Original contribution

The effects of low-dose ephedrine on intubating conditions following low-dose priming with cisatracurium

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Abstract

**Study Objective:** To determine whether low-dose ephedrine plus priming with low-dose cisatracurium improves intubating conditions.

**Design:** Prospective, randomized, double-blinded study.

**Setting:** Operating room.

**Patients:** 124 ASA physical status I and II patients scheduled for elective surgery.

**Interventions:** Patients were randomly assigned to 4 groups (n = 31): Group PE (priming + ephedrine), Group P (priming), Group E (ephedrine), and Group NPE (no priming, no ephedrine). All patients were induced with propofol two mg/kg and sufentanil 0.15 \(\mu\)g/kg. In the priming groups, 0.005 mg/kg (10% ED\(_{95}\)) cisatracurium was given, followed three minutes later by 0.145 mg/kg of cisatracurium. In Groups E and NPE, a single dose of 0.15 mg/kg cisatracurium was given. Intravenous ephedrine 70 \(\mu\)g/kg was given in Groups PE and E. Tracheal intubation was attempted 60 seconds after the intubating dose of cisatracurium and was considered successful only if performed within 20 seconds.

**Measurements:** Intubating conditions were graded. Heart rate and non-invasive blood pressure, at one-minute intervals, were recorded during and 5 minutes after induction.

**Main Results:** The tracheas of all patients in Group PE were successfully intubated within 20 seconds versus 74% in Group P, 77% in Group E, and 64% in Group NPE (\(P < 0.001\) vs. Group PE). Intubating conditions were graded good to excellent in all PE patients, but in only 52% of Groups P and E, and 48% of NPE patients (\(P < 0.001\)). Hemodynamic variables were comparable among groups (\(P = \text{ns}\)).

**Conclusions:** Low-dose ephedrine plus priming with low-dose cisatracurium before an intubating dose, significantly improved clinical intubating conditions at 60 seconds.

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1. Introduction

Cisatracurium, an intermediate-acting neuromuscular blocking agent (NMBA), is a stereo-isomer of atracurium, but with only minor release of histamine, minor production of laudanosine, and slower onset time [1,2]. The time to maximal neuromuscular block for equipotent doses is up to two minutes longer with cisatracurium than with atracurium [3].

Large doses of cisatracurium may shorten onset time. A dose of 0.15 mg/kg (three ED_{95}) has an average onset time of 220 seconds, while onset time with 0.2 mg/kg (4 ED_{95}) is 162 seconds. These times are still much slower than succinylcholine or rocuronium [4].

Onset time of a NMBA may be accelerated by the priming principle; that is, administration of a small subparalyzing dose of the agent several minutes before the principal intubating dose [5]. Puhrringer et al. showed that the priming combination of cisatracurium 15 µg/kg followed after 4 minutes by cisatracurium 85 µg/kg produced a statistically significant reduction in onset time (180 ± 60 sec) when compared with a single bolus of cisatracurium (240 ± 48 sec) [6].

The onset of action of a NMBA is also influenced by the speed with which the agent is delivered to the synaptic cleft. This interval appears to be inversely proportional to cardiac output (CO) and muscle perfusion [7]. Ephedrine is a weak, indirect, and direct-acting sympathomimetic agent that produces, via α1 adrenoceptors, venoconstriction to a greater degree than arterial constriction. These actions improve venous return and increase CO. Ephedrine’s mild β action restores heart rate (HR) simultaneously with improvement in venous return [8]. Albert et al. [9] reported that a low dose (70 µg/kg) of ephedrine given before induction of anesthesia improves tracheal intubating conditions two minutes after cisatracurium 0.15 mg/kg. Leykin et al. [10] showed that ephedrine in combination with propofol significantly improved clinical intubating conditions following priming with rocuronium compared with priming without ephedrine, ephedrine without priming, and propofol alone.

The hypothesis that low-dose ephedrine would improve clinical intubating conditions following priming with cisatracurium was studied. We also studied whether a low priming dose of cisatracurium followed by an intubating dose of cisatracurium would minimize adverse effects of the priming dose during the three minutes of priming interval, and whether low doses of ephedrine were devoid of adverse hemodynamic consequences.

