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A Randomized Comparative Study of Preoperative Nebulization with Fentanyl, Dexmedetomidine or Magnesium Sulphate for Blunting Hemodynamic Response to Laryngoscopy and Tracheal Intubation

Article History:

Name of Author:

Dr Sukriti Atram[1], Dr Subashini[2], Dr Kajol Bangeja[3]

Affiliation:

[1]Associate Professor, Department of Anaesthesiology and critical care, Grant Government medical College, Mumbai
[2]Junior Resident 3, Department of Anaesthesiology and critical care, Grant Government medical College, Mumbai
[3]Junior Resident 2, Department of Anaesthesiology and critical care, Grant Government medical College, Mumbai

Corresponding Author:

Dr Sukriti Atram

Department of Anaesthesiology Grant Government Medical College, Mumbai

Email id:- sukritiatram@gmail.com

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Abstract: **Background:** Laryngoscopy and endotracheal intubation provoke a sympathoadrenal stress response, resulting in tachycardia and hypertension that may precipitate myocardial ischaemia, arrhythmias, or cerebrovascular events in susceptible patients. Fentanyl, dexmedetomidine and magnesium sulphate have each been used to attenuate this response, and nebulization provides a non-invasive preoperative route of administration.

Methods: In this prospective, randomized, double-blind trial, 171 adult patients (ASA I-lI, 18-60 years) scheduled for elective surgery requiring endotracheal intubation were allocated into three equal groups (n=57) to receive nebulized fentanyl 1 µg/kg, dexmedetomidine 1 µg/kg or magnesium sulphate 40 mg/kg diluted to 5 ml with normal saline, administered over 15-20 minutes before induction. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at baseline, after nebulization, during laryngoscopy and intubation, and serially up to 2 hours post-intubation. Data were analyzed using ANOVA and chi-square tests with $p<0.05$ considered statistically significant.

Results: Baseline HR was comparable between groups ($p>0.05$), confirming successful randomization. The first significant intergroup difference in HR occurred during laryngoscopy ($p=0.021$), with dexmedetomidine showing better control. From 10 minutes post-intubation onwards, dexmedetomidine produced a progressive and statistically significant reduction in HR, with the greatest effect at 1 hour (T10: 79.95 ± 5.92 bpm vs 88.35 ± 1.70 bpm with fentanyl; $p<0.001$, $\eta^2=0.37$). SBP and MAP showed higher baseline values in the dexmedetomidine group but converged after nebulization and remained more stable during laryngoscopy and intubation (SBP $p=0.001$ at laryngoscopy, $p=0.016$ at intubation). Late post-intubation DBP and MAP (T8-T10) were significantly lower with dexmedetomidine, indicating sustained hemodynamic control. No episodes of bradycardia, hypotension, postoperative nausea and vomiting, or postoperative sore throat were observed in any group.

Conclusion: Nebulized fentanyl, dexmedetomidine and magnesium sulphate all attenuate the hemodynamic response to laryngoscopy and tracheal intubation. Nebulized dexmedetomidine 1 µg/kg provides more consistent and prolonged control of HR and blood pressure and may be preferred for optimizing perioperative hemodynamic stability in ASA I-II adults.

Keywords: Dexmedetomidine, Fentanyl; Magnesium sulphate, Nebulization, Hemodynamic response, Laryngoscopy, Tracheal intubation.

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INTRODUCTION

Endotracheal intubation is an essential procedure in anaesthesia practice but is associated with significant airway manipulation and stimulation of pharyngolaryngeal and tracheal nociceptors, leading to a pronounced hemodynamic stress response. The resultant surges in heart rate (HR) and blood pressure are usually transient in healthy individuals, but in patients with cardiovascular or cerebrovascular disease they may precipitate myocardial ischaemia, arrhythmias, heart failure or stroke. [1-4] The pressor response typically begins within seconds of laryngoscopy, peaks at 1-2 minutes and returns to baseline within 5 minutes, mediated by increases in circulating catecholamines, myocardial oxygen demand and dysrhythmogenic potential.

