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Intravenous dexmedetomidine (0.5µg/kg) versus intravenous esmolol (1.5mg/kg) given before extubation: Hemodynamic changes

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Abstract
Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine. The administration of a bolus of 1 µg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in young healthy patients. The initial reaction can be explained by the peripheral alpha 2B adrenoceptors stimulation of vascular smooth muscles and "can be attenuated by a slow infusion over 10 or more minutes". The study population (90 patients) was randomly divided into three groups with 30 patients in each group using computer generated random numbers and was placed in sealed envelopes containing the name of the group and patient was asked to pick up the envelope. The envelope was opened by senior anaesthesiologist who was assigned to prepare the solutions and was not involved with the study. Basal mean arterial pressures were comparable between the groups and was statistically insignificant (p=0.22). The changes in MAP were similar to that of SBP. Insignificant rise in MAP was observed during extubation in group D and Group E whereas the rise was highly significant in group C and reached pre extubation values only after 15 mins.

Keywords: Intravenous dexmedetomidine, intravenous esmolol, hemodynamic changes

Introduction
Dexmedetomidine hydrochloride, an imidazole compound is the pharmacologically active s-enantiomer of medetomidine, that had been used as veterinary anaesthetic agent for many years. Dexmedetomidine is the dextro enantiomer of medetomidine, the methylated derivative of etomidine, its specificity for the alpha-2 receptor is 8 times that of clonidine, with an alpha-2:alpha-1 binding affinity ratio of 1620:1 and its effects are dose dependently reversed by administration of a selective alpha-2 antagonist such as atipamezole [1].
Specific alpha-2 receptor subtypes mediate the varied pharmacodynamic effects of Dexmedetomidine. Agonism at alpha 2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion [60]. Agonism at the alpha -2B receptor suppresses shivering centrally, promotes analgesia at spinal cord sites and induces vasoconstriction in peripheral arteries. The alpha 2C receptors are associated with modulation of cognition, sensory processing, mood and stimulant-induced locomotor activity and regulation of epinephrine outflow from the adrenal medulla. Inhibition of nor epinephrine release appears to be equally affected by all three alpha-2 receptor subtypes [2].
Dexmedetomidine is considered as the full agonist at alpha-2 receptors compared to clonidine which is considered as a partial agonist at alpha-2 adrenoceptors. The selectivity of Dexmedetomidine to alpha-2 receptors compared to alpha-1 receptors is 1600:1, whereas with clonidine it is 220:1. The selectivity is dose dependant, at low to medium doses and on slow infusion, high levels of alpha-2 selectivity is observed, while high doses or rapid infusions of low doses are associated with both alpha-1 and alpha-2 activities [3].
Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of dexmedetomidine. The administration of a bolus of 1 µg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in young healthy patients. The initial reaction can be explained by the peripheral alpha 2B adrenoceptors stimulation of vascular smooth muscles and "can be attenuated by a slow infusion over 10 or more minutes".

Even at slower infusion rates however the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7% with a decrease in heart rate between 16% and 18%. The initial response lasts for 5-10 minutes and is followed by a decrease in blood pressure of approximately 10%-20% below baseline values; both these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulant effects. Another possible explanation for the subsequent heart rate decrease is the stimulation of presynaptic alpha-2 adrenoceptors, leading to a decrease in norepinephrine release [4].

The application of a single high dose of Dexmedetomidine reduced norepinephrine release by as much as 92% in young healthy volunteers. The release of epinephrine is also reduced by the same amount. The baroreceptor reflex is well preserved in patients who received dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented. These results illustrate that cardiovascular response is evoked mainly by decrease in central sympathetic outflow [5].

Dexmedetomidine could result in cardiovascular depression i.e. bradycardia and hypotension. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received Dexmedetomidine, especially high doses. Usually these temporary effects were successfully treated with atropine or ephedrine and volume infusions [6].

Methodology

Study Design: "A Prospective, double blind, randomized, placebo controlled study".

Sample Size: Was estimated by using the Mean HR at one minute post-extubation in three groups from the study by Vansh Priya *et al*. [31] Mean HR at one minute post-extubation in Group I was 132±9.6 bpm, in Group II was 84.6± 10.1 bpm and in Group III was 95 ± 15.9 bpm. Using the mean difference between three groups in Mean HR, at 95% Confidence limit and 80% power sample size of 27 was obtained in each group. With 10% non response sample size of 27 + 2.7 ≈ 30 cases were included in each group.

Inclusion criteria

Normal adult patients of either sex, aged between 18 – 60 years belonging to ASA class I, without any co-morbid disease, admitted for elective surgeries under general anaesthesia.

