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Efficacy of 3ED$_{95}$ Vs 6ED$_{95}$ Dose of Cisatracurium with Magnesium Sulphate for Endotracheal Intubation in Patients Undergoing General Anaesthesia: A Randomised Double-Blinded Study

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KEYWORDS

Cisatracurium, Hemodynamics, Intubation, Magnesium Sulfate, Neuromuscular Blockade, Neuromuscular Blocking Agents

ABSTRACT:

Background and aim:

Cisatracurium is an effective non-depolarising neuromuscular blocker, but has a relatively slow onset. Magnesium sulphate (MgSO4) may potentiate its effect and improve intubating conditions. The study aimed to determine the optimal dose of cisatracurium for endotracheal intubation when used with MgSO4.

Methods:

In this randomised controlled study, 70 patients undergoing elective surgeries under general anaesthesia were randomly allocated into two groups: Group A (cisatracurium 3ED95 + MgSO4) and Group B (cisatracurium 6ED95 + MgSO4). The primary outcome was the onset time of neuromuscular blockade. The secondary outcomes included the ease of intubation, duration of action of intubating dose, total dose of Cisatracurium used, haemodynamic changes and complications. The Chi-square test was applied for categorical data, and a P value < 0.05 was considered statistically significant.

Results:

The demographic data were comparable between the groups. Mean onset time for neuromuscular blockade was slightly longer in Group A (116.8 ± 4.8 sec) than in Group B (114.7 ± 5.1 sec), but the difference was not statistically significant (P = 0.081). Mehta's Gradation of Ease of Intubation scores were identical between groups (P = 1.000). The time to first maintenance dose, haemodynamic variables, and complications did not differ significantly. Serum magnesium levels remained comparable at all measured intervals.

Conclusion:

The 3ED95 dose of cisatracurium combined with MgSO4 provides similar neuromuscular blockade and intubating conditions comparable to those achieved with a 6ED$_{95}$ dose, with stable haemodynamics in both groups.

INTRODUCTION

General anaesthesia comprises five essential components: unconsciousness, amnesia, analgesia, immobility, and attenuation of autonomic responses to noxious stimulation.[1] Neuromuscular blocking agents (NMBAs) contribute to the immobility component by producing smooth muscle relaxation.[2] For optimal clinical utility, NMBAs should provide a rapid onset, brief duration of action, minimal haemodynamic disturbances, absence of

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residual neuromuscular blockade, and the ability to facilitate optimal intubating conditions – characterised by complete jaw relaxation, fully open vocal cords, and absence of an intubation response.[3]

Cisatracurium, a non-depolarising benzylisoquinolinium NMBA, has an ED_{95} of 0.05 mg/kg. A dose equivalent to 2–3 times the ED_{95} is typically required to achieve sufficient relaxation of the laryngeal muscles for successful endotracheal intubation.[4] However, cisatracurium has an onset time of 2.5 to 3 minutes, which is relatively prolonged and may be suboptimal in situations where rapid airway control is required.[5]

Magnesium sulphate ($MgSO_4$) potentiates the effects of non-depolarising NMBAs, including cisatracurium, by reducing the excitability of muscle fibres and diminishing the amplitude of end-plate potential.[6] Clinically, magnesium sulphate is also used in the management of arrhythmias, asthma, acute respiratory failure, and pre-eclampsia.[7]

Despite cisatracurium's effectiveness, its relatively slow onset of action poses a limitation in clinical settings requiring rapid tracheal intubation. Co-administration of MgSO4 with cisatracurium may shorten the onset time and facilitate more rapid attainment of ideal intubating conditions.[8] The primary objective of this study was to compare ideal intubation conditions in terms of the onset of action of two different ED_{95} doses ($3ED_{95}$ vs. $6ED_{95}$) of cisatracurium with $MgSO_4$. Secondary objectives included evaluating ease of intubation, duration of action, total Cisatracurium dose required, haemodynamic effects, and associated complications in both dosing groups. The hypothesis was that the $3ED_{95}$ cisatracurium has similar characteristics compared with the $6ED_{95}$ cisatracurium.