After the introduction of neuromuscular blocking agents such as d-tubocurarine and succinylcholine, clinicians increasingly recognised episodes of severe hypertension, tachycardia, arrhythmias and even asystole occurring around laryngoscopy and intubation. Since then, a wide range of pharmacological strategies has been evaluated to attenuate this response, including opioids, volatile anaesthetics, beta-adrenergic blockers, calcium channel blockers, lidocaine, alpha-2 adrenergic agonists and magnesium sulphate. [3,4,8-10,14,19-23]

Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, provides sedation, anxiolysis, analgesia and sympatholysis while maintaining relative respiratory stability. [5-7] However, intravenous bolus dosing may be associated with bradycardia and hypotension, particularly in susceptible patients. To mitigate these adverse effects, alternative routes such as intranasal and nebulised administration have been explored.

Fentanyl, a potent μ-opioid receptor agonist, has long been used to blunt intubation-related stress and is known to reduce the sympathetic response when administered intravenously prior to laryngoscopy. [8-10] Nebulised fentanyl achieves rapid systemic absorption via the pulmonary route and has been shown by various authors to attenuate tachycardia and hypertension during intubation without significant respiratory compromise. [9,19-21]

Magnesium sulphate, a divalent cation with calcium channel-blocking and vasodilatory properties, attenuates the stress response by inhibiting catecholamine release from the adrenal medulla and decreasing circulating norepinephrine levels. Studies by Puri et al. and others have demonstrated that intravenous magnesium sulphate blunts the hemodynamic response to laryngoscopy and intubation and may provide additional benefits such as bronchodilation. Nebulised magnesium sulphate has been reported to exert clinically important bronchodilator and modest hemodynamic effects.[10]

Although several investigators have evaluated nebulised dexmedetomidine, fentanyl or magnesium sulphate individually against saline or intravenous comparators, there is limited head-to-head evidence directly comparing these three nebulised agents in the same clinical setting.[17-23,26,30,32,35,36,38-42] The present prospective, randomised, double-blind study was therefore designed to compare the efficacy and safety of preoperative nebulisation with fentanyl, dexmedetomidine and magnesium sulphate in attenuating the hemodynamic response to laryngoscopy and tracheal intubation in ASA I-II adult patients undergoing elective surgery

MATERIALS AND METHODS

Study design and setting

This prospective, randomized, double-blind, parallel-group clinical trial was conducted over 1.6 years at Tertiary Hospital , Mumbai, after approval from the Institutional Ethics Committee (IEC/PG/212/JULY/2024) and registration with the Clinical Trials Registry–India (CTRI/2025/01/079170). The study adhered to the Declaration of Helsinki and CONSORT guidelines.

Participants

Adult patients aged 18-60 years, of either sex, with ASA physical status I-II, Mallampati grade I-ll , and scheduled for elective surgery under general anaesthesia with endotracheal

intubation were eligible. Exclusion criteria included anticipated difficult airway, significant cardiovascular, respiratory, hepatic or renal disease, pregnancy, known allergy to study drugs, beta-blocker or calcium channel blocker therapy, morbid obesity and refusal to participate. Written informed consent was obtained from all participants.

Randomization and blinding
Using computer-generated random numbers and concealed allocation via sealed opaque envelopes, 171 patients were assigned to three equal groups (n=57): Group F (fentanyl), Group D (dexmedetomidine) and Group M (magnesium sulphate). A resident not involved in data collection prepared the study drugs in identical nebulizer chambers, and both the attending anaesthesiologist and the patient were blinded to group allocation.

Interventions
Patients in Group F received nebulized fentanyl 1 µg/kg, Group D received nebulized dexmedetomidine 1 µg/kg and Group M received nebulized magnesium sulphate 40 mg/kg, each diluted with normal saline to a total volume of 5 ml. Nebulization was delivered via face mask over 15-20 minutes in the preoperative holding area.