2. Materials and methods

After approval from the Santa Maria degli Angeli Hospital Institutional Ethics Committee and patients’ written, informed consent for the study, 124 ASA physical status I and II patients, aged 18 to 65 years, and scheduled for elective surgery were enrolled in the study. Patients with anticipated difficult airway (based on Mallampati score, neck circumference, thyromental distance, and interdental distance); hypertension; those taking medications known to interact with NMBA or ephedrine, obesity; or evidence of neuromuscular, cardiovascular, respiratory, hepatic, or renal disease, were excluded from the study.

No premedication was administered. On arrival at the operating room (OR), electrocardiographic (ECG) electrodes were applied and oxygen saturation was monitored by pulse oximetry (SpO₂). Blood pressure (BP) and HR were recorded at baseline and every minute for the 5 minutes following tracheal intubation. Measurements were performed immediately prior to the intubating dose. The presence of arrhythmias on the ECG monitor was recorded.

Prior to administering the priming dose, patients were preoxygenated for 5 minutes. The priming technique consisted of a dose of cisatracurium 0.05 mg/kg (10% ED_{95}) followed three minutes later by an intubating dose of cisatracurium 0.145 mg/kg. During the priming interval, patients were also oxygenated and closely monitored for signs of discomfort, palpebral ptosis, diplopia or respiratory difficulty. Orotracheal intubation was attempted 60 seconds after the intubating dose and was considered successful only if performed within 20 seconds.

In the control groups, the same protocol was applied except that sham priming was performed by injection of an equivalent volume of normal saline followed three minutes later by a single intubating dose of cisatracurium 0.15 mg/kg. Tracheal intubation was performed and assessed by an anesthesiologist with at least 10 years of clinical experience, who was blinded to group allocation and not involved in the protocol.

Intubating conditions were graded according to the criteria of Cooper et al. [11], which comprise jaw relaxation, vocal cord position, and response to intubation. Jaw relaxation: 0 = poor, 1 = minimal, 2 = moderate, and 3 = good; vocal cord position: 0 = closed, 1 = closing, 2 = moving, and 3 = open; response to intubation: 0 = severe
coughing and bucking, 1 = mild coughing, 2 = light diaphragmatic movement, and 3 = no movement. A score of 8 or 9 was considered excellent, 6 or 7 good, 3 to 5 poor, and 0 to 2 bad. Excellent and good conditions were considered clinically acceptable.

On postoperative day one, patients were questioned for perception of any discomfort during the priming interval.

2.1. Statistical analysis

Sample size calculation was based on the results of a previous pilot study. A power analysis was performed using acceptable intubating conditions as the primary outcome measure. Assuming an expected proportion of patients with acceptable intubating conditions of 80% for the Group PE versus 50% for Group NPE, 31 subjects per treatment group provided 80% power to detect statistical significance, under a 2-sided test conducted on the $\alpha = 0.05$ level.

The study was planned also to compare the efficacy of Group PE versus Groups E and P. No formal adjustment of the type I error was performed because the comparisons were a priori ordered according to clinical relevance. The $\alpha$-level for the three tests was controlled for multiplicity using a prioritization method of adjustment for multiple testing. Under this method of statistical testing, the test was significant at the $\alpha = 0.05$ level. Specifically, the initial test was the superiority of Group PE versus Group NPE. If the initial test showed the superiority of the first group, then the superiority of the investigational treatment versus Group E was conducted. Finally, if the second test confirmed the superiority of the first group, too, then the superiority between the investigational treatment and Group P was conducted. All other comparisons between groups were evaluated only for explanatory reasons. This “prioritization method of adjustment for multiple testing” concerned only the primary outcome.

Demographic and baseline characteristics were summarized by descriptive statistics (no. of subjects, means, standard deviations, medians, minimums, and maximums) or frequency distributions (nos. and percentages), as appropriate. Group comparability was assessed by analysis of variance (ANOVA) for continuous variables with treatment as factor, and by Chi-square or Fisher’s exact test for discrete variables.

Intubating conditions were analyzed by descriptive statistics. Comparisons between treatment groups were assessed by the non-parametric Mann-Whitney test for comparisons between couples of treatments, or by non-parametric Kruskal-Wallis test for overall comparison between treatments.