METHODS

This single-center, hospital-based, prospective, randomised, double-blinded, controlled study was conducted over 18 months between July 2023 and December 2024, and was registered with Clinical Trials Registry of India (CTRI/2024/06/068788). The study followed the Declaration of Helsinki, 2013 principles and Good Clinical Practice guidelines. Approval was obtained from the Institutional Human Ethics Committee with reference number AV/IHEC/2023/033 dated 25/05/2023. Enrolment proceeded upon receipt of written informed consent. Patients between 18 and 65 years of age, of both genders, ASA I and II, undergoing elective surgeries under general anaesthesia, were included. Patients taking magnesium supplements, with arrhythmias, neuromuscular diseases, on beta blockers or antiarrhythmic drugs, using medications that influence neuromuscular functions (for example, calcium channel blockers, phenytoin, aminoglycosides), with electrolyte abnormalities, hepatic or renal insufficiency, known allergies, pregnant and breastfeeding women were excluded.

The patients were randomly assigned to two groups of 35 each based on computer-generated random numbers. Group allocation was concealed using sequentially numbered opaque sealed envelopes. Group A patients received a $3ED_{95}$ dose of cisatracurium, and Group B patients received a $6ED_{95}$ dose of cisatracurium.

A detailed preoperative assessment was conducted, including serum magnesium levels, measured 24 hours before surgery. On the day of surgery, standard ASA monitors were connected, and a wide-bore IV cannula was secured. Neuromuscular function was monitored using train-of-four (TOF) stimulation, with two surface electrodes placed over the ulnar nerve on the volar aspect of the wrist.

Both groups received intravenous $MgSO_4$ of 50 mg/kg diluted in 100 ml of 0.9% normal saline, administered as an infusion. Premedication consisted of Ondansetron (0.1 mg/kg), Glycopyrrolate (0.004 mg/kg), Midazolam (0.05 mg/kg), and Fentanyl (2 mcg/kg) intravenously. Anaesthesia was induced with Propofol intravenously at a dose of 2 mg/kg. Group A received cisatracurium at a dose of 0.15 mg/kg (3ED95), Group B received cisatracurium at a dose of 0.3 mg/kg (6ED95).

Onset time for achieving ideal intubating conditions was defined as the time from the initial dose of Cisatracurium to 95% suppression of the T1 response. Endotracheal intubation was performed by an experienced anaesthesiologist using an appropriately sized endotracheal tube. Ease of intubation was assessed using Mehta's Gradation of Ease of Intubation. Heart rate (HR), mean arterial blood pressure (MAP) were monitored throughout the procedure. Both the anaesthesiologist performing intubation and the patient were blinded to group assignment.

Anaesthesia was maintained with 50% nitrous oxide and 50% oxygen, along with isoflurane titrated to the patient's requirements. Maintenance dose of cisatracurium (0.05 mg/kg) was administered when TOF had recovered to

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25% of the control T1 value. Reversal of neuromuscular blockade was achieved using Neostigmine (0.5 mg/kg) & Glycopyrrolate (0.004 mg/kg) under TOF monitoring. The data was recorded by another anesthesiologist who was not part of the procedure, which included the onset time of cisatracurium, Mehta's grade of intubation, time to first maintenance dose, total dose of cisatracurium required, haemodynamic parameters such as heart rate and mean arterial pressure every 5 min for the first 15 minutes post-intubation and incidence of complications and serum magnesium levels at 2 hours and 24 hours postoperatively. Mehta's Gradation of Ease of Intubation - Excellent (Grade I): Easy passage of tube without bucking, Good (Grade II): Passage of tube with slight bucking, Fair (Grade III): Passage of tube with moderate bucking, Impossible (Grade IV): Intubation could not be performed with three attempts.[9]

A sample size of 70 participants (35 per group) was calculated using a statistical formula for comparing two independent means, based on an anticipated mean difference of 2 minutes in duration of action, with a standard deviation of 2.5 minutes as reported by Rehman et al.[10] A 5% significance level and 90% study power were considered to ensure result reliability. We used a nonprobability consecutive sampling technique to enrol patients. Statistical analysis conducted using Statistical Package for the Social Sciences (SPSS) version 29.0 (IBM Corp.; Armonk, NY, USA). Categorical variables summarised as frequencies and percentages. Continuous variables were presented as mean ± standard deviation. To compare the onset time between two groups, an independent 't' test applied for data with a normal distribution, Mann-Whitney U test was employed for non-normally distributed data.