On arrival in the operating room, standard ASA monitoring (ECG, non-invasive blood pressure, pulse oximetry) was instituted. Anaesthesia was induced with intravenous agents as per institutional protocol (agent details as in the source document), muscle relaxation achieved and direct laryngoscopy with appropriate Macintosh blade performed by experienced anaesthesiologists, followed by endotracheal intubation within a standardized time frame.

Outcome measures
Hemodynamic variables (HR, SBP, DBP, MAP) were recorded at the following time points: pre-nebulization (T01), post-nebulization (T02), pre-intubation (T03), during laryngoscopy (TL), during intubation (TI), and at 1, 2, 3, 5, 10, 15, 20, 25, 30 minutes, 1 hour (T10) and 2 hours (T11) after intubation. Patients were observed for adverse events including bradycardia, hypotension, arrhythmias, desaturation, postoperative nausea and vomiting (PONV) and postoperative sore throat (POST).

Rescue treatments (e.g. atropine for bradycardia, vasopressors for hypotension, additional opioids or beta-blockers for marked hypertension/tachycardia) were administered as per predefined thresholds.

Sample size
The sample size of 171 (57 per group) was derived from previous literature and online sample size calculations to detect clinically meaningful differences in hemodynamic responses between groups with adequate power, accounting for potential dropouts.

Statistical analysis
Data were analyzed using SPSS software. Continuous variables were expressed as mean ± standard deviation and compared using one-way ANOVA, with post-hoc tests where appropriate. Categorical variables were compared with chi-square tests. A p value <0.05 was considered statistically significant, and effect sizes were expressed as eta-squared (η^2).

RESULTS AND OBSERVATION

Participant characteristics
All 171 randomized patients completed the study protocol and were included in the analysis. The three groups were comparable with respect to age (overall mean 32.05 ± 21.28 years, range 18-60 years), sex distribution and baseline clinical characteristics.

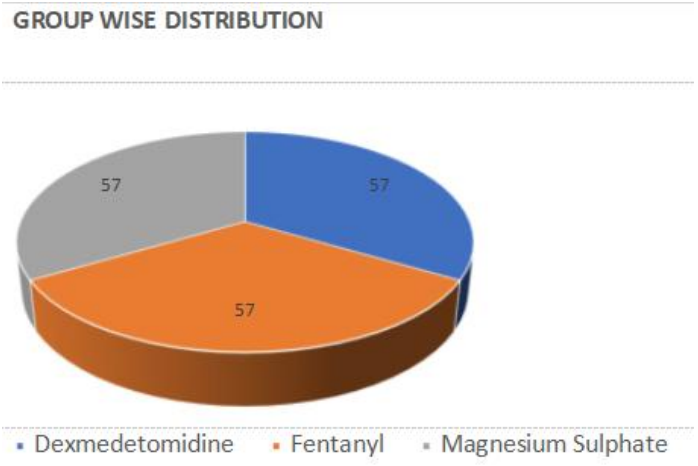

Figure 1: Age distribution among the groups

Heart rate
Baseline HR at T01-T03 did not differ significantly between groups (T01: F=0.730, p=0.483; T02: F=1.266, p=0.285, T03: F=1.627, p=0.200), confirming successful randomization. The first statistically significant difference was seen at laryngoscopy (TL: F=3.970, p=0.021, η^2=0.045), where dexmedetomidine produced better HR control compared with fentanyl and magnesium

sulphate. During the early post-intubation period (T1-T4), although mean values tended to favour dexmedetomidine, intergroup differences were not statistically significant.

From T5 onwards (10 minutes to 2 hours), highly significant differences emerged, with dexmedetomidine showing progressively lower HR values. At T10 (1 hour), mean HR was 79.95 ± 5.92 bpm in the dexmedetomidine group versus 88.35 ± 1.70 bpm in the fentanyl group and 85.32 ± 4.99 bpm in the magnesium sulphate group ($F=49.289$, $p<0.001$, $\eta^2=0.370$). Effect sizes increased from small at T5 ($\eta^2=0.045$) to very large at T10, indicating robust and sustained bradycardic effect with dexmedetomidine.

