



SCIENTIFIC ARTICLE

Influence of Hypnotics on Cisatracurium-induced Neuromuscular Block. Use of Acceleromyography

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Abstract

Background and objective: Different drugs, including hypnotics, may influence the pharmacodynamic effects of neuromuscular blockers (NMB). The aim of this study was to evaluate the influence of propofol and etomidate on cisatracurium-induced neuromuscular blockade.

Method: We included 60 patients, ASA I and II, undergoing elective surgery under general anesthesia in the study and randomly allocated them into two groups, according to their hypnotic drug: G1 (propofol) and GII (etomidate). Patients received intramuscular (IM) midazolam (0.1 mg.kg⁻¹) as premedication and we performed induction with propofol (2.5 mg.kg⁻¹) or etomidate (0.3 mg.kg⁻¹), preceded by fentanyl (250 mg) and followed by cisatracurium (0.1 mg.kg⁻¹). The patients were ventilated with 100% oxygen until obtaining a reduction of 95% or more in the adductor pollicis response amplitude, with subsequent laryngoscopy and tracheal intubation. Neuromuscular function was monitored by acceleromyography. We evaluated the onset of action of cisatracurium, tracheal intubation conditions, and hemodynamic repercussions.

Results: The mean time and standard deviations of cisatracurium onset were: G1 (86.6 ± 14.3 s) and GII (116.9 ± 11.6 s), with a significant difference (p < 0, 0001). Intubation conditions were acceptable in 100% of G1 and 53.3% of GII patients (p < 0.0001).

Conclusion: Induction of neuromuscular blockade with cisatracurium was faster, with better intubation conditions in patients receiving propofol compared to those receiving etomidate, without hemodynamic repercussions.

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Introduction

The onset of action of a neuromuscular blocker (NMB) may be defined as the interval between the end of its injection and maximum depression of a peripheral muscle response, with adductor pollicis the most frequently used in clinical practice¹. This time interval can be influenced by factors, such as hypnotics and those associated with neuromuscular block monitoring (e.g., time to muscle stabilization, control, and frequency of stimulation used)¹⁻⁵. Among drugs used in anesthesia, some hypnotics have certain peculiarities and different mechanisms, with may interfere with muscle relaxation induced by nondepolarizing neuromuscular blockers (NDNMB)^{5,6-8}. Among benzylisoquinolinic neuromuscular blockers, cisatracurium has a highly selective affinity to the motor endplate, which may explain the absence of autonomic ganglion and vagal effects and the low potential for histamine release. Cisatracurium has a high neuromuscular blocking potency, which contributes to its slow onset of action⁹.

The aim of this study was to evaluate comparatively the influence of propofol and etomidate on cisatracurium-induced neuromuscular block.

Method

Randomized clinical trials were conducted after approval by the Medical and Research Ethics Committee and signed informed consent. The study included female patients, physical status ASA I-II, scheduled for elective surgery under general anesthesia with tracheal intubation and mechanical ventilation. Exclusion criteria were patients with neuromuscular, renal or hepatic diseases, electrolyte and acid-basic changes, history of gastroesophageal reflux disease, use of drugs interacting with neuromuscular blockers, and those with indicative signs of difficulty to perform the laryngoscopic and tracheal intubation maneuvers (Mallampati III and IV).

Sample size calculation was based on a previous study by Muñoz et al.¹⁰ in which the times of rocuronium onset of action were 48.2 ± 1.85 and 51.2 ± 13.8 seconds with propofol and etomidate used respectively as hypnotic agents for induction of anesthesia, representing a percentage difference of 6% between drug associations. Other authors¹¹ also reported 4.6 ± 0.3 minutes for the onset of cisatracurium (ZED95) in anesthesia with propofol used as hypnotic. There were no studies in the literature comparing the association of etomidate and cisatracurium; thus, we assumed an expected difference of 6% by the criteria reported above. Considering a significance level of 5% and a test power of 80%, based on the parameters described above, the required size was calculated at $n = 60$.

