Original Article

Efficacy of intranasal dexmedetomidine for attenuation of laryngoscopic stress response in adult patient posted for elective lumbar spine surgery — a randomized double blinded, placebo controlled study

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Laryngoscope manipulation and endotracheal intubation are noxious stimuli capable of producing tachycardia, arrhythmias and hypertension. Intranasal dexmedetomidine, is well-tolerated and convenient option with favourable perioperative outcome in children. In this study, we tried to evaluate the efficacy of intranasal dexmedetomidine premedication to blunt the laryngoscopic stress response in adult patients. It was a randomised, prospective, double-blind placebo-controlled study. After Institutional Ethical Committee clearance, seventy adult patients of American Society of Anesthesiologists Physical Status 1 were enrolled in the study and divided into two equal groups. Both groups received oral diazepam 90 min before operation. In addition, Group DEX and Group DIA received intranasal dexmedetomidine 1µg/kg and equivalent amount of normal saline respectively about 45 minutes before induction. The general anaesthesia technique was standardised for two groups. The primary outcome of the study was to evaluate the efficacy of intranasal dexmedetomidine to attenuate the hemodynamic surge of laryngoscopy.The statistical package used were Statistica version 6 and Graphpad Prism version 5. Increase in heart rate and blood pressure after laryngoscopy were more prominent in DIA group as compared to DEX group which was statistically significant (P<0.000). Anxiety scores were less with dexmedetomidine. None of the patients had any adverse effects such as hypotension, bradycardia, respiratory depression and fall in oxygen saturation. Intranasal dexmedetomidine in a dose of 1µg/kg can successfully attenuate stress response to laryngoscopy and endotracheal intubation with adequate anxiolysis and devoid of any adverse effect.

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The augmented cardiovascular reflexes in form of tachycardia, hypertension and even myocardial infraction brought about by the noxious stimulus of laryngoscopy and intubation may be detrimental for patients with cardiovascular and cerebrovascular diseases[1]. Preoperative oral diazepam produces adequate sedation and anxiolysis which can decrease this stress response to some extent[2]. In addition to this, other pharmacological agents like intravenous (IV) lignocaine, verapamil, esmolol, nicardipine and fentanyl has been tried to blunt this response, but unfortunately none of them can completely attenuate this stress response[3].

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Dexmedetomidine (DEX) is a highly selective, short-acting, alpha 2-adrenoreceptor agonist. It has comparable sedative and anxiolytic effect like midazolam and can be administered by IV, intramuscular or intranasal route[4]. Preoperative IV DEX premedication causes adequate anxiolysis and successfully attenuate the stress response[5]. However, reports of adverse haemodynamic complications like hypotension, bradycardia and even cardiac arrest might have hindered the widespread use of IV DEX[6].

The intranasal route is a convenient and effective method of DEX administration[7]. Recently, several pediatric studies reported beneficial perioperative outcomes of intranasal DEX premedication which indicate that it could be an alternative to traditional premedication[8,9].

Till now there is no study in adult neurosurgical patient with intranasal DEX premedication. Hence in this study, we tried to evaluate the efficacy of intranasal DEX premedication in adult patients posted for lumbar spine fixation surgery.

Material and Methods

This prospective randomized, double blind, placebo controlled study was conducted at Bangur Institute of Neurosciences, IPGMER, Kolkata. The study protocol was registered at clinicaltrials.gov (CTRI/2016/10/007384). Following approval of the Institutional Ethical Committee and with written informed consent, seventy adult patients of American Society of Anaesthesiologists (ASA) physical status I, aged 18-60 years, posted for elective lumbar spine surgery were included in this study. Patients who were physically dependent on narcotics, allergic to DEX and with any other organic disease were excluded from this study. Patient with hypertension, diabetes mellitus or anticipitated difficult airway were also excluded.

Randomization was done on basis of computer generated random number list and it facilitated patient disposition into two equal groups- Group DEX (n=35) and Group DIA (n=35).The list was concealed in opaque sealed envelope that was numbered and opened sequentially after obtaining the patient's consent.

A nurse who was not involved in any other part of study opened the sealed envelopes and prepared the premedication. Intranasal dexmedetomidine was prepared from parenteral preparation (100µg/ml) in 1 ml syringe and administered in undiluted from at a dose of 1 µg /kg. Similarly, the placebo was prepared with 0.9% normal saline with equivalent volume of DEX for Group DIA patients. The appearance of DEX and placebo premedication could not be differentiated by third person. Each patient of both groups fasted for 6 hours and tablet diazepam 0.2 mg/kg was given to all patients, 90 min before operation. All the patients of both groups received corresponding drug intranasally which was dripped in equal volume into both nostrils about 45 minutes before induction.

