0.2

Ramsay Sedation Scale was used to assess the level of sedation in all the patients intraoperatively after spinal anaesthesia.

Ramsay Sedation Scale.

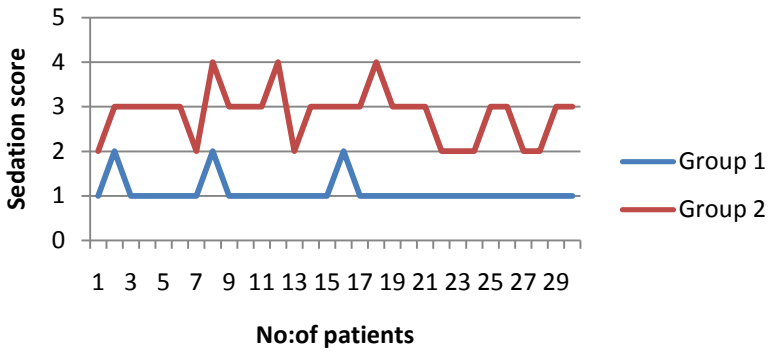
1. Patient is anxious and agitated or restless or both.
2. Patient is co-operative, oriented and tranquil.
3. Patient responds to commands only.
4. Patients exhibits brisk response to light glabellar tap or loud auditory stimulus.
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6. Patient exhibits no response.

Most of the patients in group II were sedated intraoperatively with a sedation score from 2 to 4. Only 3 of the patients in group I showed the score of 2 and all others showed a score of 1.The data were analysed and were shown in the following figure . It showed a p value <0.001.

Table 10: Sedation score between the groups

Sedation score	Group	Mean ± SD
	Group1	1.1±0.3
	Group 2	2.8±0.6

Figure 10: Inter –group comparison of sedation score



p <0.001 (Highly significant)

Group II patients had adequate analgesia intraoperatively and postoperatively. The duration of effective analgesia was measured from the time of intrathecal drug administration to the patient's first request for analgesia. Patients in group II had low VAS score at 60 minutes and 120 minutes after SAB (p<0.001). The time of their first request for rescue analgesia was also prolonged compared to group I patients (p<0.001) which are shown in the following tables and figures.

Table 11: VAS score at 60 minutes for groups I and II

VAS at 1 hr	Group	Mean ± SD
	Group1	2.4±0.9
	Group 2	0.5±0.6

Figure 11: VAS score at 60 minutes

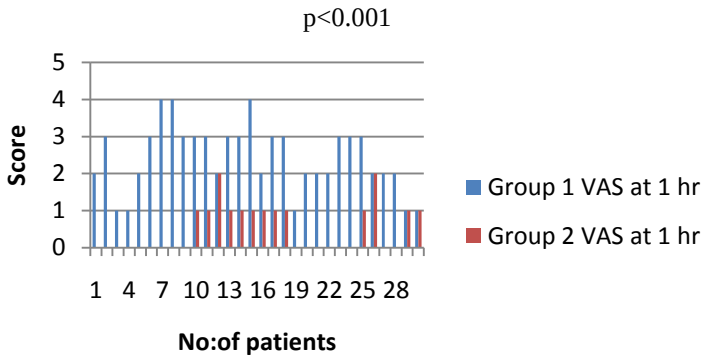
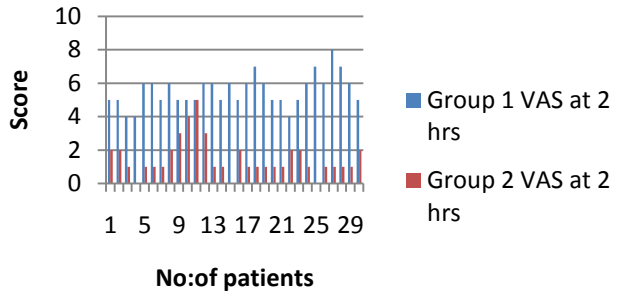


Table 12: VAS score at 120 minutes for groups I and II

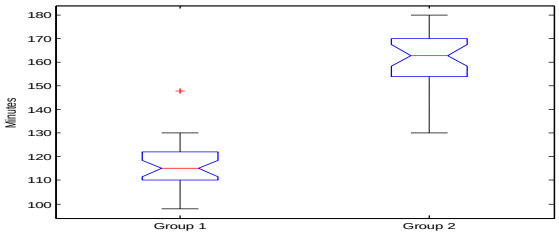
VAS at 2 hr	Group	Mean ± SD
	Group1	5.6±0.9
	Group 2	1.5±1.1