Comparisons within groups were performed for HR and BP. For these parameters, mean changes from baseline (performed immediately prior to the priming dose), their 95% confidence intervals, and paired T test were performed.

<table>
<thead>
<tr>
<th>PE</th>
<th>Priming</th>
<th>Ephedrine</th>
<th>NPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>39 ± 12.88</td>
<td>37 ± 12.14</td>
<td>40 ± 12.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 13.30</td>
<td>63 ± 12.98</td>
<td>67 ± 14.31</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 7.06</td>
<td>163 ± 9.18</td>
<td>165 ± 8.10</td>
</tr>
<tr>
<td>Men/Women</td>
<td>9/22</td>
<td>8/23</td>
<td>7/24</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. PE = priming + ephedrine, NPE = no priming, no ephedrine.
calculated. To increase precision and to compensate for any possible imbalance between groups due to the possible relationship between value measures after one minute of treatment and basal value, BP and HR were analyzed by analysis of covariance (ANCOVA) model using the corresponding baseline value as covariate and treatment as factor.

Statistical analysis was performed using SAS, version 8.2 (SAS, Cary, NC, USA), on a Windows XP operating system. Results were considered significant at a value of $P < 0.05$.

### 3. Results

All four groups were comparable with respect to age, weight, height, and gender ratio (Table 1). The tracheas of all patients in Group PE were intubated 60 seconds after the intubating dose of cisatracurium (within a 20-sec interval) compared with 74% (n = 23) of Group P ($P = 0.005$), 77% (n = 24) of Group E ($P = 0.011$), and 64% (n = 20) of Group NPE ($P < 0.001$) (Fig. 2).

Intubating conditions were clinically acceptable in all Group PE patients (100%) compared with 52% of Group P ($P = 0.010$), 52% of Group E ($P = 0.003$), and 48% of Group NPE ($P < 0.001$). The differences among the three control groups were not statistically significant (Group P vs. Group E; Group P vs. Group NPE; and Group E vs. Group NPE; $P = ns$) (Fig. 3).

Vocal cord position score during intubation did not present statistically significant differences among the studied groups ($P = 0.12$).

Response to intubation was significantly different among the groups ($P < 0.001$) and was improved in Group PE compared with the other groups ($P < 0.001$), as well as between Groups P and NPE ($P = 0.009$), and not different between Groups P and E, and Groups E and NPE (Fig. 4).

![Successful Intubating Rates](image1.png)

**Fig. 2** Percentage of successful intubations 60 seconds after the intubating dose of cisatracurium. Intubation was performed within a 20-second interval. Group PE = priming + ephedrine, Group NPE = no priming, no ephedrine. The 95% exact confidence intervals are: PE 88.78% to 100%; priming 55.39% to 88.14%; ephedrine 58.90% to 90.41%; and NPE 45.37% to 80.77%. $*P < 0.001$ vs. Group PE (Fisher’s exact test).

![Response to Intubation](image2.png)

**Fig. 4** Response to intubation: 0 = severe coughing or bucking, 1 = mild coughing, 2 = slight diaphragmatic movement, 3 = none. $*P < 0.001$ vs. Group PE (Mann-Whitney test).

![Clinically Acceptable Intubating Conditions](image3.png)

**Fig. 3** Intubating conditions at 60 seconds. $*P < 0.05$ vs. Group PE (Mann-Whitney test).

![Jaw Relaxation](image4.png)

**Fig. 5** Jaw relaxation score: 0 = poor, 1 = minimal, 2 = moderate, 3 = good. $*P < 0.05$ vs. Group PE. $†P < 0.05$ vs. Group P (Mann-Whitney test).
Jaw relaxation score was good in 84% (n = 26) and moderate in 16% (n = 5) of Group PE. Significantly better jaw relaxation was observed in Group PE than Group P (P = 0.007) but not compared with Groups E or NPE. A statistically significant difference was observed between Groups P and E (P = 0.046) and between Groups P and NPE (P = 0.017), but not between Groups E and NPE (Fig. 5).

