

Comparison between Nebulised and Intravenous Form of Magnesium Sulphate for Attenuation of Haemodynamic Response during Endotracheal Intubation in Hypertensive Patients undergoing General Anaesthesia: A Randomised Controlled Study

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ABSTRACT

Introduction: Endotracheal intubation induces a significant sympathetic pressor response, particularly in hypertensive patients, leading to Heart Rate (HR) and Blood Pressure (BP) elevations. Magnesium Sulphate (MgSO_4), administered Intravenous (i.v.) or via nebulisation, attenuates this response through calcium channel antagonism and catecholamine suppression.

Aim: To evaluate the effects of nebulised and intravenous MgSO_4 on attenuation of haemodynamic responses during endotracheal intubation in hypertensive patients undergoing general anaesthesia.

Materials and Methods: This single-blinded randomised controlled study of 100 hypertensive adults undergoing elective surgery under general anaesthesia were randomised into two groups. Group A received i.v. MgSO_4 (30 mg/kg) and group B received nebulised MgSO_4 (40 mg/kg in 5 mL saline), 15 minutes before induction. Primary outcomes included Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP), measured at baseline, postintervention, postinduction, postintubation, and at 2, 5, and 10 minutes thereafter. The secondary outcome was time to first maintenance dose of muscle relaxant, assessed by Train-

of-Four (TOF) monitoring. Data were analysed using unpaired Student's t-test and Fisher's exact test and p-values <0.05 were considered statistically significant.

Results: Demographic data, including age, height, weight, Body Mass Index (BMI), gender, and baseline characteristics were comparable between groups. Haemodynamic parameters remained statistically similar at all time points. A transient, non significant elevation in HR was observed postintubation in the nebulisation group (87.88 ± 11.17) compared with the i.v. group (84.28 ± 12.53). DBP showed a trend toward elevation at 5 minutes postintubation (75.88 ± 7.30) than the i.v. group (70.98 ± 6.39), while baseline SBP was slightly higher in the i.v. group (127.72 ± 8.31 vs. 124.42 ± 7.39). The MAP remained comparable throughout. The nebulisation group demonstrated a longer interval before neuromuscular redosing (49.1 ± 8.7 vs 44.8 ± 8.6), suggesting a trend toward prolonged blockade.

Conclusion: Both nebulised and i.v. MgSO_4 effectively maintained haemodynamic stability during induction, intubation and postintubation in hypertensive patients. Nebulised MgSO_4 , being non invasive, better tolerated, and potentially safer, offers an attractive alternative for smoother haemodynamic control, making it a promising adjunct in the anaesthetic management of hypertensive patients.

Keywords: Airway management, Neuromuscular blockade, Perioperative care

INTRODUCTION

Endotracheal intubation, particularly when facilitated through direct laryngoscopy, is known to provoke a marked haemodynamic response due to sympathetic nervous system stimulation. This 'pressor response' is characterised by elevations in HR and BP, usually tolerated by normotensive patients. In hypertensive patients, it may lead to critical complications such as myocardial infarction, pulmonary oedema, and cerebrovascular haemorrhage [1]. Effective blunting of this response is therefore a critical component of perioperative anaesthetic management in this population. Over the years, various pharmacological strategies- using opioids, vasodilators, beta-blockers, lignocaine, and α_2 -agonists have been employed to blunt this reflex surge. However, no single intervention has emerged as unequivocally superior in consistently attenuating this response across diverse patient populations [2,3].

MgSO_4 is particularly compelling due to its multifaceted mechanism of action. It acts as a calcium channel antagonist, N-methyl-D-

aspartate (NMDA) receptor blocker, and suppressor of catecholamine release from both adrenal medulla and sympathetic nerve terminals [4,5]. i.v. MgSO_4 , especially in doses ranging from 30 to 50 mg/kg, has been shown to reduce norepinephrine and epinephrine release, directly relax vascular smooth muscle, and decrease systolic BP postintubation [5,6]. The nebulised form of MgSO_4 , though less studied, is gaining traction. It is believed to act locally by desensitising airway nociceptors, thereby reducing afferent stimulation and subsequent sympathetic discharge during laryngoscopy [4]. It offers the advantages of ease of administration, improved patient comfort, and reduced systemic exposure. Despite these theoretical benefits, there is a paucity of evidence comparing the efficacy of nebulised versus i.v. MgSO_4 , especially in hypertensive patients undergoing general anaesthesia [7].

