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COMPARISON OF TWO DIFFERENT DOSES OF INTRATHECAL DEXMEDETOMIDINE AS ADJUVANT WITH ISOBARIC LEVOBUPIVACAINE IN INFRAUMBLICAL SURGERY

Anesthesiology

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ABSTRACT

BACKGROUND: To augment the subarachnoid block utility, the efficacy of newer molecules as an adjuvant is investigated constantly. Considering the favorable profile of dexmedetomidine, it could have a potential role as an adjuvant to isobaric levobupivacaine.

AIM: We evaluated the efficacy of two different doses of dexmedetomidine as an adjuvant to isobaric levobupivacaine, intrathecally.

MATERIALS AND METHODS: 120 American Society of Anaesthesiologist (ASA) Grade I and II patients undergoing infraumblical surgeries between the ages of 18-60 years and height >150 cm were randomly divided into two groups of 60 patients each: Group D3 to receive 3µg of Inj. Dexmedetomidine (0.5 ml, reconstituted using normal saline) along with 12.5 mg (2.5 ml) of 0.5% isobaric levobupivacaine and Group D5 to receive 5µg of inj. Dexmedetomidine (0.5 ml, reconstituted using normal saline) along with 12.5 mg (2.5 ml) of 0.5% isobaric levobupivacaine keeping the total volume of study drug constant in all 120 patients (3 ml). Data recordings were done for time to reach best sensory and motor block, intra- operative haemodynamic changes and duration of postoperative analgesia. Statistical analysis was done using student's t-test and Chi-square test with p-value of <0.05 considered to be significant.

RESULTS: Time to achieve desired block was less in group D5 compared to group D3. The sensory and motor blockade remained significantly prolonged in group D5 compared to group D3. Hemodynamic parameters remained stable in all three groups.

CONCLUSION: Used in a dose of 5µg (in 0.5 ml volume) as an additive in spinal anaesthesia maximal beneficial effect of dexmedetomidine can be obtained without any side effects.

KEYWORDS

Dexmedetomidine, isobaric levobupivacaine, spinal anesthesia, Bromage scale, Motor blockade, Postoperative analgesia.

INTRODUCTION

Regional anaesthesia (spinal anaesthesia) is widely used as a safe anaesthetic technique for both elective and emergency operations. Unless contraindicated, spinal anaesthesia is the preferred mode of anaesthesia in patients undergoing infraumblical surgeries . However, local anesthetics when used alone is associated with relatively short duration of action[1].

Levobupivacaine is S-enantiomer of Bupivacaine with a pharmacological structure similar to that of bupivacaine. Levobupivacaine has been shown to have a larger safety margin and less neurotoxic and cardiotoxic side-effects than bupivacaine.[2]

Over the years many drugs have been used as an additive to spinal anaesthesia in order to hasten its onset of action, prolong the duration of action and to provide adequate postoperative analgesia.

These adjuvants include *dexmedetomidine, clonidine*[3,4] *,fentanyl, neostigmine, ketamine, magnesium, many opioids and non opioids*.

Use of opioids is associated with its side effects like pruritis, nausea, vomiting,urinary retension, constipation, and respiratory depression which can be distressing for the patient.

For decades, *clonidine,* an a2-adrenergic receptor (a2-AR) agonist with a 220:1 ratio of a2:a1 receptor binding, has been widely used as an analgesic adjuvant for pain therapy[5]. a1-adrenergic receptor activity counter balanced a2-adrenergic receptor induced analgesia and, therefore, agonists with a higher a2-adrenergic receptor selectivity might be better choices for pain control[6].

Dexmedetomidine ,a newly developed a2-adrenergic receptor agonist with a 1620:1 ratio of a2:a1 receptor binding(8 ~10 fold stronger binding than clonidine), was first introduced into clinical practice as a short-term intravenous sedative in the intensive care unit[7]. Recently, studies have confirmed its potential as an adjuvant for pain treatment, mostly during acute perioperative settings, which indicated Dexmedetomidine might act as a new drug in pain control.