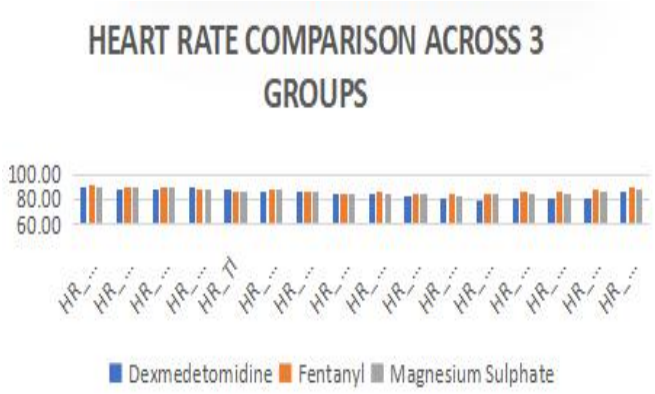

Figure 2: Heart rate comparison among the 3 groups

Systolic blood pressure
Significant baseline differences in SBP were present at T01 and T02 (T01: $F=10.182$, $p<0.001$, $\eta^2=0.108$; T02: $F=9.680$, $p<0.001$, $\eta^2=0.103$), with dexmedetomidine patients showing higher initial SBP (132.39 ± 8.54 mmHg at T01) compared with fentanyl (128.65 ± 3.61 mmHg) and magnesium sulphate (127.26 ± 5.66 mmHg). By T03, SBP had converged ($F=1.362$, $p=0.259$), suggesting early onset of dexmedetomidine's hypotensive effect.

During laryngoscopy and intubation, SBP remained more stable in the dexmedetomidine group (TL: $F=7.558$, $p=0.001$, TI: $F=4.256$, $p=0.016$), indicating better hemodynamic reserve at these critical moments. In the post-intubation period, intermittent significant differences were observed (e.g. T1, T3), with dexmedetomidine generally associated with more controlled SBP, and a late-phase divergence at T8–T10 (F up to 11.111, $p<0.001$, η^2 up to 0.117) before convergence at T11.

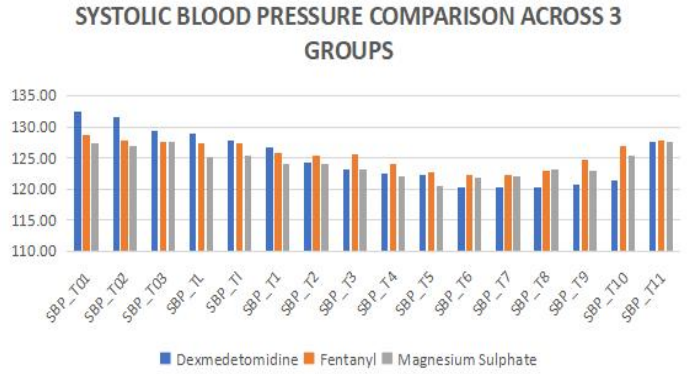

Figure 3: Systolic blood pressure comparison among the 3 groups

Diastolic blood pressure
DBP exhibited significant early intergroup differences at T01 and T02 (T01: $F=9.678$, $p<0.001$; T02: $F=12.780$, $p<0.001$), with slightly higher baseline DBP in the dexmedetomidine group. During laryngoscopy and most of the early post-intubation period, DBP values largely converged across groups, with only TI showing a significant difference ($F=4.781$, $p=0.010$).

In the later period (T8-T10), significant and clinically relevant differences re-emerged (T8: $F=11.833$, $p<0.001$, $\eta^2=0.123$; T9: $F=15.932$, $p<0.001$, $\eta^2=0.159$; T10: $F=24.394$, $p<0.001$, $\eta^2=0.225$), with dexmedetomidine associated with lower DBP and a medium-to-large effect size.