There aren't any studies in the existing literature comparing nebulised and i.v. MgSO_4 , particularly in hypertensive individuals, who are particularly susceptible to haemodynamic stress during

endotracheal intubation. Having these gaps, the current study was conducted to assess the effectiveness of nebulised MgSO₄ in reducing the haemodynamic response to intubation in hypertensive patients. This study was done to provide significant evidence that may impact clinical decision-making and encourage the integration of non invasive premedication techniques into anaesthetic protocols by focusing on a high-risk group and directly comparing two methods of delivery.

From a practical standpoint, i.v. administration has the advantage of rapid onset, making it suitable for emergency cases, but carries the risk of systemic hypotension [6,8]. Nebulised administration, by contrast, requires a longer pretreatment window (typically 15-20 minutes) to achieve optimal efficacy, but offers localised effects with minimal systemic side-effects, those planned for elective surgery [9]. This study aimed to compare the efficacy of nebulised with i.v. MgSO₄ in blunting haemodynamic responses to laryngoscopy and intubation, and its effect on neuromuscular blockade duration. The primary outcomes measures HR, SBP, DBP and MAP recorded at interval of prenebulisation (P0), postnebulisation (P1) and before i.v. magnesium sulfate administration (M0), after i.v. magnesium sulfate administration (M1), postinduction (I1), postintubation (T1), two minutes after intubation (T2), five minutes after intubation (T3), and ten minutes after intubation (T4). The secondary outcome is the requirement of the first maintenance dose of muscle relaxant when the TOF count exceeded 2, as determined by neuromuscular monitoring.

MATERIALS AND METHODS

The present study was a single-blinded, randomised clinical study conducted at the Department of Anaesthesiology, SRM Medical College Hospital and Research Centre, Tamil Nadu, India, from June 2024 to March 2025 following approval by the Institutional Ethics Committee. (IEC-ST0224-919). The study was registered with the Clinical Trials Registry (CTRI) (CTRI/2024/05/068060). Written informed consent was obtained from all participants before enrollment.

Inclusion criteria: Hypertensive patients scheduled to undergo elective general anaesthesia requiring endotracheal intubation, having an American Society of Anaesthesiologists (ASA) physical status of II or III, Mallampati classification grade I or II were included.

Exclusion criteria: Patients with anticipated difficult airway, who has BMI >30 kg/m², having history of ischaemic heart disease, and pregnant females were excluded.

Sample size calculation: Sample size was calculated using the following formula

$$n = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2 (P_1 q_1 + P_2 q_2)}{(P_1 - P_2)^2}$$

taken from the study done by Elmellegly MS et al.,

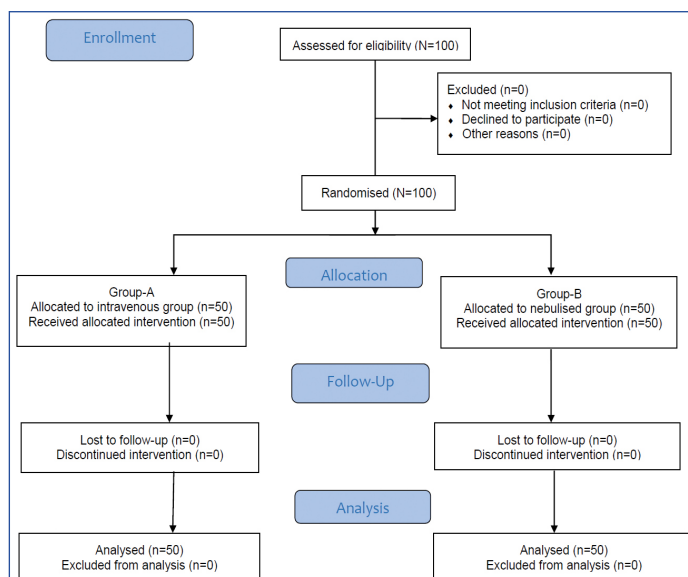
with $Z_{\alpha/2} = 1.96$ for 95% confidence interval $Z_{1-\beta} = 0.84$ for 80% power having

$$n = (1.96 + 0.84)^2 (0.02 \times 0.98 + 0.20 \times 0.80) / (0.02 - 0.20)^2 = 43 [4].$$

To ensure adequate power and account for possible dropouts sample size of 50 in each group was taken.