Exclusion criteria

- Pregnant females
- Patients with body mass index more than 28kg/m^2

The study population (90 patients) was randomly divided into three groups with 30 patients in each group using computer generated random numbers and was placed in sealed envelopes containing the name of the group and patient was asked to pick up the envelope. The envelope was opened by senior anaesthesiologist who was assigned to prepare the solutions and was not involved with the study.

Group C = Saline control group.

Group D = Dexmedetomidine (0.5µg/kg).

Group E = Esmolol group (1.5mg/kg).

Results

The basal mean heart rate were comparable between all three groups and are statically non-significant (p=0.4). There was significant decrease in heart rate in Group D after 5th minute of drug infusion compared to group E and group C.

All the three groups showed increase in heart rate during extubation. But the increase in heart rate was statistically insignificant and was lesser than basal value in Group D. There was increase in heart rate in Group E but was controlled and returned to basal values within 3 minutes whereas the increase in heart rate was significant in Group C and returned to basal values only after 15 minutes of extubation.

Tachycardia was noted in 22(73.3%) patients in group C compared to one patient (3%) in Group D and Group E which was statistically significant (p<0.001). No patient in any of the groups had bradycardia.

Post hoc analysis of the results showed that there was no significant difference in mean heart rate between group D and group E after 3 minutes of extubation. But the mean heart rate in group D was lesser at all times.

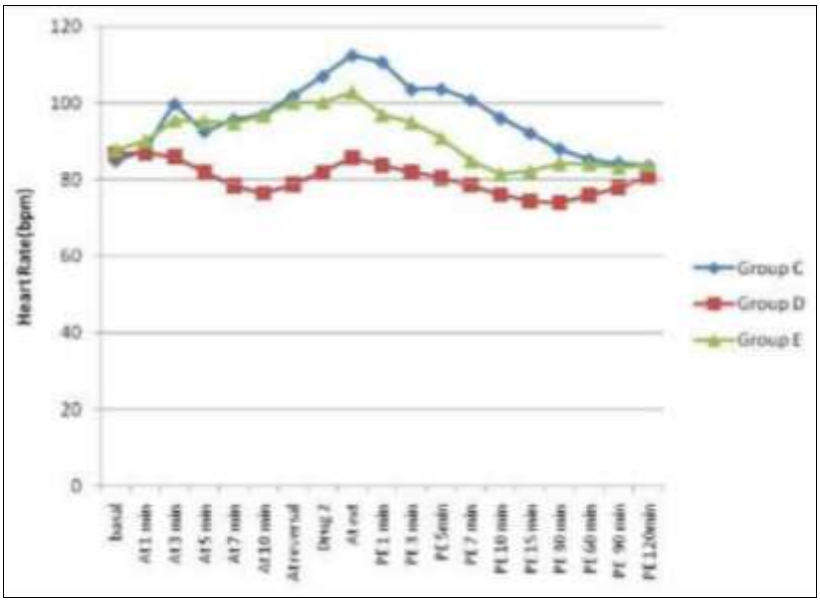

Fig 1: Showing mean heart rate comparison among all the groups

The mean basal systolic blood pressure were comparable between all three groups and are statically non-significant (p=0.28). There was significant decrease in heart rate in Group D after 3rd minute of drug infusion compared to Group E and Group C.

All the three groups showed increase in SBP during extubation. But the increase in the SBP was statistically insignificant in group D and group E, and was lesser than basal value in Group D.

Hypertension was noted in 26(86.6%) patients in group C compared to none in Group D and Group E which was statistically significant($p<0.001$). Hypotension occurred in 3 patients in group D and 4 patients in group E which was statistically significant (p=0.023) and responded to fluid administration.

Post hoc analysis of the results showed that there was no significant difference in change in SBP and incidence of hypotension between group D and group E. But there was significant rise in SBP at extubation compared to group D and group E.