In this study, we aim to compare the efficacy of two different doses (3 µg and 5 µg) of dexmedetomidine given in combination with 0.5% isobaric levobupivacaine via intrathecal route in patients undergoing infraumblical surgeries with regards to the haemodynamic stability, incidence of side effects (hypotension and bradycardia) and postoperative analgesia.

MATERIAL AND METHODS

After approval from ethical committee, the study was conducted at S.R.N. Hospital (Associated to M.L.N. Medical College, Allahabad) over a period of one year. During pre-anaesthetic visit, a complete pre-anaesthetic checkup was done. All patients were visited the day before surgery and all patients were explained the purpose of the study along with the procedure and thereafter a valid, informed and written consent was taken from all the patients undergoing study. This prospective study was conducted on 120 adult patients (60 patients in each group) of either sex belonging to American Society of Anaesthesiologists (ASA) physical status I-II, aged 18 to 60 years, scheduled for elective infra umbilical surgeries, Sample size was based on previous study[8] and determined using MedCalc software version 16.2.1. Uncooperative patients, patients with uncontrolled hypertension and diabetes, patients with allergy to the study drugs, patients with height less than 150 cm and patients having condition which are contraindication to spinal anaesthesia such as patient refusal, infection at site of injection, coagulopathy, increased intracranial pressure were excluded from the study.

After randomization and blinding, patients allocated into one of the following groups :

Group D3 : Patients who will receive 3 mcg of Inj. Dexmedetomidine (0.5 ml, reconstituted using normal saline) along with 12.5 mg(2.5 ml) of 0.5% isobaric levobupivacaine.

Group D5 : Patients who will receive 5 mcg of Inj. Dexmedetomidine (0.5 ml, reconstituted using normal saline) along with 12.5 mg(2.5 ml) of 0.5% isobaric levobupivacaine.

The patients were randomized into two groups of 60 patients; Group D3 and Group D5 using a computer generated random number table.

All patients in Group D3 received 12.5 mg of 0.5% isobaric levobupivacaine along with 3 µg of Inj. Dexmedetomidine (0.5 ml, reconstituted with normal saline) while patients in Group D5 received 5 µg of inj. Dexmedetomidine (0.5 ml, reconstituted with normal saline) along with 12.5 mg of 0.5% isobaric levobupivacaine. The total volume of study drug was kept constant in all 60 patients (3 ml).

On arrival in operation theatre, venous cannulation was done and intravenous line was secured. In the operation theatre continuous ECG monitoring, pulse oximetry (Spo2), non invasive blood pressure were instituted and initiated monitoring.

Under all aseptic precautions, lumbar puncture was performed in lateral position at L3-4 interspace through midline approach using 25-gauge Quincke spinal needle and the drug delivered at speed of 0.2ml/sec. No other sedative drugs were used in addition unless the regression of clinical anaesthesia or analgesia occurs than expected allocation.

On completion of spinal injection, all patients were monitored for the following :

1). Heart rate, Oxygen saturation (SPO_2) and non-invasive blood pressure (mean arterial pressure) was measured at every 5 minutes for first 15 minutes and then every 15 minutes for the rest of surgery. Heart rate < 50 bpm was considered bradycardia and treated with incremental doses of Inj. Atropine 0.4 mg I/V. A decrease in mean arterial pressure >20% of the baseline blood pressure is considered hypotension and treated with incremental doses of Inj. Mephentermine 6 mg I/V. Oxygen supplementation was given if oxygen saturation falls below 92%.

2). Onset of sensory block was determined by the time from administration of drug to loss of pinprick sensation till T_6 level and the highest level of sensory block achieved was noted down (checked every 30 seconds from administration of drug till 15 minutes by loss of sharp sensation to atraumatic pinprick with a 26 gauge blunt tip needle in midclavicular line bilaterally).