Study Procedure

Preoperative assessments were performed on patients who met the inclusion criteria. Participants were randomly assigned to one of two groups using a computerised randomisation. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. Single blinding was maintained. The Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist was used to develop this trial [Table/Fig-1]. Patients followed routine preoperative protocols, including fasting as per ASA guidelines. All patients received standard premedication with Tablet Alprazolam 0.25 mg, Tablet Ranitidine 150 mg, and Tablet Metoclopramide 10 mg on the



[Table/Fig-1]: CONSORT flow diagram.

night before and two hours before surgery. On the day of surgery, baseline monitors {Electrocardiogram (ECG), Non Invasive Blood Pressure (NIBP), Peripheral Capillary Oxygen Saturation (SpO₂)} were applied in the premedication room.

- Group A {Intravenous (i.v.) group}: Patients received MgSO₄ 30 mg/kg intravenously.
- Group B (Nebulisation group): Patients received MgSO₄ 40 mg/kg diluted in 5 mL normal saline via nebulisation over 15 minutes in the sitting position.

Drug dosages were standardised based on previous studies [9,10].

Following the administration of MgSO₄, vital parameters were monitored and documented. Premedications included glycopyrrolate 10 µg/kg, midazolam 0.05 mg/kg, and ondansetron 0.1 mg/kg. Induction was carried out with fentanyl 2 µg/kg and propofol 2 mg/kg. Vecuronium 0.1 mg/kg was administered for muscle relaxation. Endotracheal intubation was performed using direct laryngoscopy. Patients were mechanically ventilated in volume control mode and anaesthesia was maintained (Carestation 660, General Electric company, Chicago, Illinois, USA), with standardised ventilatory settings with oxygen-nitrous mixture and sevoflurane as an inhalational agent.

The haemodynamic parameters (HR, SBP, DBP, and MAP) were measured at multiple time points: Before i.v. MgSO₄ (M0), Pre-nebulisation (P0), After i.v. MgSO₄ (M1), postnebulisation (P1), postinduction (I1), immediately after intubation (T1), 2, 5, and 10 minutes after intubation (T2, T3, and T4, respectively). The secondary outcome was the time to administer first maintenance dose of muscle relaxant, assessed using TOF monitoring, specifically when TOF >2.

During the study period, if any fall in SBP >20% from the baseline for >60 seconds was treated with i.v. fluid bolus if required, ephedrine 6 mg was administered. Any increase in SBP >30% from baseline for >60 seconds was treated with i.v. esmolol 0.5 mg/kg and bradycardia (HR <45/min) treated with i.v. atropine 0.6 mg. The case was handled as per general anaesthesia protocol, and the trachea was extubated at the end of the surgery when the TOF >0.9.

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 30.0. Continuous variables were presented as mean±standard deviation and compared using the unpaired Student's t-test. Categorical data were analysed using Fisher's -exact. A p-value <0.05 was considered statistically significant. No subgroup or adjusted analyses were performed.

RESULTS

Demographic and baseline characteristics: The comparison of demographic and anthropometric characteristics between nebulisation and intravenous (i.v.) revealed no statistically significant differences. The distribution of these baseline variables is visually illustrated in [Table/Fig-2].

Parameters	Nebulisation (n=50) (mean±SD)	Intravenous (n=50) (mean±SD)	p-value Student's t-test
Age (years)	46.18±7.17	46.18±7.17	1.00
Height (cm)	166.08±10.30	165.72±10.46	0.86
Weight (kg)	71.56±6.80	69.32±9.67	0.18
			Fisher's exact test
BMI (kg/m ²)	25.96±2.20	25.22±2.56	0.12
Gender (Male/Female)	27/23	27/23	1.00

[Table/Fig-2]: Comparison of demographic and anthropometric characteristics between nebulisation and i.v. groups.

Heart Rate (HR) Response over Time: The HR was comparable between the two groups at all measured time points. HR remained similar in both the nebulisation and i.v. groups following MgSO₄ administration, postinduction, and at 2, 5, and 10 minutes. A transient rise in HR was noted postintubation in the nebulisation group (87.88±11.17) compared to the i.v. group (84.28±12.53); however, this difference was not statistically significant [Table/Fig-3].