In preoperative preparation room an intravenous access was secured and infusion ringer lactate was started. Standard monitors like pulse oximetry, non invasive blood pressure (NIBP), ECG and BIS monitor were attached to patients.

Patient's alertness and sedation during preoperative period were assessed by Observer's Assessment of Alertness/Sedation (OAA/S) scale [respond rapidly to name spoken in normal tone =5, lethargic response =4, delayed response=3, respond after mild shaking =2, respond after painful stimulus =1, no response =0] at 10 min interval till induction . Haemodynamic parameters like HR, systolic, diastolic and mean arterial blood pressure (SBP, DBP and MAP), respiratory rate (RR) and SpO_2 were also monitored at same time intervals. Patients anxiety during preoperative period was assessed by 4-point anxiety score at baseline and again before induction (1=combative, 2=anxious, 3=calm, and 4=amiable).

In operative room intravenous glycopyrolate (5mµ/kg) and fentanyl (2mµ/kg) was administered just before induction. A standard anaesthetic technique was followed in every patient. After preoxygenation with 100% oxygen for 3 min, all patients were induced with 2.5% thiopentone sodium (3-5 mg/kg) and trachea was intubated with appropriate size cuffed endotracheal tube by an experienced anaesthesiologist with Inj. rocuronium (0.6 mg/kg) as muscle relaxant. Laryngoscopy and intubation was limited to maximum 15 s in all patients, failure to which the patient was excluded from study. Anaesthesia was maintained with 66% N_2O, 33% O_2 and 0.5% sevoflurane and muscle relaxant.

No surgical intervention was allowed until 10 min after induction and BIS was maintained within 50-55. HR, SBP, DBP, MAP and SpO_2 were recorded at specific time interval -- preinduction, induction, after intubation and then every 1 min interval till 5min, at 7 min and 10 min after intubation. Tachycardia was defined when HR > 100/min for more than 10 sec and hypertension when MAP was increased >20% of the pre operative value for more than 1 min.

The primary outcome of the study was to evaluate the efficacy of intranasal dexmedetomidine premedication reflected by difference in changes of heart Rate (HR) between two groups. Secondary outcomes were measured by comparing alertness and sedation by OAA/S scale, anxiety by anxiety score and changes in haemodynamic parameters during the study period. Any adverse effect like bradycardia, hypotension and respiratory depression was also noted.

Sample size for this study was based on heart rate as primary outcome measure. It is calculated that 35 subjects will be required per group in order to detect a difference of 10 beats/min in heart rate in immediate post intubation period with 80% power and 5% probability in Type 1 error. This calculation assumes a standard deviation of 15 based on previous studies for heart rate parameter and is a two sided testing[7-9]. Sample size calculation was done using nMaster 2.0 software (dept. of Biostatistics CMC Vellore).

Software used for statistical analysis was Statistica version 6 and Graphpad Prism version 5. Data was summarised by routine descriptive statistics such as mean and standard deviation for numerical variables and counts and percentages for categorical variables. Numerical variables were compared between groups by students independent sample's T test if normally distributed or by Mann-Whitney U test if skewed.Chi square test or Fissure's exact test were employed for intergroup comparison of categorical variables. All analysis was two-tailed and $P<0.05$ was considered as statistically significant.

Results

All the demographic characteristics like age, sex, height and body weight were comparable between two groups (Table 1).

All the patients of both groups were alert and awake at the beginning of the study i.e. comparable in terms of OAA/S scale (5 ±0; $P>0.05$) and they tolerated intranasal medi-

cation well without sneezing or irritation. Baseline haemodynamic parameters in both groups were also comparable (P>0.05).

In both groups the HR were decreased from the baseline value during preoperative period, but in DEX group the decrease in HR was more prominent (14%) than DIA group (3.3%). During intergroup comparison, statistically significant difference (P <0.05) in HR between the two groups were shown at 20, 30 and 40 minutes after intranasal drug administration (Fig 2).

Similarly in preoperative period, SBP, DBP and MAP all were decreased from baseline values in both groups of patient. However, the changes were more in DEX group (11.4%, 9%, and 11% respectively) than DIA group (4%, 3% and 3.3% respectively). During intergroup comparison, statistically significant difference (P <0.05) between the two groups were shown at 20, 30 and 40 minutes after intranasal drug administration (Figs 3-5).

Preoperative OAA/S scores in DEX group were lower than DIA group at 30 and 40 min after intranasal drug administration which was statistically significant (p<0.0001). In both the groups oxygen saturation remained stable (spO_2 median 100%) throughout the study period.