3). Onset of motor block was determined by the time from administration of drug to motor block upto Bromage score 3 (checked every 30 seconds from administration of spinal anaesthetic drug till 15 minutes assessed by Modified Bromage Motor score.)

MODIFIED BROMAGE SCALE[9]

Table 1. Modified Bromage Scale

Score	Response
0	No motor block
1	Inability to raise extended leg, able to move knees and feet.
2	Inability to raise extended leg and move knees, able to move feet
3	Complete block of motor limb.

4). Sedation score was evaluated using Ramsay sedation scale[10] (1 - Anxious, agitated or restless or both. 2-Co-operative, oriented and tranquil.3 - Responding to commands only. 4 - Brisk response to light glabellar tap or loud auditory stimulus.5 - Sluggish response to light glabellar tap or loud auditory stimulus.6 - No response to light glabellar tap.)

5). Duration of sensory block was defined by the time taken by sensory block to regress from maximum sensory block level upto S2 dermatome level (assessed by pin prick method every 15 minutes following intrathecal injection).

6). Duration of motor block was defined by the time taken by motor block to recover upto Bromage score 1 (was assessed every 15 minutes following intrathecal solution injection).

7). Post Operative analgesia checked with help of VAS (visual analogue scale) score and will give rescue analgesia with Inj. Diclofenac 75 mg Intravenous in 100 ml Normal Saline when VAS score is ≥4. Duration of analgesia [time from completion of administration of drug to first requirement of analgesic supplement (VAS ≥4). The VAS score of ≥4 constituted the end point of the study. Visual Analogue Score[11] (VAS- consisting of score 0 to 10 with score 0 – no pain to score 10 – worst possible pain) was explained to every patient preoperatively.

8). Complications, if any – Nausea, Vomiting, Bradycardia, Hypotension, Sedation, Pruritus, Shivering, Hypoxemia.

Statistical Analysis

All the data obtained were analysed statistically using Microsoft Excel 2010 and statistical software plug-ins. Chi square test and student t-test (unpaired) were used where appropriate to test the significance of data. Data are being presented as mean ± SD and a 'p' value of <0.05 was considered significant.

RESULTS

The two groups analysed were similar in terms of demographic profile including patients' age, sex, weight and height with no statistically significant difference [Table-2]. The mean time to reach highest sensory block (T6) dermatome was faster in group D5, 6.88 minutes±0.62 (D3)/ 5.13 minutes±0.52 (D5) while the time to reach Bromage scale 3 was 7.91±0.51 minutes in D3 and 6.7±0.54 minutes in D5 which was also statistically significant. The total duration of surgery was almost similar in both Groups (75.75 minutes (D3 group): 84.66 minutes (D5 Group) [Table 3].

The change in haemodynamics was similar (p>0.05) and gradual in both the groups with a fall in blood pressure and heart rate in the first 10 minutes after spinal anaesthesia and a steady course there after with slight increase towards the end of surgery as the effect of the drugs begin to wear down [Table 4]. Similar results were noted in mean arterial pressure [Table 5]. Two patients each in both the groups needed one rescue bolus dose of Inj. Mephenteramine 6 mg to treat fall in systolic blood pressure less than 20% of the baseline.

A statistically significant difference (p<0.0001) was observed in time of post operative analgesia with Group D3 having 347.33 minutes while in Group D5 the time was 510.75 minutes [Bar diagram 1].