RESULTS

A total of 82 patients were assessed for eligibility. Twelve were excluded-seven did not meet the inclusion criteria, and five declined participation. Seventy patients were enrolled and randomised into two equal groups of 35 each (Figure 1).

Demographic characteristics, including age, gender, weight and American Society of Anesthesiologists-Physical Status (ASA-PS) classification, were comparable in both groups (Table 1).

The mean onset time of neuromuscular blockade was 114.7 ± 5.1 seconds in Group B and 116.8 ± 4.8 seconds in Group A. The difference was not statistically significant ($P = 0.081$) (Table 2). The mean time to first maintenance dose was 83.6 ± 7.1 minutes in Group B and 86.1 ± 4.9 minutes in Group A, with no significant difference ($P = 0.091$) (Table 2). The total cisatracurium dose required was 19.7 ± 2.2 mg in Group B and 10.1 ± 1.9 mg in Group A, with a statistically significant difference ($P < 0.001$) (Table 2).

Haemodynamic measurements like heart rate and mean arterial pressure were obtained and were found to have no statistical difference at any time point (Figure 2).

Ease of intubation, assessed using Mehta's Gradation, was similar in both groups, with an identical mean score of 1.5 (SD 0.5, P = 1.000) (Table 3). Complications were infrequent and comparable: each group had one case (2.9%) of bradycardia; Group B had one case (2.9%) of hypotension; respiratory depression occurred in two patients (5.7%) in Group A and one patient (2.9%) in Group B, with no statistically significant differences (Table 3).

Serum magnesium levels were comparable between the groups at baseline, 2 hours and 24 hours post-administration (Table 3).

DISCUSSION

This study compared the efficacy of $3ED_{95}$ and $6ED_{95}$ doses of cisatracurium administered with $MgSO_4$ to determine the optimal dosing strategy for facilitating endotracheal intubation. The results demonstrated that onset time, time to the first maintenance dose, ease of intubation, haemodynamic changes, and complication rates were comparable between the two groups. As expected, the total dose of cisatracurium administered was significantly higher in the $6ED_{95}$ group. These findings support the hypothesis that a $3ED_{95}$ dose of cisatracurium provides effectiveness comparable to $6ED_{95}$ dose when used in conjunction with $MgSO_4$.

Onset of Neuromuscular Blockade

In the present study, onset time did not differ significantly between the two groups. This finding contrasts with earlier studies by Kumar et al.[4] and Paul et al.[11], who reported a slower onset of neuromuscular blockade with lower doses of cisatracurium when used alone. The discrepancy may be attributed to the potentiating effect of $MgSO_4$, which enhances neuromuscular blockade by reducing presynaptic acetylcholine release and decreasing postsynaptic membrane excitability.

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Na et al.[13] demonstrated that magnesium significantly potentiates non-depolarizing neuromuscular blockers and shortens the time to adequate intubating conditions, thereby minimizing dose-dependent differences in onset. Similar observations have been reported by Fuchs-Buder et al.[14], who noted that magnesium pretreatment improves the onset characteristics of intermediate-acting neuromuscular blocking agents.

Duration of Neuromuscular Blockade

The duration of neuromuscular blockade, assessed by the time to first maintenance dose, was comparable between both groups. This finding is consistent with the study by Ashwini et al.[11], who reported similar durations of action with lower and higher doses of cisatracurium when combined with $MgSO_4$. Magnesium has been shown to prolong neuromuscular blockade by decreasing acetylcholine availability at the neuromuscular junction, which may equalize duration despite differences in initial cisatracurium dose. Telci et al.[15] similarly reported prolonged and stable neuromuscular blockade when magnesium was used as an adjuvant.

Total Cisatracurium Requirement

As anticipated, the total amount of cisatracurium required was significantly higher in Group B (6ED95) compared with Group A (3ED95), reflecting the difference in initial administered doses (0.30 mg/kg vs. 0.15 mg/kg). This observation aligns with pharmacodynamic principles and has been consistently reported in prior dose-comparison studies of cisatracurium.[4],[11] Importantly, despite the lower cumulative dose in Group A, clinical efficacy was maintained, highlighting the dose-sparing effect of $MgSO_4$.