When the preoperative anxiety score was compared between two groups, it is shown that 97% patient of DEX group remain calm and amiable (score>2) compared to 71% patients in DIA group which was also statistically significant (P=0.001).

In both groups, the maximal increase in heart rate and blood pressure were noted during tracheal intubation and remained elevated for up to 10 min. The maximal increase in heart rate was more in DIA group (22%) than DEX group (9%). During intergroup comparison, statistically significant difference of HR (P<0.0001) was found during and up to 10 min after intubation (P<0.0001) .

During intubation, increase in SBP, DBP and MAP from baseline value were more in DIA group (30%, 25% and 7% respectively), compared to DEX group (8%, 10% and 5% respectively). All the values were statistically significant during inter group comparison (P <0.0001).

There was no incidence of hypoxia (SPO2<94%), respiratory depression (RR <8/min), significant bradycardia (HR<50/min) and hypotension (MAP <20% from baseline) in either group of patients.

Discussion

The principal finding of this study was that intranasal DEX premedication at a dose 1µg/kg can successfully attenuate hemodynamic stress response to laryngoscopy and intubation reflected by less increase in HR and BP than placebo group. It also reduces preoperative anxiety score without any adverse effect.

The hemodynamic changes brought about by laryngoscopy were first described by Reid and Brace[10]. Proper use of premedication may decrease this stress response[3]. Recently role of DEX, a highly selective a-2 receptor agonists, has been studied as premedication[11]. The presynaptic activation of a-2A receptors in locus caeruleus inhibits noradrenalin release and causes sedation and hypnosis. Post-synaptic activation of a-2 receptors in central nervous system decreases sympathetic activity leading to bradycardia and hypotension[12].

DEX is widely used in intensive care units for its unique sedative, hypnotic, anxiolytic, sympatholytic, antisecretory and analgesic properties. It has a reversal drug for its sedative effect called as atipamezole, acts by increasing the central turnover of noradrenalin. All this characteristics of DEX are highly attributable as an ideal premedication agent[13,14]. It produces an EEG activity similar to natural sleep[15].

Role of preoperative intravenous dexmedetomidine for attenuation of laryngoscopic stress response have been well documented in various studies[5,16]. It is also evidenced that with IV DEX, sedative effect is more pronounced than analgesic effect with bradycardia and hypotension. IV dexmedetomidine may cause biphasic alternation of MAP

Table 1 — *Demographic characters of the patients in two groups*

Demographic and other parameters of patients	Group DEX (n=35) Mean± SD	Group DIA (n=35) Mean± SD	P value
Age in years	40.71±10.91	42.03±12.58	0.6419
Sex (M/F)	22/13	19/16	0.642
Height in metre	1.623±0.075	1.625±0.065	0.892
Weight in Kg	60±6.894	61.03±7.350	0.5480
BMI in Kg/m²	22.75±1.7	23.10±2.388	0.480

Abbreviations: DEX=dexmedetomidine, DIA- diazepam, BMI- body mass index. SD = Standard deviation.
p value in the last column is for age, height, weight and BMI (Students unpaired t test) and sex (Fisher's exact test), P < 0.05- significant.

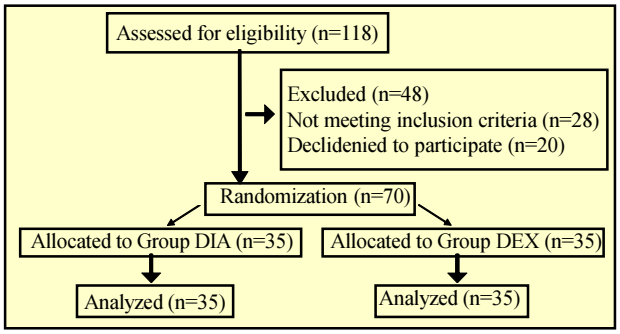

Fig 1 — Consort transparent reporting of trial -- Flow of patients in the trial.(DEX—dexmedetomidine, DIA- diazepam)

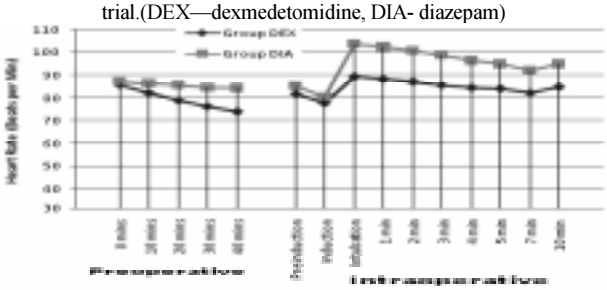

Fig 2 — Comparison of heart rate between two groups (HR= heart rate, DEX- dexmedetomidine, DIA- diazepam)