Figure 12: VAS score at 120 minutes



p<0.001

Figure 13: Time for request for first rescue analgesia



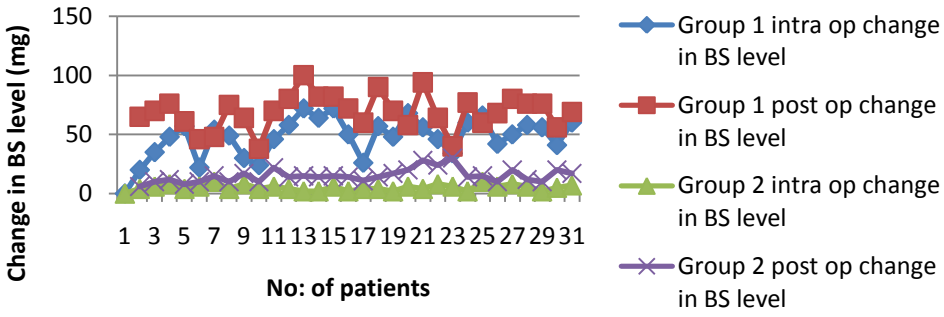
P <0.001

In group II patients due to adequate sedation and analgesia, their change in intraoperative and postoperative blood sugar level from the preoperative basic values were minimal compared to the changes in group I patients (p<0.001) which are shown in the following table and figure. Both the groups received only plain normal saline drip preoperatively before surgery and intraoperatively

Table 13: Inter group comparison of changes in blood sugar level

Intra op change in BS level	Group	Mean ± SD
	Group1	48.9±14.7
	Group 2	5.2±2.3
Post op change in BS level	Group1	68.9±14.6
	Group 2	15.1±5.7

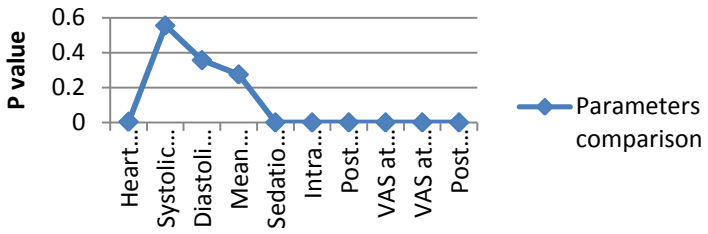
Figure 14: Changes in blood sugar level



p< 0.001

To summarize, our study results showed the values which were statistically significant in heart rate, sedation score, VAS score at 1 hour and 2 hours after SAB, intraoperative and postoperative changes in blood sugar level and the time for first analgesic need in group II patients who received dexmeditomidine just before SAB. It is shown in the following figure 14.

Figure 15: Inter group comparison of the observed parameters



IV. Discussion

Diabetic patients with poorly controlled blood sugar level often present with lower extremity ulcerations and infection.Lower extremity amputation is the final option where the conservative measures fail. Low dose spinal anaesthesia is safe, reliable method of choice in these conditions to undergo surgery in a final attempt to control sepsis [19] [20] [21] [22]. Excellant anaesthesia and analgesia is obtained by using 1ml of 0.5% Hyperbaric Bupivacaine with cardiovascular stability and no effect on respiratory function and autonomic system.No incidence of hypotension and bradyardia were observed. Mild to moderate motor block with is seen. But the duration of analgesia is limited to 45 to 60 minutes.

Dexmeditomidine is a more selective alpha 2-A receptor agonist than clonidine , with alpha 2: alpha 1 binding ratio of 1620:1 compared to 220:1 for clonidine [34]. It produces sedation and anxiolysis by binding to alpha 2 receptors in the locus ceruleus thereby diminishing the release of noradrenaline and inhibiting the sympathetic activity .Thus it decreases the heartrate and the blood pressure [35]. Supraspinal , direct analgesia and vasoconstricton activities are involved in the mechanism of action of intravenous dexmeditomidine on spinal anaesthesia. It has a dual effect by both enhancing local anaesthetic action and providing sedation. It induces sedation which resembles natural sleep by means of sleep modulation and respiration control [17][36]. The patients will be cooperative without clouding of consciousness which is different from the drugs that act on GABA receptors , such as propofol or midazolam [37]. There is better oxygen saturation and Ramsay sedation score than midazolam [38].

Here in our study, IV administered dexmeditomidine injection just before spinal anaesthesia, reduced the stress response by providing adequate sedation and anxiolysis intraoperatively and analgesia both intraoperatively and post operatively.It also reduced the stress hyperglycemia by producing minimal change in the blood sugar concentration from the basic level. Intraoperatively, there was statistically significant decrease in heart rate in group II but no incidence of bradycardia was noted. (p value 0.003) . There was no difference in systolic , diastolic blood pressure and mean arterial pressure between the groups I and II (p value 0.5), (p value0.3),(pvalue0.2) respectively.

In previous study by SS Harsoor, there was a significant decrease in heart rate on using IV dexmeditomidine 0.5 mcg/kg bolus over 10 min prior to SAB,followed by infusion of 0.5mcg /kg/hr for the duration of surgery. Similar findings were seen in the studies by Kumkum Gupta[6], Kaya et al[39]. AI Mustafa t al and Tekin et al reported no significant difference in mean arterial pressure in the dexmeditomidine group and the control group[27].