Haemodynamic Responses

Haemodynamic parameters, including heart rate and mean arterial pressure, increased transiently during intubation but remained comparable between groups at all measured time points. These findings are consistent with previous studies reporting haemodynamic stability with cisatracurium, attributed to its minimal histamine release and organ-independent Hofmann elimination.[4],[12]

Additionally, magnesium has sympatholytic and vasodilatory properties that blunt catecholamine release during laryngoscopy and intubation. Puri et al.[16] and Elsharnouby et al.[17] reported similar haemodynamic stability when magnesium was used as an adjunct during induction of anaesthesia.

Ease of Intubation

Mehta's gradation of ease of intubation scores were identical in both groups, indicating that both 3ED95 and 6ED95 doses of cisatracurium, when combined with $MgSO_4$, provided optimal and comparable intubating conditions. This finding differs from Kumar et al.[4], who reported superior intubation conditions with higher doses of cisatracurium in the absence of magnesium.

The present results suggest that $MgSO_4$ augments neuromuscular blockade sufficiently to ensure excellent intubating conditions even at lower doses. This observation is supported by Sun et al.[18], who demonstrated improved intubation scores and reduced requirement for higher doses of neuromuscular blockers when magnesium was administered prior to induction.

Complications and Safety Profile

Complication rates were low and comparable between groups, with bradycardia being infrequent and clinically insignificant. These findings are consistent with the well-established safety profiles of both cisatracurium and $MgSO_4$. Serum magnesium levels remained within comparable ranges in both groups, indicating consistent systemic exposure and absence of magnesium toxicity. Similar safety outcomes have been reported by Koinig et al.[19] and Schulz-Stubner et al.[20], reinforcing the safety of magnesium as an anaesthetic adjuvant.

Limitations

The limitations of this study include its single-centre design and relatively small sample size, which may limit the generalizability of the findings. Magnesium sulphate was administered at a fixed dose, and individual variability in pharmacokinetics and pharmacodynamics may influence neuromuscular effects. Future large-scale, multicentre studies are recommended to evaluate varying $MgSO_4$ dosing regimens, assess outcomes in diverse patient populations, and examine long-term safety, postoperative recovery profiles, and residual neuromuscular blockade.

CONCLUSION

A $3ED_{95}$ dose of cisatracurium administered with magnesium sulphate provides effective neuromuscular blockade with stable haemodynamic parameters and

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intubating conditions comparable to those achieved with a $6ED_{95}$ dose. These findings suggest that the lower dose may serve as an optimal strategy for endotracheal intubation, avoiding unnecessary increases in drug requirement without compromising clinical efficacy.

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Table 1: Baseline characteristics of the study groups

		Group A N = 35	Group B N = 35	*P*-value
Age (years)		48.1±4.5	47.6±2.8	0.889
Gender	Female	19 (54.3)	18 (51.4)	0.811
	Male	16 (45.7)	17 (48.6)	
Weight (kg)		66.4±12.0	69.3±8.5	0.250
ASA-PS	1	14 (40.0)	17 (48.6)	0.470
	2	21 (60.0)	18 (51.4)	
Time to onset (seconds)		116.8±4.8	114.7±5.1	0.081
Time to first maintenance dose (minutes)		86.1±4.9)	83.6±7.1	0.091
Total dose of Cisatracurium		10.1±1.9	19.7±2.2	<0.001*

Data presented as mean ± standard deviation or frequency (percentage). Kg = kilogram, ASA-PS = American Society of Anesthesiologists-Physical Status

* - statistically significant

Table 2: Comparison of onset of action, time to first maintenance dose and total dose of cisatracurium

	Group A N = 35	Group B N = 35	*P*-value
Time to onset (seconds)	116.8±4.8	114.7±5.1	0.081
Time to first maintenance dose (minutes)	86.1±4.9	83.6±7.1	0.091
Total dose of Cisatracurium	10.1±1.9	19.7±2.2	<0.001*