Heart rate	Nebulisation (mean±SD)	Intravenous (mean±SD)	p-value Student's t-test
Baseline	85.72±10.87	84.04±12.30	0.30
Post MgSO ₄	82.08±10.20	83.08±12.25	0.53
Postinduction	85.44±9.93	84.22±10.31	0.39
Postintubation	87.88±11.17	84.28±12.53	0.47
2 min	85.38±10.78	83.44±12.61	0.24
5 min	82.60±10.17	82.16±12.21	0.78
10 min	80.40±10.31	79.18±11.71	0.43

[Table/Fig-3]: Comparison of Heart Rate (HR) (BPM) between nebulisation and i.v. groups at key time points.

Systolic Blood Pressure (SBP): The SBP was comparable between the two groups throughout the study period. Although the i.v. group showed a slightly higher SBP at baseline (127.72±9.20 vs. 124.42±8.31), the difference was not statistically significant. Following MgSO₄ administration, SBP values remained similar between the groups, including at postinduction, immediate postintubation, and 2, 5, and 10 minutes interval of postintubation. Overall, both groups demonstrated stable and comparable SBP trends without significant intergroup variation [Table/Fig-4].

Systolic blood pressure	Nebulisation (mean±SD)	Intravenous (mean±SD)	p-value Student's t-test
Baseline	124.42±8.69	127.72±9.20	0.20
Post MgSO ₄	124.42±8.86	125.58±9.81	0.38
Postinduction	122.46±9.97	121.86±7.48	0.63
Postintubation	122.06±9.02	121.70±8.19	0.76
2 min	123.26±9.62	121.28±9.69	0.14
5 min	123.60±8.14	122.74±10.50	0.51
10 min	122.74±8.60	121.48±9.81	0.33

[Table/Fig-4]: Comparison of Systolic Blood Pressure (SBP) (mmHg) between nebulisation and i.v. groups.

Diastolic Blood Pressure (DBP): The DBP remained comparable between the two groups throughout the study period. At baseline, the nebulisation group showed a slightly higher DBP (79.00±6.17) than the i.v. group (77.14±8.06), without statistical significance. This similarity persisted after MgSO₄ administration, postinduction,

postintubation, and at 2 and 10 minutes. A marginal trend toward significance was noted at five minutes postintubation, where DBP was higher in the nebulisation group (75.88±7.30) than the i.v. group (70.98±6.39). However, none of the differences were statistically significant, indicating similar DBP responses in both groups [Table/Fig-5].

Diastolic blood pressure	Nebulisation (mean±SD)	Intravenous (mean±SD)	p-value Student's t-test
Baseline	79.00±6.16	77.14±8.06	0.27
Post MgSO ₄	77.80±5.20	75.74±7.69	0.06
Postinduction	78.84±6.61	75.98±6.92	0.21
Postintubation	78.38±2.67	75.88±6.31	0.06
2 min	77.64±7.22	74.68±8.35	0.11
5 min	75.88±7.30	70.98±6.38	0.05
10 min	75.60±5.67	71.78±5.08	0.06

[Table/Fig-5]: Comparison of Diastolic Blood Pressure (DBP) (mmHg) between nebulisation and i.v. groups.

Mean Arterial Pressure (MAP): The MAP was similar in both nebulisation and i.v. groups at all measured time points- baseline, post MgSO₄ administration, after induction, and at 0, 2, 5, and 10 minutes postintubation. At five minutes postintubation, the MAP was slightly higher in the nebulisation group (81.52±10.10) compared to the i.v. group (79.44±7.70), but the difference was not statistically significant. Overall, there were no statistically significant differences in MAP at any recorded time point between the nebulisation and i.v. groups [Table/Fig-6].

MAP	Nebulisation (mean±SD)	Intravenous (mean±SD)	p-value Student's t-test
Baseline	89.10±7.96	90.94±8.45	0.11
Post MgSO ₄	85.80±10.21	84.58±9.52	0.38
Postinduction	77.84±10.70	78.34±9.16	0.72
Postintubation	83.54±8.49	81.52±9.34	0.11
2 min	81.92±9.44	82.36±8.27	0.72
5 min	81.52±10.10	79.44±7.70	0.10
10 min	80.84±8.27	78.90±9.14	0.11

[Table/Fig-6]: Comparison of Mean Arterial Pressure (mmHg) between nebulisation and i.v. groups.