The baseline values of mean arterial pressure (MAP) and HR did not differ among the groups. MAP did not differ significantly among the groups at one, two, three, 4, or 5 minutes after tracheal intubation. There was a significant decrease in MAP in all groups versus each baseline value (P < 0.001) (Table 2). There was no statistically significant difference in HR among the studied groups or within each group (Table 2).

During the priming interval, no signs of patient discomfort, palpebral ptosis, blurred vision, respiratory difficulty, or hypoxia were observed or reported. Moreover, no patient presented with arrhythmias during the study period.

### 4. Discussion

The combination of low-dose ephedrine (70 μg/kg) and a low priming dose (0.005 mg/kg) of cisatracurium significantly improved clinical intubating conditions 60 seconds after the intubating dose of cisatracurium, when compared with priming without ephedrine, ephedrine without priming, and the combination of sham priming and sham ephedrine. Of clinical relevance, no signs of muscular weakness or evidence of respiratory difficulty were noted by the observer or reported by the patients. There were no adverse effects related to ephedrine administration.

The rationale for the divided dose technique of administration of NMBAs for facilitation of rapid tracheal intubation is based on the high margin of safety of neuromuscular transmission, which allows 70% to 75% occupancy of the cholinergic receptors without any significant effect on neuromuscular activity [5]. The priming principle relies on the assumption that the administration of a second larger dose of a muscle relaxant, at the time of peak effect of the priming dose, rapidly increases receptor occupancy to the 90% to 92% level required for profound neuromuscular block [5]. The priming dose also can be expected to identify those patients who are unusually sensitive to NMBAs [5,12]. However, during the relatively long priming interval, the awake patient may suffer from distressing symptoms of muscle weakness such as blurred vision, dysphagia, and respiratory difficulty [13]. The size of the priming dose, intubating dose, and the priming interval are therefore crucial in the efficacy of the priming technique and in the reduction of incidence of possible side effects [14].

Deepika et al. showed that following priming with cisatracurium 0.01 mg/kg (20% of ED₉₅), a 0.14 mg/kg intubating dose (three ED₉₅) offered good to excellent intubating conditions in all patients after 85 ± 22 seconds and pharmacodynamics very similar to that of cisatracurium 0.2 mg/kg, with the added benefit of shorter clinical duration (57 ± 9 min vs. 67 ± 9 min) [15]. On the other hand, Mencke et al. reported that cisatracurium 0.01 mg/kg given 6 minutes before succinylcholine was associated with signs of muscle weakness in 13 of 15 patients [16]. In a theoretical analysis of safety and timing of the priming dose, Kopman et al. concluded that a dose equivalent to 10% of ED₉₅ rarely produces a measurable neuromuscular effect [17]. Accordingly, in the present investigation we selected a priming dose of 10% of ED₉₅ (0.005 mg/kg) and a three-minute interval between the priming and intubating doses, which probably

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean arterial pressure and heart rate before and for 5 minutes</th>
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<tbody>
<tr>
<td></td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>Min after induction</td>
<td>PE</td>
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<tr>
<td>BL</td>
<td>88 ± 14</td>
</tr>
<tr>
<td>1</td>
<td>97 ± 19</td>
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<tr>
<td>2</td>
<td>87 ± 16</td>
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<td>5</td>
<td>76 ± 14*</td>
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<tr>
<td>Heart Rate</td>
<td></td>
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<tr>
<td>BL</td>
<td>78 ± 15</td>
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<td>1</td>
<td>85 ± 19</td>
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<td>4</td>
<td>76 ± 14</td>
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<td>5</td>
<td>76 ± 14</td>
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</tbody>
</table>

Mean arterial pressure (mmHg) and heart rate (beats/min), as mean ± SD BL = baseline. PE = priming+ephedrine, NPE = no priming no ephedrine. *P < 0.001 vs. BL.
accounted for the absence of both subjective and clinically adverse effects during the priming interval.

The onset time of muscle relaxants depends on the rate at which a pharmacologically effective concentration is achieved in the biophase; that is, at the neuromuscular cleft. In turn, this rate is influenced by several factors, such as potency of the drug, dose given, and cardiovascular status, namely CO and muscle blood flow [18]. Ephedrine, which produces an increase in both CO and muscle blood flow, reduces the onset time of rocuronium but not vecuronium [19-21]. Besides ephedrine, induction agents such as etomidate and ketamine, which maintain CO and BP, accelerate the onset of neuromuscular block and improve intubating conditions when used in association with rocuronium [22,23].