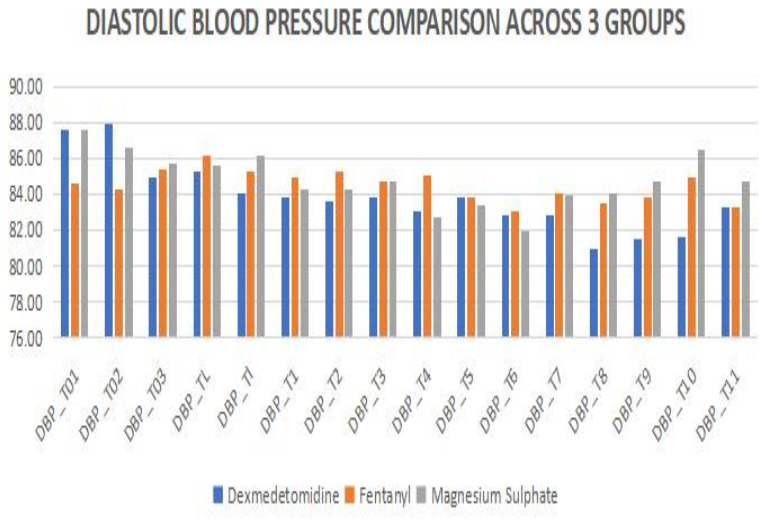

Figure 4: Diastolic blood pressure comparison among the 3 groups

Mean arterial pressure
MAP followed a similar pattern. Large baseline differences were observed at T01 ($F=35.520$,

$p<0.001$, $\eta^2=0.297$) and T02 ($F=13.388$, $p<0.001$, $\eta^2=0.137$), with higher MAP in the dexmedetomidine group. Subsequently, values converged through T03-T6, except for a transient difference at T4 ($F=4.246$, $p=0.016$).

During the late monitoring period (T7-T11), a secondary divergence appeared (T7: $F=4.873$, $p=0.009$, T8: $F=10.169$, $p<0.001$; T9: $F=6.297$, $p=0.002$, T11: $F=4.278$, $p=0.015$), reflecting sustained effects of the three agents on overall perfusion pressure, with dexmedetomidine favouring lower and more stable MAP.

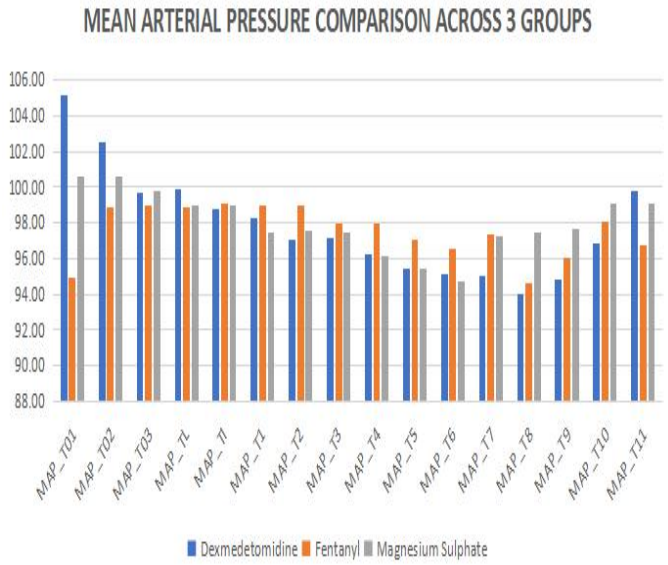

Figure 5: Mean arterial pressure comparison among the 3 groups

Adverse events

No episodes of bradycardia, hypotension, PONV or POST were recorded in any of the three groups. All patients tolerated nebulization well, with no reported bronchospasm, cough or laryngospasm.