Data presented as mean ± standard deviation

* - statistically significant

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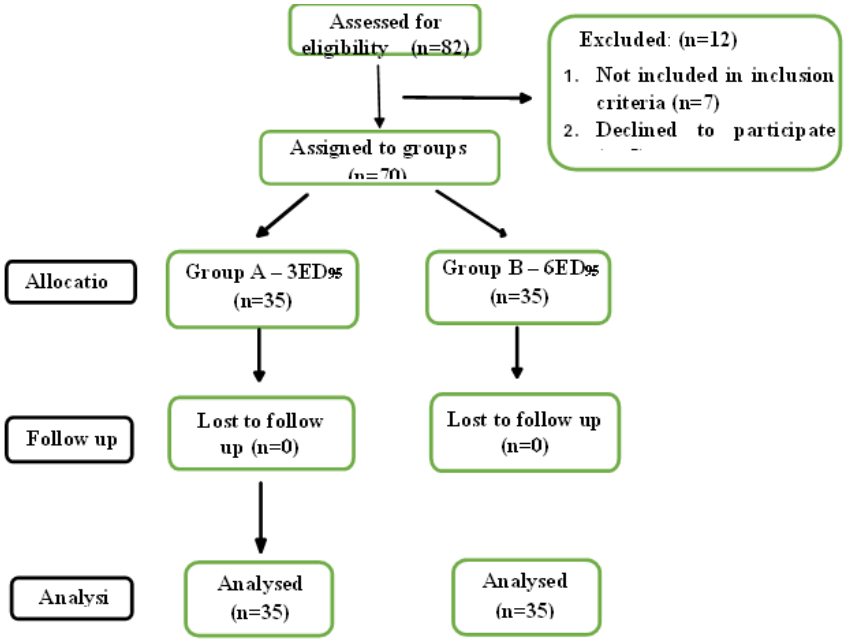
Table 3: Comparison of study groups, by ease of intubation, complications, and magnesium levels

		Group A N = 35	Group B N = 35	*P*-value
Mehta's Gradation of Ease of Intubation		1.5±0.5	1.5±0.5	1.000
Complications				
Bradycardia	Yes	1 (2.9)	1 (2.9)	1.000
	No	34 (97.1)	34 (97.1)	
Hypotension	Yes	0 (0.0)	1 (2.9)	0.314
	No	35 (100)	34 (97.1)	
Respiratory depression	Yes	2 (5.7)	1 (2.9)	0.555
	No	33 (94.3)	34 (97.1)	
Magnesium levels (ionised; mg/dl)				
Baseline (24 hours before surgery)		1.8±0.1	1.8±0.2	1.000
Postoperative – 2 hours		2.2±0.2	2.3±0.3	0.106
Postoperative – 24 hours		1.9±0.4	2.0±0.2	0.190

Data presented as mean ± standard deviation or frequency (percentage)

Figure 1 - Consolidated Standards of Reporting Trials (CONSORT) flow chart



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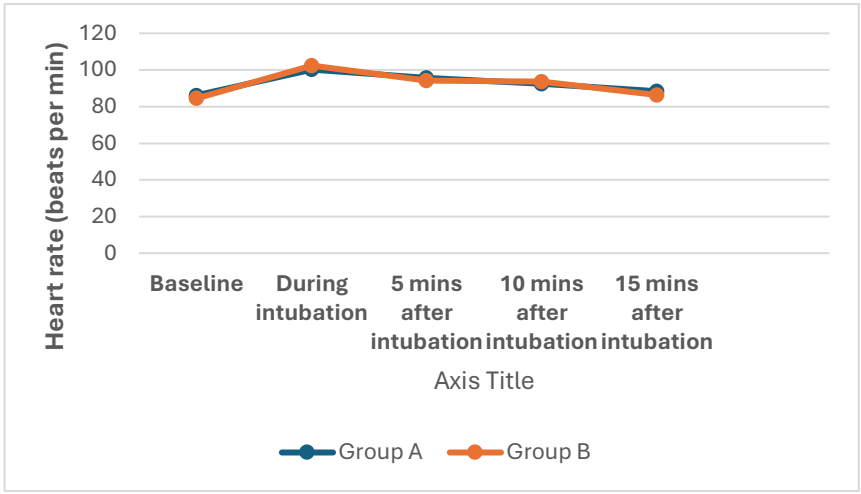

Figure 2 - Comparison of mean heart rate between the two groups. Group A – 3ED95 cisatracurium, Group B – 6ED95 cisatracurium