Time to First Maintenance Dose of Muscle Relaxant: The secondary outcome assessed the time to administration of the first maintenance dose of muscle relaxant, guided by TOF monitoring. The nebulisation group (cases) had a longer mean interval (49.1±8.7 minutes) compared to the i.v. group (controls: 44.8±8.6 minutes), although this difference did not achieve statistical significance (p-value=0.06). These findings suggest a possible trend toward prolonged neuromuscular blockade in the nebulised group, warranting further investigation in larger trials [Table/Fig-7].

Parameter	Group		p-value Student's t-test
	Nebulisation (mean±SD)	Intravenous (mean±SD)	
Time for first dose	49.1±8.7	44.8±8.6	0.06

[Table/Fig-7]: Comparison of time to first maintenance muscle relaxant dose (minutes) between groups.

Events and complications: Two patients (4%) in i.v. MgSO₄ had transient hypotension at laryngoscopy and intubation, which was treated with i.v. fluid bolus. Postextubation, none of the patients had inadequate cough, gag, or swallowing reflexes.

DISCUSSION

This randomised controlled trial compared the efficacy of nebulised versus i.v. MgSO₄ in attenuating the haemodynamic stress response to endotracheal intubation in hypertensive patients undergoing

elective surgery under general anaesthesia. While i.v. MgSO₄ acts rapidly by inhibiting catecholamine release from the adrenal medulla and sympathetic nerve terminals [6,11], nebulised MgSO₄ may provide a more localised effect on airway nociceptors, reducing reflex sympathetic stimulation [4,9]. This present study findings demonstrates both modes of administration offered comparable haemodynamic stability throughout the peri-intubation period, with no clinically significant or sustained differences in HR, SBP, DBP, or MAP between the groups.

In this study, a transient, non significant increase in HR was observed immediately after intubation in the nebulisation group compared to the i.v. group (p-value=0.47), which normalised at subsequent time points. This transient rise may reflect a slightly delayed onset of mucosal absorption relative to the immediate systemic action of i.v. administration [12]. Similarly, the study by Elmeligy MS et al., has shown that nebulised MgSO₄ (e.g., 240 mg) can significantly attenuate haemodynamic surges and stress-induced hypertension during laryngoscopy [4]. These effects are attributed to the dual mechanisms of MgSO₄ systemic calcium channel blockade when administered intravenously, and localised NMDA receptor antagonism when delivered via inhalation [4].

Both groups in this present study demonstrated stable and comparable SBP trends without significant intergroup variation. The elevated baseline SBP in the i.v. group (p-value=0.20) equalised following MgSO₄ administration, and SBP remained statistically comparable between groups thereafter. DBP also followed similar patterns, with no significant intergroup differences observed postintervention. Prior studies have reported significant SBP reductions with i.v. MgSO₄ in hypertensive populations [6,13,14].

The MAP was similar in both nebulisation and i.v. groups at all measured time points-baseline, post MgSO₄ administration, after induction, and at 0, 2, 5, and 10 minutes postintubation. At five minutes postintubation, the MAP was slightly higher in the nebulisation group (81.52±10.10) compared to the i.v. group (79.44±7.70), but the difference was not statistically significant. In the study by Shrestha K et al., changes in MAP at 1, 5, 10 minutes postintubation were not statistically significant [7].

The time to the first muscle relaxant dose, as guided by TOF monitoring, was longer in the nebulisation group. Although not statistically significant (p-value=0.06), this trend aligns with the known pharmacodynamic effects of magnesium, which acts as a calcium antagonist at neuromuscular junctions, thereby enhancing muscle relaxation [10]. Most research in this area focuses on systemic i.v. magnesium, which has well-documented effects on enhancing neuromuscular blockade [8].

Previous literature has also evaluated the efficacy of nebulised dexmedetomidine and MgSO₄ in blunting the pressor response. Dexmedetomidine, an α_2 -adrenergic agonist, reduces norepinephrine release and enhances vagal tone, thereby promoting haemodynamic stability. Its nebulised form offers high bioavailability- approximately 65% via nasal and 82% via buccal routes- and has been used effectively at 1 µg/kg doses [15-17]. Studies comparing nebulised MgSO₄ (40 mg/kg) with dexmedetomidine have demonstrated similar efficacy in reducing HR and BP elevations by both mgso4 and dexmedetomidine, with the added benefit of avoiding rebound tachycardia [7,8,18]. Evidence from these comparative trials suggests that nebulised MgSO₄ offers comparable efficacy to dexmedetomidine in controlling haemodynamic fluctuations during airway manipulation, with some studies indicating marginally better diastolic pressure stability in the dexmedetomidine group [9,19,20]. Collectively, these findings support the role of nebulised MgSO₄ as a viable and potentially safer alternative to traditional i.v. agents in mitigating the intubation response.