DISCUSSION

All three nebulised regimens in our study-fentanyl 1 µg/kg, dexmedetomidine 1 µg/kg and magnesium sulphate 40 mg/kg effectively attenuated the hemodynamic response to laryngoscopy and tracheal intubation, with nebulised dexmedetomidine providing the most consistent and sustained control of heart rate and blood pressure. Baseline HR values were comparable across groups, confirming successful randomisation, and the first significant divergence appeared during laryngoscopy, where dexmedetomidine showed superior attenuation of tachycardia. This pattern aligns with the known α2-adrenergic agonist action of dexmedetomidine, which blunts sympathetic outflow while maintaining overall hemodynamic stability. [5-7]

Heart rate responses

In our trial, the first statistically significant difference in HR occurred at laryngoscopy (TL), with dexmedetomidine demonstrating better control compared with fentanyl and magnesium sulphate. This is comparable to the findings of Kumar et al. who observed a markedly reduced stress response after laryngoscopy in patients receiving nebulised dexmedetomidine compared with saline. Misra et al. also reported a significantly lower trend in HR rise following laryngoscopy in patients premedicated with nebulised dexmedetomidine compared with placebo, which is consistent with the progressive bradycardia seen from T5 onwards in our study.

Despite mean HR values favouring dexmedetomidine, the immediate post-intubation period (T1-T4) did not show statistically significant differences between groups, suggesting that all three agents provided adequate short-term cardiovascular stability. From 10 minutes after intubation (T5) until 2 hours (T11), however, dexmedetomidine produced a sustained and clinically meaningful reduction in HR, with the largest effect at 1 hour (T10). This pattern is in agreement with the prolonged sympatholytic effect reported for dexmedetomidine by Mahajan et al. and other authors, and supports the concept of controlled bradycardia that may be cardioprotective during longer procedures. [27,31,35,38-41]

Systolic blood pressure responses

In our cohort, the dexmedetomidine group had higher baseline SBP than the fentanyl and magnesium groups, but SBP converged by the pre-intubation time point (T03), indicating early onset of the drug's hypotensive effect. Sheth et al. demonstrated significantly lower SBP in patients receiving nebulised dexmedetomidine compared with nebulised saline, a finding echoed by the lower and more stable SBP we observed in the dexmedetomidine group during laryngoscopy and intubation. Shrivastava et al. similarly reported better SBP control following laryngoscopy in patients pretreated with nebulised dexmedetomidine, which parallels the reduced SBP fluctuations and significant p values at TL and TI in our study.[31,7].

During the early post-intubation phase (T1-T4), we observed intermittent significant differences in SBP, again favouring dexmedetomidine, suggesting more controlled blood pressure during haemodynamic stabilisation. Shukla et al. noted comparable findings when low-dose intravenous dexmedetomidine was compared with fentanyl and magnesium sulphate, reporting significantly lower

SBP at several early post-intubation time points in the dexmedetomidine group. Taken together, these data suggest that both nebulised and intravenous dexmedetomidine reliably blunt hypertensive surges associated with airway manipulation.[33]

Diastolic blood pressure responses

Our study showed early differences in DBP, with dexmedetomidine and magnesium sulphate groups having slightly higher baseline values, followed by convergence during laryngoscopy and most of the early post-intubation period. Only intubation (TI) itself showed a statistically significant difference in DBP, with all three agents producing a fall in mean DBP, indicating effective equalisation of diastolic pressures. Mahajan et al. reported that both intravenous dexmedetomidine and magnesium sulphate significantly reduced DBP compared with placebo at all time points following laryngoscopy and intubation, which is in agreement with our observation that both drugs attenuated diastolic responses.[27]

In the late post-intubation phase (T8-T10), we found significantly lower DBP values in the dexmedetomidine group, with medium to large effect sizes, suggesting a sustained vasodilatory and sympatholytic effect. Sheth et al. also demonstrated significantly lower DBP at 1, 5 and 10 minutes after intubation in patients receiving nebulised dexmedetomidine compared with saline, reinforcing the long-lasting impact of this route of administration on diastolic pressure.[31]

