Dexmedetomidine infusion as an anaesthetic adjuvant for maintenance of anaesthesia in patients undergoing major surgeries (A comparison of two different doses)

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Abstract

Objectives: To compare the effect of Dexmedetomidine 0.2µg/kg/hr and 0.4µg/kg/hr infusions as an adjuvant for maintenance of anaesthesia in surgeries under GA, on the following parameters: 1) Changes in hemodynamic parameters; 2) Requirement of inhaled anesthetic agents and muscle relaxants; 3) Assessment of post operative sedation and analgesia.

Material and Methods: Total of 60 patients was selected for these studies conducted between 2012 and 2014 and were randomly divided into 2 groups. Group A (inj. Dexmedetomidine 0.2 µg/kg/hr) and Group B (inj. Dexmedetomidine 0.4µg/kg/hr). All patients belonging to ASA I and II of both sexes aged 18 to 60 yrs, were included in this double blinded parallel grouped comparative randomised study. Haemodynamics were monitored before giving the study drug and post induction along with concentrations of inhalational agents and muscle relaxants being recorded 1 minute post induction, 5 min post induction, thereafter every 15 min till end of surgery and field of surgery was assessed via FOS bleeding score.

Results: Both the groups were comparable in terms of age, weight and gender. (p>0.05) statistically not significant. Dexmedetomidine 0.4 µg/kg/hr (Group B) showed a maximum reduction of 41.3% in the mean Iso concentration requirement compared to 31.4% in (group A). Difference was statistically very highly significant (p<0.001).Group B showed 20% greater reduction in the requirement of muscle relaxants intraoperatively than Group A. It was statistically very highly significant (p<0.001).Group B showed a maximum reduction of 20% in heart rate with respect to baseline in comparison to 7% reduction in Group A Difference was statistically very highly significant(p<0.001).
The fall in systolic BP was 15.7% in Group B compared to 3.5% reduction in Group A with respect to baseline. Difference was statistically very highly significant (p<0.001). The reduction in diastolic blood pressure was 13% in Group B compared to 3% in Group A. Difference was statistically very highly significant (p<0.001). Ramsay sedation score in Group B at 1 hour post operatively was higher compared to Group A (p<0.05) whereas at 4 hours it was comparable.VAS pain score was 6 in group B compared to 6.7 in Group A, (p<0.001) statistically very highly significant. Duration of analgesia was longer in Group B (18 hours) compared to Group A (6 hours).

Conclusion: Dexmedetomidine 0.4 µg/kg/hr appears to be better than dexmedetomidine 0.2µg/kg/hr. and provides greater reduction in requirement of anaesthetic agents, better haemodynamic stability, sedation and analgesia.

Keywords: hemodynamic parameters, dexmedetomidine, FOS bleeding score

1. Introduction

A good intraoperative surgical field is met when there occurs minimal bleeding, during surgery and when a sympathetic state has been successfully achieved. A good level of intraoperative sedation reduces the stress response and provides anxiolysis. Of the numerous drugs administered in the past, sedative-hypnotics are associated with a tendency to prolong mechanical ventilation and delayed post operative recovery.

Raised preoperative anxiety levels adversely impacts postoperative pain and recovery. De Groote al have demonstrated that less anxious patients experience less pain. Studies by Maranets and Kain suggested that anxious patients require increasing doses of anaesthetic agents in order to establish and maintain a haemodynamically stable state. The development of dexmedetomidine is an attempt to provide the surgeon with a good surgical field and ensure haemodynamic stability and sympatholysis. It possesses the characteristics of an ideal sedative-hypnotic agent as mentioned below:1:

- Rapid onset of action
- Allows rapid recovery after discontinuation
- Maintains a unique sedation(patient appears to be asleep but are readily arousable)3

Dexmedetomidine is the most recent agent in this group of α2 agonists approved by FDA in 1999 for use in humans for analgesia and sedation4. It is increasingly being used as a sedative for monitored anaesthesia care because of its analgesic properties, “co-operative sedation”, and lack of respiratory depression5. Although safe bradycardia and hypotension are the most predictable and frequent side effects.6 Dexmedetomidine has shown to consistently reduce anaesthetic requirements. In particular this review focuses on dexmedetomidine utilization as an infusion in Spine surgeries and ENT surgeries and to compare the efficacy of two different doses of dexmedetomidine infusion on intraoperative hemodynamics, requirement of anaesthetic agents and post operative sedation and analgesia.