The i.v. MgSO₄ has also been shown to significantly reduce systolic blood pressure in hypertensive patients when compared to

placebo, with reported p-values as low as 0.003 [6]. These findings underscore the potential role of magnesium, via both systemic and inhalational routes, as a viable adjunct in modulating haemodynamic stress responses during airway manipulation. A study with nebulised fentanyl has shown promise for postoperative analgesia; its role in attenuating the intubation-induced pressor response remains insufficiently studied [21]. In contrast, i.v. fentanyl (2 µg/kg) is a widely used premedication for blunting laryngoscopy-associated sympathetic surges [6], though higher doses or combination therapies are often necessary for optimal suppression [17].

The safety profile of nebulised magnesium is an important consideration in its clinical utility. While i.v. MgSO₄ at doses ≥40 mg/kg has been associated with dose-dependent hypotension and may require vigilant haemodynamic monitoring [6,8], nebulised administration achieves localised airway effects with minimal systemic absorption, potentially lowering the risk of adverse events [22].

This study's strengths include its randomised controlled design, standardised anaesthetic and monitoring protocols, and multi-parameter haemodynamic evaluation across multiple peri-intubation time points. Importantly, neuromuscular blockade was objectively assessed using TOF monitoring, offering pharmacodynamic insight into magnesium's muscle relaxant effects [23]. Nebulised MgSO₄ appears to be a promising, non invasive adjunct for attenuating the pressor response to laryngoscopy, particularly in hypertensive patients with the comparable haemodynamic trends, ease of administration, and lower systemic exposure supports its continued investigation. Nebulisation may be especially useful in settings requiring minimal invasiveness or where i.v. access is limited.

Further large-scale studies are warranted to refine optimal dosing, timing, and patient selection criteria. Hybrid strategies combining preoperative nebulisation with low-dose i.v. magnesium may offer synergistic benefits, particularly in high-risk cohorts. Additionally, Nebulised MgSO₄ can lower drug costs while still producing a similar attenuation of the haemodynamic stress response in perioperative treatment when used in place of more expensive medications like dexmedetomidine. Additionally, MgSO₄ is widely accessible, has a good safety record, and doesn't need any extra handling or monitoring outside of the parameters of conventional perioperative procedures. This makes it especially useful in environments with limited resources. The cost of MgSO₄ is low in both forms, and since the total doses used are similar, there is little difference in the direct price of the drug. The i.v. administration usually requires an i.v. cannula, infusion set, and fluid bag. Nebulised administration requires a nebuliser device and mask or mouthpiece; but the expense may increase if disposable kits are used. The i.v. has more systemic side-effects like hypotension, bradycardia which requires additional drug treatment if indicated that may add treatment costs. Nebulised has fewer side-effects, potentially saving on interventions. The i.v. is more cost-effective in busy theatres; nebulised may be better for high-risk patients.

Limitation(s)

The study was limited by its single-blinded design, moderate sample size, and the absence of serum magnesium measurements, which could have helped correlate pharmacokinetic levels with clinical outcomes. Future research could benefit from larger, multicenter trials with stratified patient risk profiles, extended postoperative follow-up, and incorporation of biochemical markers to elucidate mechanisms of action.

CONCLUSION(S)

Both nebulised and i.v. MgSO₄ were effective in maintaining haemodynamic stability during endotracheal intubation in hypertensive patients, while the nebulised form of MgSO₄ offers the additional benefits of a non invasive, better-tolerated, and potentially safer alternative for smoother haemodynamic control-making it

a promising adjunct to reduce intubation stress response in the anaesthetic management of hypertensive patients. The nebulisation group demonstrated a longer mean interval for neuromuscular redosing, suggesting a trend toward prolonged blockade. There were no reported side-effects in either group, suggesting that both agents are safe for use in this context.

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