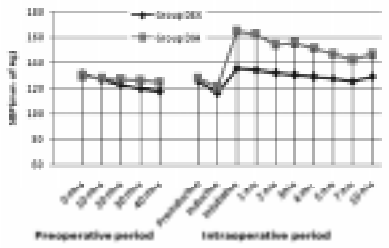

Fig 3 — Comparison of systolic blood pressure between two groups (SBP=Systolic blood pressure DEX- dexmedetomidine, DIA- diazepam)

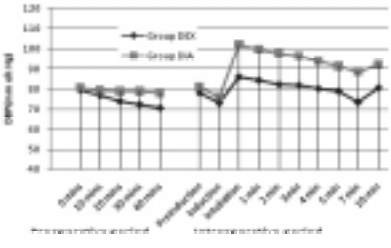

Fig 4 — Comparison of diastolic blood pressure between two groups (DBP=Diastolic blood pressure, DEX- dexmedetomidine, DIA- diazepam)

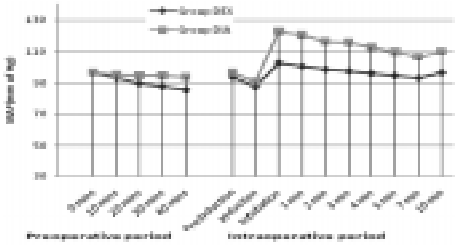

Fig 5 — Comparison of mean blood pressure between two groups (MAP=Mean arterial pressure, DEX- dexmedetomidine, DIA- diazepam)

which is undesirable in anaesthesia and harmful for patients particularly those with impaired cardiac function. In this study, we try to evaluate the effect of DEX premedication through alternative route to avoid the undesirable effects.

The intranasal administration of drug is easy as it is painless, odourless and tasteless without need of IV line. The onset of action of intranasal DEX is early within 20 minutes, as it bypasses the first pass metabolism. Due to high vascularity of the subepithelial surface of the nasal cavity, drugs may access the systemic circulation directly. It can penetrate the blood–brain barrier and reaches directly to the central nervous system. Nasal premedication with midazolam and dexmedetomidine has been studied as alternatives to oral premedication with comparable results[15,17].

Intranasal route has been successfully used as a sedative in children for magnetic resonance imaging and computerized tomography scan and for burn dressing[18,8]. It has also been used as premedication for dental extraction under local anaesthesia[19]. The better efficacy of intranasal dexmedetomidine than conventional premedication like diazepam or alprazolam, is already proved in other studies[15].

Another study done by Iriola T et al revealed that median time to reach peak plasma concentration of intranasal DEX was 38-45mins[20]. So in our study, we administered intranasal dexmedetomidine 45 min before induction so that peak plasma level was achieved before providing any stimulus to the patient.

To decrease stress response, it is prudent to keep the laryngoscopy time as less as possible. Hence, the laryngoscopy time has been limited to 15 s in this study.

In our study, the sedation score achieved with 1 mμ/kg intranasal dexmedetomidine group was ideal as the patients were well sedated, without any respiratory depression or decrease in peripheral oxygen saturation. Pre and post intubation HR and BP were also less in intranasal DEX-premedicated patients . However, these were well tolerated in our patients without requirement of clinical intervention. Similar manageable hemodynamic responses were also documented in previous studies[7,21,22].

In our study, oral diazepam was used as preanaesthetic medication in both groups in similar manner. Therefore observable difference between two groups was likely due to effect of intranasal DEX.

This study has several limitations. Intranasal DEX has longer premedication time (45 min). This study focused on selected patients with lower perioperative risk, but effects of intranasal DEX may differ with coexisting diseases and in elderly patients. Sprayed or atomized delivery can markedly improve uptake, time to onset, and pharmacological efficacy of intranasal medication. Any intranasal pathology should be excluded before trial recruitment. The anaesthetic and analgesic sparing effects, recovery profile were also not noted. Invasive blood pressure monitoring was not used and plasma catecholamine level monitoring was not performed due to the limited facilities available at our set-up. Further study in a large patient population will be required to establish the safety profiles of intranasal dexmedetomidine.

Conclusion

Intranasal dexmedetomidine at 1μg/kg dose, when administered 45 min before induction, can successfully attenuate the haemodynamic stress response to laryngoscopy and endotracheal intubation. It also causes adequate anxiolysis without any significant cardiovascular or respiratory adverse effect.

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