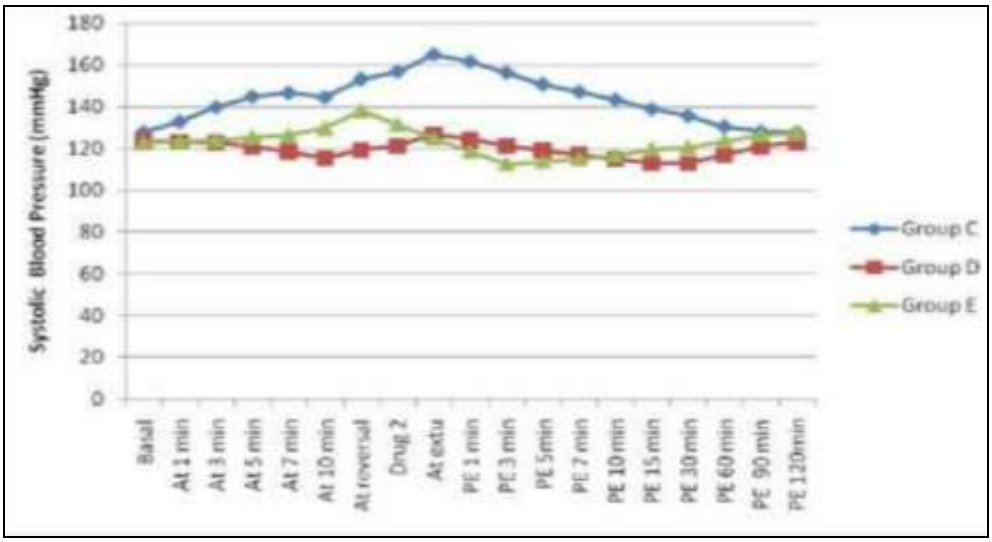

Fig 2: Showing intergroup comparison of systolic blood pressure changes in three groups

Basal mean diastolic blood pressure were comparable between the three groups and was statistically insignificant (p=0.35). The changes in DBP were similar to that of SBP. Insignificant rise in DBP was observed during extubation in group D and Group E whereas the rise was significant in group C and reached pre extubation values only after 15 mins.

The DBP was lower in group D and Group E compared to Group C at all times following extubation upto 90 minutes post extubation.

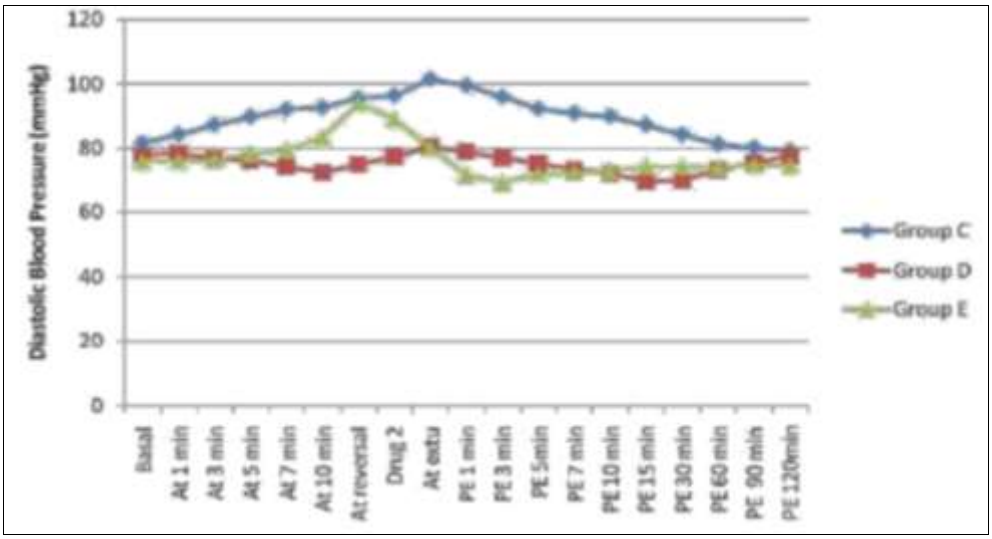

Fig 3: Showing the intergroup comparison of Diastolic Blood Pressure (mm Hg) changes between all three groups

Basal mean arterial pressures were comparable between the groups and was statistically insignificant (p=0.22). The changes in MAP were similar to that of SBP. Insignificant rise in MAP was observed during extubation in group D and Group E whereas the rise was highly significant in group C and reached pre extubation values only after 15 mins.

The MAP was lower in group D and Group E compared to Group C at all times following extubation upto 90 minutes post extubation.

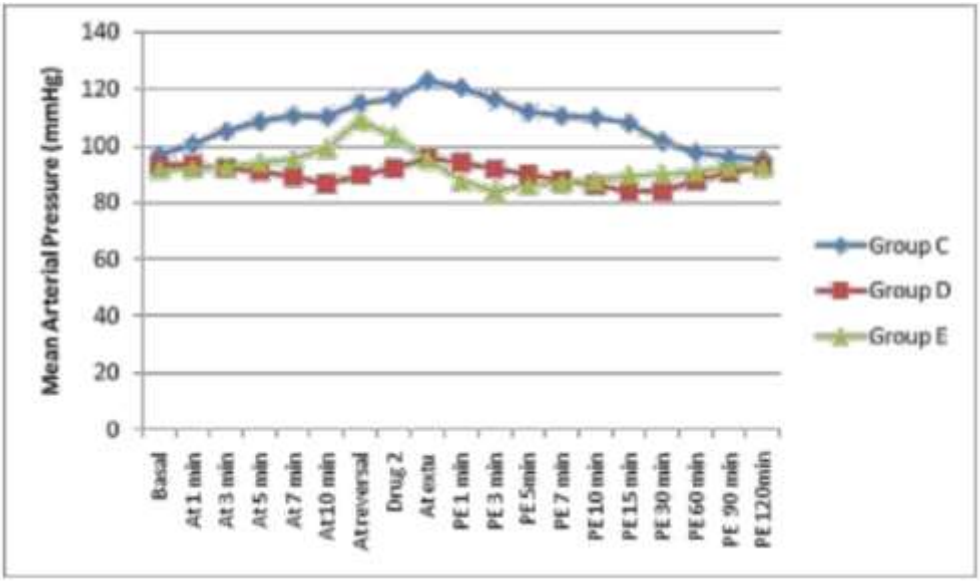

Fig 4: Showing the intergroup comparison of Mean Arterial Pressure (mm Hg) changes between all three groups.