2. Material and Methods

After approval from the institutional ethical committee and informed written consent from patients, in this prospective, randomized study conducted between (2012-2014), 60 patients aged 18-60yrs of ASA Status I and II were selected and scheduled for elective Spine and ENT surgeries lasting for ≤120 mins.

All patients were subjected to detailed pre-anesthetic evaluation, routine and special investigations with clinical history and systemic examination. These patients were randomly divided in to 2 groups of 30 each and dexmedetomidine infusion was started as follows:
Group A: Inj. Dexmedetomidine loading dose 0.5µg/kg over 10 mins and maintenance dose 0.2µg/kg/hr.
Group B: Inj. Dexmedetomidine loading dose 0.5µg/kg over 10 mins and maintenance dose 0.4µg/kg/hr.

All patients with known allergy to any drug, hepatic renal and cardiovascular dysfunction, pregnant or breast feeding were excluded from the study. Patients were kept nil orally 6-8 hrs prior to induction.

2.1 Preanaesthetic preparation:

After shifting the patient to the operating room baseline vitals were recorded using multipara monitor measuring heart rate (HR), systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Peripheral oxygen saturation (SPO2) and preloading was started at 6ml/kg/hr. All patients were pre medicated with inj. Glycopyrrollate 0.004mg/kg and Ondansetron 0.1mg/kg IV in operation theatre. Dexmedetomidine loading dose at 0.5µg/kg/body weight was administered over 10min in all patients. All patients were induced with inj. Thiopentone till the loss of eyelash reflex and intubation facilitated with Inj. Succinylcholine 2mg/kg intravenously. Anaesthesia was maintained with nitrous oxide and oxygen mixture (60:40) and Isoflurane using a closed circuit. After 1min of intubation, maintenance infusion of Dexmedetomidine was started as following and stopped 15 min before surgery.

Group A: Inj. Dexmedetomidine 0.2µg/kg/hr
Group B: Inj. Dexmedetomidine 0.4µg/kg/hr

After the effect of succinylcholine had dissipated, Inj. Vecuronium bromide 0.08mg/kg bolus dose was administered, with additional 0.02mg/kg doses to achieve and maintain 80% relaxation, as assessed with a neuromuscular monitor.

Intraoperative monitoring was documented during preinduction, after loading dose of dexmedetomidine, after induction, and then every 15 minutes till the end of surgery.

Intra-operatively, isoflurane was started at a vaporizer dial concentration of 0.4% and was increased by 0.2% increments at ten minute intervals until hemodynamic variables were such that MAP was maintained within +20% to +15% and HR within -20% to +20% limits off the patient’s preoperative baseline values. Isoflurane concentration was also increased if any clinical signs of light anaesthesia such as hypertension, tachycardia, sweating and movement were observed. After the hemodynamic values had been maintained for 4 mins the concentration of isoflurane was reduced by 0.2% decrements. Isoflurane was shut off 15 minutes before end of surgery. Atropine (0.6) mg was administered if heart rate decreased to less than 50 beats per minute. Hypotension (SBP <90 mmHg) was treated with vasopressors such as ephedrine.

Residual neuromuscular blockade was reversed in Inj. Glycopyrrollate 0.008 mg/kg and Inj Neostigmine 0.05 mg /kg and patient was extubated.

2.2 Parameters Evaluated

1. Reduction in ISO concentration from baseline and average requirement of muscle relaxants were recorded
2. Heart Rate, Systolic blood pressure, Diastolic Blood Pressure were recorded prior to drug infusion, preinduction, 1min post intubation, 5 min post intubation and then every 15min till end of surgery.
3. Sedation was evaluated using Ramsay Sedation Scale which was measured before induction and then till 4 hours post extubation.