DISCUSSION

In our study, we found that dexmedetomidine in a dose of 3 µg and 5 µg in 0.5 ml volume is an effective additive to isobaric levobupivacaine 0.5% in spinal anaesthesia producing good haemodynamic stability during the intraoperative period and a prolonged postoperative analgesia. The dose dependent side effects of dexmedetomidine namely hypotension and bradycardia were not seen with doses of 3 µg and 5 µg; although, the duration of postoperative analgesia was significantly longer with dexmedetomidine in 5 µg dose compared to 3 µg doses. Since its FDA approval for use in humans as a short term medication for sedation/analgesia in the intensive care unit, researchers have been exploring the prospect of using dexmedetomidine as an additive in spinal analgesia taking into advantage its highly selective agonistic action for intrathecal α2 receptors which have antinociceptive actions for both somatic and visceral pain[12]. Dexmedetomidine prolongs the sensory block by depressing the release of C fibres transmitters and by hyperpolarisation of post synaptic dorsal horn neurons [13,14].

Table 2: Demographic profile of patients (n=120)

Parameter	Group D3	Group D5	T value	P value
Age (in year)	35.53±10.65	35.4±9.75	0.0697	0.9445
Height (in cms)	163.53±6.009	164.91±6.200	1.2380	0.2182
Weight (in kg)	63.28±8.99	64.15±10.86	0.4780	0.6335
ASA (I: II)	51:9	53:7		

Parameter	Group D3	Group D5	P value
TTHSB (min)	6.88±0.62	5.13±0.52	<0.0001
TTBS3 (min)	7.916 ± 0.513	6.7 ± 0.546	<0.0001
TDOS (min)	75.75 ± 28.23	84.66±39.29	0.1564
TTFRA (min)	347.33 ± 25.15	510.75 ± 27.69	<0.0001

[Table 3]: Summary of various parameters analysed.TTHSB= time to highest sensory block (T6); TTBS4 = time to Bromage scale 3; TDOS = total duration of surgery; TTFRA = time to first rescue analgesia. Students t-test was used for analysis of above parameters with a p-value of < 0.05 considered significant.

Heart rate (per minute)	Group I D3 (n=60)	Group II D5 (n=60)	T value	P value
Baseline	79.53 ± 7.16	81.43 ± 8.97	1.2823	0.2022
5 minute	78.52 ± 6.90	80.63 ± 9.28	1.4200	0.1582
10 minute	77.89 ± 6.98	79.36 ± 9.83	0.9445	0.3469
15 minute	77.3 ± 6.5	78.61 ± 9.06	0.9100	0.3647
30 minute	77.13 ± 6.86	78.71 ± 8.05	1.1572	0.2495

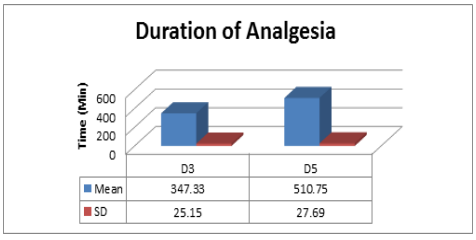
45 minute	77.87 ± 5.95	78.21 ± 6.73	0.2932	0.7699
60 minute	78.18 ± 5.99	77.98 ± 5.61	0.1888	0.8506
75 minute	78.13 ± 5.12	77.8 ± 5.29	0.3472	0.7290
90 minute	78.21 ± 4.88	78.16 ± 4.8	0.0561	0.9554

[Table 4]: Comparison of mean heart rate between two groups.D3= Dexmedetomidine 3 µg; D5= Dexmedetomidine 5 µg;. p-value calculated using Student's t-test with a p-value of <0.05 considered statistically significant.