Discussion

In our study we observed that HR did not show a significant rise compared to basal value from 2nd minute of drug administration, during reversal, at extubation and any period post extubation in dexmedetomidine group. But in control group, there was a significant rise in HR compared to basal value. In esmolol group there was no increase in heart rate during extubation compared to pre esmolol value. Incidence of tachycardia was 74% in control group, 3% in Dexmedetomidine group and esmolol group. The rise in HR in control group was more persistent than study group.

This observation is in concurrence with the study done by Jain D *et al*, Sriranga Rao *et al*. where the pulse rate in dexmedetomidine group remained below the pre-DEX values (baseline value) *et al*. time intervals following extubation [7].

In our study both dexmedetomodine and esmolol were equally effective in controlling heart rate response to extubation in contrary to Vanish Priya *et al* who observed that dexmedetomidine to be effective than esmolol probably due to the lower esmolol dosage 0.5mg/kg used in their study compared to 1.5 mg/kg used in ours.

Bradycardia was not observed in any of the patients. This finding is in concurrence with other studies which did not observe statistically significan incidence of bradycardia.

SBP, DBP and MAP values were significantly lower in Dexmedetomidine compared to baseline values at all times from the time of dexmedetomidine infusion to post extubation 30 minutes. This is in conjunction with the study conducted by Jain D *et al*. [7] in which study group patients received 1 µg/kg of dexmedetomidine and they did not observe any significant change ($p<0.05$) in the blood pressure in dexmedetomidine group throughout the study period. Similarly the SBP, DBP, MAP values in esmolol group remained below the predrug values. On the contrary, systolic blood pressure rose significantly ($p<0.05$) in control group following extubation as observed in our study which we achieved with 0.5 µg/kg of dexmedetomidine and 1.5mg of esmolol.

In our study none of the patients in dexmedetomidine group and esmolol group had hypertension as against 74% in control group.

This observation is in contradiction with the study done by Recep Aksu *et al*. [8] and Sharma *et al*. [9] who observed significantly increased SBP at 1 and 5 minutes after extubation. Probably this is due to infusion of dexmedetomidine over 5 minutes (Recep Aksu *et al*) and over 1 min (Sharma *et al*) rather than slow infusion.

Dexmedetomidine by virtue of its analgesic and sedative properties is known to blunt airway reflexes. 94% patients in study group had smooth extubation as against only 70% patients in control group and esmolol group.

Incidence of coughing was significantly higher in control group and esmolol group than when compared to dexmedetomidine group (24%, 26% vs 10% respectively). This is in accordance with study done by Recep Aksu *et al*. [10] and Mikami M *et al*. [11] Mikami *et al*. who did a novel investigational study on the ability of dexmedetomidine, lidocaine or remifentanil to attenuate direct cholinergic nerve stimulation, C-fiber stimulation studied using isolated tracheal rings from male guinea pigs. They found that dexmedetomidine but not lidocaine or remifentanil attenuates acetylcholine release during cholinergic EFS in the airway and may provide a plausible mechanism for the observed utility of dexmedetomidine in attenuating airway reactivity during airway manipulation. Dexmedetomidine also attenuates C-fiber mediated contraction, which may be the underlying mechanism for cough suppression by dexmedetomidine. Guler G *et al*. [12] also noted the effect of dexmedetomidine on children undergoing adenotonsillectomy wherein dexmedetomidine group had significantly decreased incidence and severity of agitation and a smooth extubation without any increase in incidence of side effects. Also, the number of severe coughs per patient was significantly decreased in study drug group when compared with control group. This further supports our observation.

Mean extubation score as measured by extubation quality 5 point scale was significantly lower in dexmedetomidine group in comparison to esmolol and control group which correlates to study done by Bindu *et al*. Hence dexmeditomidine improves extubation quality.

SpO_2 values were comparable in both the groups with no incidence of desaturation. Also, no bronchospasm or laryngospasm was observed in either of the groups.

Conclusion

Our study demonstrates that intravenous single dose of Inj Dexmedetomidine 0.5µg/kg body weight administered over 10 minutes and inj Esmolol 1.5mg/kg body weight given over 1 minute before extubation, both drugs are equally effective in attenuating haemodynamic responses to extubation.

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