In our study , intraoperative Ramsay sedation scores were significantly higher in the dexmeditomidine group as compared to the control group. ($p< 0.001$). They were co-operative and arousable[5]. There was no difference in the SpO2 levels between both the groups during surgery and in the post operative period similar to the study results of AI Mustafa et al,Kumkum Gupta. Adequate sedation has been reported with lower dose of dexmeditomidine [0.5 mcg/kg][26][40][41].

Several clinical studies have investigated the effects of intravenous dexmeditomidine on spinal anaesthesia as it can prolong the prolong the duration of sensory blockade [6] [7] [8] [9] [10]. Few studies have directly compared the different doses of dexmeditomidine -0.5mcg/kg and 1mcg /kg. The analgesic ceiling effect of dexmeditomidine was apparent at a dose of 0.5mcg/kg in a previous study [42]. The supra spinal ,spinal or direct analgesia and vasoconstriction activities are involved . Dexmeditomidine produces differential blockade by preferentially blocking the A alpha fibres involved in the sensory conduction over the unmyelinated C fibres involved in the motor conduction.[43]. The previous studies by Ahmed M.S.,Kumkum Gupta, Sang Hi Park,Nikhila R ,Mi H yeon Lee,Jia Song,Stevie JN Sangma,Hong JY concluded that intravenous dexmeditomidine significantly

prolonged the duration of sensory and motor block of hyperbaric spinal bupivacaine. Kaya et al observed in his study that the duration of motor block was not affected by dexmeditomidine.
Here in our study, all patients in dexmeditomidine group had adequate intraoperative and post operative analgesia. The time required for the first dose of rescue analgesia was significantly prolonged in them ($p<0.001$). Their VAS score at 60 minutes and 120 minutes after spinal anaesthesia were low when compared to group I patients ($p< 0.001$). Similar findings were seen in the previous studies.

Incidence of shivering under spinal anaesthesia has been reported around 40 to 60% [45],[46]. Shivering increases oxygen consumption and increases catecholamine levels causing discomfort to the patient subjecting them to higher risk of cardiovascular complications.[45]. Dexmeditomidine has antishivering property by lowering shivering and vasoconstriction threshold without causing respiratory depression, nausea –vomiting unlike the other antishivering drugs like meperidine [47] [48]. It has also central hypothalamic themoregulatoy effects [49]. Intravenous dexmeditomidine in the dose range of 0.5mcg /kg has been used successfully for prevention of shivering after general and regional anaesthesia.[50]. Here in our study, in group II patients, shivering was not observed. In group I except for 6 patients, all others had grade 2 to grade 3 shivering. .

In group II patients ,due to adequate sedation and analgesia , their change in the intraoperative and postoperative blood sugar levels from their preoperative basic values were minimal compared compared to changes in group I patients ($p<0.001$). Both groups received only plain normal saline drip without injection insulin preoperatively and intraoperatively. So, stress hyperglycemia was prevented which may be due to decreased sympathetic outflow and decreased circulating levels of catecholamines and other stress hormones by dexmeditomidine [1] [2] [24] [32].
Also in previous studies by Sisi Li, Yang Yang,Cong Yu,Ying Yao proved with the evidence that reduction in the postoperative inflammatory and oxidative stress played important role in dexmeditomidine postoperative analgesic effects [30].

Few experimental studies in animals have shown the organ protective effects of dexmeditomidine on myocardial protection [49] [44]. neuronal protection in spinal cord injury and reduction in cerebral vasospasm after sub arachnoid haemorrhage [23] [50], prevention of retinal apoptosis in retinal ischemia[51], preventive effects in acute lung injury [52], visceral and renal protection in ischemic reperfusion injury [53]. In our study, intravenous dexmeditomidine in the dosage of 0.5mcg/kg given 5 minutes before spinal anaesthesia reduced the stress response to surgery by producing adequate sedation and analgesia thereby reducing the stress hyperglycemia in diabetic patients. It reduced the anxious level of the patients and prolonged the time for the first analgesic need. No incidence of bradycardia ,hypotension, respiratory depression, nausea, vomiting , shivering and neurological deficit were seen. The postoperative outcome was very good in group II patients.

V. Conclusion

The diabetic patients undergoing lowerlimb amputation under lowdose spinal anaesthesia benefit from intravenous dexmeditomidine in the dosage of 0.5mcg/kg given 5 minutes before the SAB where their psychological stress is reduced as they have good sedation without respiratory depression and adequate analgesia both intraoperatively and post operatively with haemodynamic stability . Stress induced hyperglycemia due to anaesthesia and surgery risks is prevented.

Competing interests

We (authors) declare that there is no conflict of interest in terms of financial and personal relationships with other people or organization that could not appropriately manipulate our work.

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