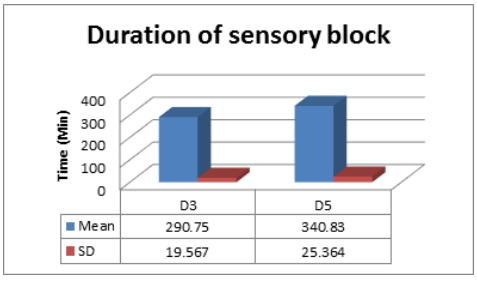
Mean Arterial Pressure (mm Hg)	Group I D3 (n=60)	Group II D5 (n=60)	P Value
Baseline	90.55 ± 5.01	90.05 ± 5.35	0.5982 (NS)
5 minute	89.71 ± 4.98	88.05 ± 5.03	0.0718 (NS)
10 minute	88.16 ± 5.55	86.23 ± 6.16	0.0739 (NS)
15 minute	87.43 ± 5.72	85.55 ± 5.59	0.0712 (NS)
30 minute	87.35 ± 5.14	85.11 ± 6.11	0.0318 (NS)
45 minute	87.31 ± 4.91	85.53 ± 5.45	0.0626 (NS)
60 minute	87.68 ± 5.05	86.13 ± 5.30	0,1037 (NS)
75 minute	87.75 ± 5.13	86.9 ± 4.63	0.3427 (NS)
90 minute	88.43 ± 4.83	87.23 ± 4.41	0.1579 (NS)

[Table 5]: Comparison of mean MAP between the two groups.D3= Dexmedetomidine 3 µg; D5= Dexmedetomidine 5 µg;. MAP= mean arterial pressure. p-value calculated using Student's t-test with a p-value of <0.05 considered statistically significant.

BAR DIAGRAM 1: DISTRIBUTION OF DURATION OF ANALGESIA IN TWO GROUPS



BAR DIAGRAM 2: DISTRIBUTION OF DURATION OF SENSORY BLOCK IN TWO GROUPS



In the study conducted by Shaikh SI and Dattatri R patients were randomly allocated into three groups of 30 patients each with the first group received 15 mg of 0.5% hyperbaric bupivacaine with normal saline, second group received 15 mg of hyperbaric bupivacaine with 5 µg and the third group received 15 mg of hyperbaric bupivacaine with 10 µg of dexmedetomidine with normal saline to a total volume of 3.5 ml[15]. They found that the mean time taken to attain sensory block of T10 dermatome and motor block of Bromage 4 grade was significantly rapid in second and third group as compared to bupivacaine group. The time taken for regression of sensory block and the time to first rescue analgesic also significantly increased by addition of dexmedetomidine in a dose dependent manner. The findings of our study were similar to that of Shaikh SI and Dattatri R with dexmedetomidine 5 µg added to hyperbaric bupivacaine producing a shorter time to attain a Bromage scale of 4 and a longer time to rescue analgesia as compared to dexmedetomidine 3 µg.

A meta analysis on the effect of different doses of intrathecal dexmedetomidine on spinal anaesthesia conducted by Zhang Y et al., which included nine studies with Jaded score of 3-5 on various doses of dexmedetomidine concluded that the action of spinal anaesthesia may be prolonged by increasing the dose of intrathecal dexmedetomidine but the risk of bradycardia is increased at the same time[16]. In our study, the incidence of hypotension and bradycardia was not significant with dexmedetomidine being used in 3 µg and 5 µg doses intrathecally but the duration of postoperative analgesia was comparable to that achieved by higher doses of dexmedetomidine as in other studies.

Study conducted by Nayagam HA et al., concluded that dexmedetomidine in a dose of 5 µg is ideal for use as an additive in spinal anaesthesia[3]. The findings of our study are on a similar line with 5 µg dose producing a prolonged duration of postoperative analgesia compared to dexmedetomidine in 3 µg dose.

Study conducted by Sudheesh K et al., used dexmedetomidine in doses of 3 µg and 5 µg as an additive to spinal anaesthesia in patients undergoing ambulatory perianal surgeries and found the changes in haemodynamic parameters during the intraoperative period were similar in both the groups with overall gradual decrease in haemodynamic parameters below the baseline value[8]. We have reported a similar pattern of haemodynamic changes in our study.

CONCLUSION

Dexmedetomidine is an effective additive to spinal anaesthesia which provides a stable haemodynamics and prolonged postoperative analgesia. Used in a dose of 5 µg (in 0.5 ml volume) maximal beneficial effect of dexmedetomidine can be obtained.

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