Mean arterial pressure responses

Dexmedetomidine-treated patients in our series had the highest MAP at baseline, but MAP rapidly converged between groups after nebulisation and during laryngoscopy and early post-intubation. At around 10 minutes after intubation, dexmedetomidine produced lower MAP values than fentanyl and magnesium sulphate, a trend comparable to that reported by Paul et al., who showed significantly lower MAP and better intubating conditions with nebulised dexmedetomidine relative to saline. Later in the monitoring period (T7-T11), we observed a secondary divergence of MAP between groups, again reflecting sustained differences in vascular tone and perfusion pressure with dexmedetomidine.[38]

Shukla et al. and Grover et al. also reported differential trajectories of MAP when comparing dexmedetomidine, fentanyl and magnesium sulphate, with dexmedetomidine often providing the most favourable attenuation of the pressor response. Our results support these observations and extend them to a purely nebulised regimen, reinforcing nebulised dexmedetomidine as a viable alternative to intravenous dosing.[33,36]

Side effects

None of the patients in our trial developed PONV or POST, and nebulisation was well tolerated in all three groups. Misra et al. similarly reported no increase in adverse events with nebulised dexmedetomidine compared with saline, and Gill et al. found that both nebulised dexmedetomidine and magnesium sulphate reduced the incidence of POST, with no clinically important safety concerns. The absence of significant bradycardia, hypotension or respiratory compromise in our cohort is encouraging and suggests that nebulised administration at these doses is safe in ASA I-lI adults.[28,43]

Overall interpretation

Across HR, SBP, DBP and MAP, our findings are concordant with those of multiple investigators who have studied nebulised and intravenous dexmedetomidine, fentanyl and magnesium sulphate for attenuation of intubation-related stress.[17-23,27-33,35,36,38-43] Our data add to this body of evidence by directly comparing nebulised fentanyl, dexmedetomidine and magnesium sulphate within a single randomised, double-blind trial and by characterising late (up to 2-hour) hemodynamic trends, which are less frequently reported. In this context, nebulised dexmedetomidine emerges as the most reliable agent for sustained hemodynamic control without compromising safety.

Strengths

A major strength of this study is its prospective, randomised, double-blind design with equal allocation to three active nebulised agents and standardised anaesthetic technique across all groups.

Comprehensive hemodynamic monitoring from pre-nebulisation to 2 hours after intubation allowed detailed temporal characterisation of the cardiovascular response.

The sample size was adequate and based on prior evidence and formal calculations, and the study was conducted at a high-volume tertiary care centre, enhancing internal validity.

limitations

A single-centre trial limited to ASA I–II adults aged 18-60 years with anticipated easy airways undergoing elective surgery, which restricts generalisability to high-risk populations and emergency settings.

One dose of each nebulised agent was evaluated; alternative dosing regimens or combinations might

further optimise efficacy and safety.

Baseline differences in blood pressure, despite randomisation, could have influenced some comparisons, although convergence after nebulisation suggests a predominant pharmacological effect.

Long-term cardiovascular outcomes, anaesthetic and opioid-sparing effects and recovery profiles were not evaluated and warrant further study.

CONCLUSION

Preoperative nebulization with fentanyl 1 µg/kg, dexmedetomidine 1 µg/kg or magnesium sulphate 40 mg/kg effectively attenuates the hemodynamic response to laryngoscopy and tracheal intubation in ASA I-lI adults undergoing elective surgery. Among the three, nebulised dexmedetomidine offers more consistent and sustained control of HR and blood pressure, without increasing adverse events, and may therefore be preferred when perioperative hemodynamic stability is a priority. Further multi centre, dose- finding studies in high- risk cardiac and geriatric populations are warranted to confirm these observations, define optimal dosing strategies and assess potential impacts on intraoperative anaesthetic requirements and postoperative outcomes.

Conflict of interest: Nil

Financial disclosure : Nil

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