The use of ephedrine to increase the onset time of cisatracurium was previously investigated. Albert et al. studied 30 patients anesthetized with sufentanil and propofol who were randomly divided into two groups to receive ether ephedrine 70 μg/kg saline three seconds before propofol [9]. Tracheal intubation was performed two minutes after the administration of cisatracurium 0.15 mg/kg. The frequency of excellent intubating conditions was higher after ephedrine (86.6%) than after saline (40%) injection. In the present study, tracheal intubation was attempted after only one minute. The dose of ephedrine and cisatracurium was the same. Although the tracheas of all patients receiving both priming dose and ephedrine were successfully intubated, there were no significant differences in the rate of successful intubation between Groups E and NPE. The discrepancy with what was observed by Albert et al. [9] may explain the shorter interval between cisatracurium administration and the attempt at endotracheal intubation. We intentionally chose an interval of one minute instead of two to mimic a more relevant clinical scenario.

Ephedrine in doses of 70, 140, 210, and 260 μg/kg is effective in the prevention of hypotension following induction of anesthesia with propofol [20,24]. The administration of ephedrine 70 μg/kg is associated with a reduction in the onset time of rocuronium [9,18,19,25]. Such a dose has the additional advantage of avoiding increases in HR and MAP, which may be detrimental in patients with limited cardiac reserves [9,18,19,25]. Larger doses of ephedrine (eg, 210 μg/kg) induce a statistically significant increase in MAP and HR during induction of anesthesia [10,20]. Ezri et al. [19] showed that ephedrine 70 μg/kg was sufficient to promote a sustained increase in CO despite the absence of tachycardia and elevated MAP versus baseline. This apparent discrepancy is explained by the weak sympathomimetic effect of ephedrine that produces venoconstriction to a greater degree than arterial constriction, causing redistribution of blood centrally, improving venous return, and, hence, increasing CO [12]. The mild beta- and alpha-1 action that accounts for the increase in HR and MAP are observed with higher doses [12]. The observations of Ezri et al., therefore, support the hemodynamic hypothesis of action of ephedrine in promoting the improved intubating conditions that we observed. No significant increase in HR or MAP following the 70 μg/kg administration was noted.

The rationale for combining the priming principle with ephedrine is based on the partial occupancy of the cholinergic receptors by the priming dose and the acceleration by ephedrine of the residual receptor occupancy once the intubating dose of neuromuscular blocker is administered, hence, further reducing the time interval to clinically acceptable intubating conditions.

In a previous study, ephedrine in combination with propofol significantly improved clinical intubating conditions at 30 seconds following priming with rocuronium when compared with priming without ephedrine, ephedrine without priming, and propofol alone [10]. While the clinical utility of reducing acceptable intubating conditions at 30 seconds might be questionable in the case of rocuronium, the long onset of cisatracurium might be effectively and safely reduced by the combination of priming and ephedrine [26,27]. Moreover, the association between ketamine and priming with rocuronium also improves clinical intubating conditions at 30 seconds after an intubating dose of rocuronium, in line with the hemodynamic hypothesis of action of ephedrine [28].

Our trial intentionally evaluated only clinical intubation conditions, without monitoring the degree of neuromuscular blockade. Kopman et al. showed that excellent intubating conditions did not correspond to comparable effects on twitch response measured at the adductor pollicis [29].

Several limitations of the study exist. Cardiac output was not measured, yet other work [9] has clearly shown that the very same dose of ephedrine used in the present study promotes an increase in CO that is strictly correlated with the reduction in onset time. The effects of ephedrine on muscular blood flow have not been measured so far in the clinical setting. Hence, differences in regional blood flow promoted by ephedrine may only be speculated. A synergistic effect rather than simply additive effect of ephedrine and priming cannot be excluded.

In conclusion, low-dose ephedrine significantly improved clinical intubating conditions at 60 seconds following low-dose priming with cisatracurium compared with priming without ephedrine, ephedrine without priming, and the combination of sham priming and sham ephedrine. There were no adverse effects related either to ephedrine or priming.

References