Table 1 – The following Ramsay sedation scale will be used

<table>
<thead>
<tr>
<th>Score</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Anxious and agitated or restless or both</td>
</tr>
<tr>
<td>2.</td>
<td>Co-operative, oriented, tranquil</td>
</tr>
<tr>
<td>3.</td>
<td>Responsive to verbal commands, drowsy</td>
</tr>
<tr>
<td>4.</td>
<td>Asleep, brisk response to light, glabellar tap or auditory stimulus</td>
</tr>
<tr>
<td>5.</td>
<td>Asleep, slow response to light glabellar tap or auditory stimulus</td>
</tr>
<tr>
<td>6.</td>
<td>No response to stimulation</td>
</tr>
</tbody>
</table>

4. Pain relief by VAS score

Duration of analgesia was considered from the time of extubation till the first complaint of pain (VAS Score >4), when the first dose of rescue analgesic in the form is inj. Diclofenac Sodium 75mg IM was administered. Patients were explained the VAS score and asked to grade the pain as per the scale.

Figure 1: Linear visual analogue scale

2.3 Statistical methods

Data were validated and analyzed by Graph pad prism. Microsoft word and excel was used to generate graph, tables etc. The interference based on P value will be made as follows:

P>0.05 - Not significant.
P<0.05 - Significant.
P<0.01 - Highly significant.
P<0.001 - Very Highly significant.

Statistical analysis was done with non-paired (two tailed, independent) student t-test for continuous data. Results were expressed as mean ± SD.

3. Results

Demographic variables and duration of surgery were comparable in both the groups (p<0.05), not significant.

Table 2: Demographic variables

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Group A (D 0.2)</th>
<th>Group B (D 0.4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>39.2±10.31</td>
<td>33.97±13.56</td>
<td>0.098</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>57.63±4.62</td>
<td>54.67±7.66</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>13:17</td>
<td>12:18</td>
<td>1.000</td>
</tr>
</tbody>
</table>

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There was a 41.3% reduction in requirement of isofluorane in group B and 31.4% in group A. The difference was statistically very highly significant (p<0.001).

Similarly a 20% reduction in the dose of muscle relaxants was observed in group B compared to group A. (p<0.001) statistically very highly significant.

Table 2: Mean concentration of muscle relaxant used, Ramsay sedation score, VAS Score

<table>
<thead>
<tr>
<th></th>
<th>Group A (D 0.2)</th>
<th>Group B (D 0.4)</th>
<th>n=50 for both groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of muscle relaxant required during surgery (mg)</td>
<td>10.06±1.17</td>
<td>8.069±1.42</td>
<td>30</td>
<td>0.000</td>
</tr>
<tr>
<td>Average Ramsay sedation score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Hour</td>
<td>1±0</td>
<td>1±0</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>4 Hour</td>
<td>1±0</td>
<td>1±0</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>VAS Pain Score &gt;4</td>
<td>6 Hours</td>
<td>18 Hours</td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

Hemodynamically patients were stable throughout the surgery with lower mean SBP and DBP and heart rates observed in group B compared to group A. The mean fall in heart rate was 20% in group B compared to 7.5% in group A starting from 30 minutes to 120 minutes of surgery (P<0.001).

The mean reduction in SBP and DBP was 15.7% and 13% in group B respectively compared to 3.5% and 2.3% in group A respectively (P<0.001)
Ramsay sedation score was comparable in both the groups post operatively. (P>0.05) Score was less than 3 in both groups from extubation till 4 hrs post operatively.

VAS scores were lower in group B in comparison to group A. The number of patients requiring rescue analgesia were only 5 in group B (16.7%) compared to 30 in group A(100%) (p<0.001), difference was statistically very highly significant. The VAS score was >4 within 6 hours in group A, and within 18 hours in group B.

4. Discussion

Alpha-2 agonists are known to afford haemodynamic stability during the intra operative period due to sympatholytic properties. These clinical characteristics make this iv agent a potentially attractive adjunct for surgeries conducted under GA in the ENT and Spine surgeries. Dexmedetomidine offers a potential advantage in surgeries performed on spine in prone position with additional desirable end points being neuroprotection and good surgical bloodless field.14

AEMS others than synaptic nor epinephrine depletion must be involved in anaesthetic effects of alpha 2 agonist, probably at a central post synaptic alpha 2 adrenoreceptor. They increase potassium influx, causing hyperpolarisation and decrease excitability of neurons, hence reducing the dose of the required muscle relaxant by prolonging its duration of action.14

Khan et al15 in 1999 studied the effects of Dexmedetomidine on isoflurane requirements using concentrations 0.3 nanogram per ml and 0.6 nanogram per ml of dex and found that both the above concentrations decrease anaesthetic requirements for isoflurane by 35% and 50% respectively.

Similarly Pooname et al 2002 conducted an observational study using dexmedetomidine infusion in a dose of 0.2 microgram/kg/hr, in laparoscopic surgeries and concluded that 30% less end tidal concentration of isoflurane was required for maintenance of anaesthesia.

Kenya et al16 analysed the efficacy of dexmedetomidine to show a reduction of isoflurane requirement by 32% at end of surgery in Dex group as compared to control.

Aantaeta e17 and Jaakolaa et al18 studied the MAC reducing effects of dexmedetomidine infusion with target plasma concentrations 0.3 nanogram per ml and 0.6 nanogram per ml similar to our study.

Taskanenet al, Ayoglu et al and Feld et al studied dexmedetomidine infusion as an adjuvant in surgeries under GA and confirmed its anaesthetic sparing effects.9,10,20

Durmasset al21 studied the efficacy of dexmedetomidine iv infusion in concentration 0.5 microgram per kg per hr infusion during maintenance of anaesthesia for elective middle ear operations and concluded that isoflurane consumption was significantly reduced in dexmedetomidine group as compared to control (p<0.05).

4.1 HAEMODYNAMICS

4.1.1 Heart Rate

Alpha-2 receptors are involved in regulating the autonomic and cardiovascular systems, located on blood vessels where they mediate vasocostriction, on the sympathetic terminals where they inhibited nor epinephrine release. Their activation leads to reduction of tonic levels of sympathetic outflow and augmented cardiac vagal activity.27

To avoid the initial transient hypertension we have used the infusion over a period of 10 min with a dose of 0.5 µg/ kg as the loading dose. As a biphasic cardiovascular response has been described after administration of dexmedetomidine. A bolus of 1 µg/kg results in a transient increase in arterial blood pressure and a reflex decrease in heart rate in young healthy patients. This response can be mitigated by slow infusion of the drug over 10 min.25

The haemodynamic effects of dexmedetomidine result from peripheral and central mechanisms. The alpha-2b receptors located on vascular smooth muscles mediate vasocostriction. The central action as described above is through the activation of alpha 2 receptors in the CNS. The net effect of alpha 2 adrenoreceptor action is modest reduction in BP, and modest reduction in HR.14,24

The maximum mean reduction in HR in group B was observed to be 20% compared to baseline preinduction values, and was 7.8% in group A with respect to the preinduction value respectively (p<0.001) statistically very highly significant.

Parikh et al25 compared the efficacy of dexmedetomidine concentration (0.2microgram/ kg/ hr) and concluded that dexmedetomidine group had a significant fall in HR (15-20%) (p<0.001) from 2min after start of infusion till end of surgery in comparison to control group.25

In healthy volunteers, dexmedetomidine decreases the circulating catecholamines upto 90% thereby producing sympatholysis and haemodynamic stability. The effect of α2 agonists on haemodynamics is biphasic an immediate increase in systemic arterial pressure(mediated by stimulation of peripheral α2 adrenoreceptors) followed by longer lasting reduction in pressure caused by stimulation of alpha -2 receptors in the CNS. In conclusion dexmedetomidine significantly attenuates responses to noxious stimuli, increases intraoperative cardiovascular stability out of which most of the effects are concentration dependent.26

Neha Parikh et al19,20 proved that mean SBP fell from 125 to 113 with loading dose of dexmedetomidine(p=0.009) and mean DBP fell from 68 to 56 using doses (0.2 µg/kg/ hr iv infusion as an anaesthetic adjuvant in laproscopic surgeries under GA. In several reports dexmedetomidine infusion rates ranging from (0.4-10 µg/ kg/ hr have been used during bariatric surgery.9,20,27

Khan et al15 used concentration 0.3 nanogram / ml and 0.6nanogram / ml of dexmedetomidine infusion and concluded that mean SBP and DBP were significantly less (p<0.001 and 0.009) for both low and high Dex groups compared to placebo.

Patel et al28 observed an average fall of 8% in SBP and 8.16% fall in DBP in test group compared to 3.6% increase in systolic and 3.3 % increase in DBP of control group till 60 min(p<0.05) post extubation. Our findings corroborated with findings of the above mentioned authors in a similar pattern.
4.1.2 Sedation
Dexmedetomidine exerts its sedative and anxiolytic effects through activation of α₂ receptors in locus ceruleus, a major site of noradrenergic innervations in CNS. The locus ceruleus has been implicated as a key modulator for a variety of critical brain functions, including arousal, sleep, and anxiety. The sedation produced by α₂-adrenoceptor agonists unlike that produced by traditional sedatives such as Benzodiazepines and Propofol does not depend primarily on activation of GABA system. Dexmedetomidine produces a ‘co-operative form of sedation’ in which patients easily transition from sleep to wakefulness and task performance when aroused. Cognitive integrity is well preserved in patients receiving dexmedetomidine, as far as spine surgeries is concerned, dexmedetomidine allowed authors to achieve a level of sedation and analgesia sufficient to complete the required neurophysiological testing. Hence its use in stereotactic implantation of DBS, cortical mapping, and awake craniotomy, finds justification when used at low rates of (0.1-0.3 µg/kg/hr).14

Is helpful for intraoperative fine testing in procedures where sedation and mild analgesia are the only anaesthetic requirements15. Aho and Erkola16 and Sardesai17 have studied the effects of dexmedetomidine infusion in a concentration of 0.2 µg/kg/hr and concluded that good sedation levels were achieved with dexmedetomidine.

Parikh et al18 compared the sedative properties of dexmedetomidine vs midazolam – fentanyl in patients undergoing tympanoplasty. They concluded that Dexmedetomidine in doses of 0.2 µg/kg/hr gave higher satisfaction scores. The above study was comparable to the results of our study where no stastically significant difference was observed between group A and group B and the mean Ramsay sedation score was found to lie between 1 and 2.

4.1.3 Analgesia
Alpha 2 agonists have been recognised as having significant analgesic effects. The analgesic potential of alpha 2 agonists however does not approximate the potency of opioids.9 Nevertheless alpha 2 agonists offer specific advantages in certain types of pain in which opioid relief is suboptimal such as in neuropathic pain.20

The primary site of action was thought to be the Substantia Gelatinosa of spinal cord at alpha-2c receptors by inhibiting the firing of nociceptive neurons and in the dorsal horns where dexmedetomidine reduces the release of nociceptive neurotransmitters like substance P. It reduces opioid requirement by 30–50 %.31,32

The improved specificity of dexmedetomidine for the alpha 2 receptors, specially for 2 A subtype, causes it to be a much more effective analgesic agent. Systemic use shows narcotic sparing.33,34 Jakolaet al35 and Gurbetet al36 evaluated the administration of different doses of dexmedetomidine and found that its analgesic effect was maximized at 0.5 µg/kg

In similar studies done by Hall et al37 observed 20-30% reduction in pain VAS scores among subjects who received small dose dexmedetomidine infusions in comparison to control.

The above studies corroborate with the findings of our study. Mean VAS pain score was less than 6 in group B (4.6) at 24 hrs post extubation compared to mean VAS Score of 6.7 at 24 hours in Group A. A value >4 of VAS score was taken as the cut off for requirement of rescue analgesia duration post extubation than group A result was(p<0.001) very highly significant.

We conclude that dexmedetomidine 0.4 µg/kg/hr was more effective than 0.2 µg/kg/hr as an adjuvant agent in reducing the requirement of intraoperative anesthetic agents, providing good hemodynamic stability, analgesia and sedation in ENT and spine surgeries.

5. Conclusion
Thus it can be concluded that dexmedetomidine infusion in a dose of 0.4 microgram per kg per hour compared to the dose of 0.2 microgram per kg per hour provides good hemodynamic stability, reduced requirements of intraoperative anesthetic agents, good sedation and post operative pain relief. It is a suitable and efficacious adjuvant for maintenance of anaesthesia in ENT and Spine surgeries.

References

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