Therefore, 30 subjects were included into two groups according to the hypnotic drug used for anesthesia induction using SAS 9.1 software: propofol (Group I, $n = 30$) and etomidate (Group II, $n = 30$). In both groups, we administered cisatracurium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$) during 5 seconds, corresponding to two times the ED95. Premedication consisted of IM midazolam ($0.1 \text{ mg} \cdot \text{kg}^{-1}$), 30 minutes before anesthesia induction. In the operating room, a peripheral vein was catheterized for hydration and drug administration. Anesthesia induction was achieved with fentanyl ($250 \mu\text{g}$), followed by propofol ($2.5 \text{ mg} \cdot \text{kg}^{-1}$) or etomidate ($0.3 \text{ mg} \cdot \text{kg}^{-1}$) and cisatracurium ($0.1 \text{ mg} \cdot \text{kg}^{-1}$). We used a mask with 100% oxygen to ventilate

patients, performing laryngoscopic and tracheal intubation maneuvers after obtaining 95% reduction or more in the control response amplitude of the thumb adductor muscle.

We use the cardioplex in DII lead, pulse oximetry, capnography, and noninvasive blood pressure for continuous monitoring. Neuromuscular transmission monitor (Acceleromyograph - TOF-GUARD) was used for neuromuscular block evaluation. Before induction, supramaximal stimuli (0.1 Hz) were applied for five minutes to stabilize the control response, using surface electrodes on the wrist, in the ulnar nerve pathway. We placed an acceleration transducer (piezoelectric) on the thumb distal phalanx of the monitored limb and a temperature sensor on the thenar region skin. During and after anesthetic induction, neuromuscular function was monitored continuously with isolated stimuli until achieving complete neuromuscular block. Adductor pollicis responses shown in bar graphs and digital numbers were stored on a memory card and subsequently reproduced in a compatible computer, previously programmed. Data tracings of muscular responses (Figure 1) showed: 1) hypnotic injection; 2) cisatracurium injection; 3) cisatracurium onset time (tracheal intubation).

The evaluation included: 1) cisatracurium onset time (time interval [sec] between starting cisatracurium injection and obtaining $\geq 95\%$ reduction in the amplitude response of adductor pollicis muscle); 2) clinical condition of tracheal intubation according to the scores proposed by Viby-Mogensen et al.², considering the following variables: difficult laryngoscopy (degree), vocal cords position, and reaction to tracheal tube insertion (Table 1) - intubation was considered acceptable when all variables were considered excellent or good and unacceptable when at least one variable was considered poor; 3) hemodynamic parameters (mean arterial pressure [MAP] and heart rate [HR]), measured immediately before anesthesia induction (T0), after anesthesia induction, before laryngoscopy and tracheal intubation (M1), and 1 minute after intubation (M2).

We used Student's t-test for statistical analysis of patients' characteristics and neuromuscular blocker onset of action, Fisher's exact test to evaluate tracheal intubation conditions and MANOVA and Mann-Whitney tests to assess hemodynamic parameters. A level of 5% ($p < 0.05$) was considered significant. The software used for analysis was SAS version 10.2.

Results

There was no significant difference between groups regarding age, weight, and ASA physical status (Table 2).

The time to onset action of cisatracurium was significantly lower ($p < 0.0001$) in Group I (86.6 ± 14.3 seconds) than in Group II (116.9 ± 11.6 seconds).

Tracheal intubation clinical conditions were considered acceptable (excellent or good) in all patients in Group I and acceptable in 16 (53.3%) and unacceptable (poor) in 14 (46.7%) patients in Group II, with a significant difference between groups ($p < 0.0001$). Laryngoscopy was considered excellent in all patients of both groups. Regarding vocal cords position and movement, all patients in Group I had excellent scores and one patient in Group II had a good score (open

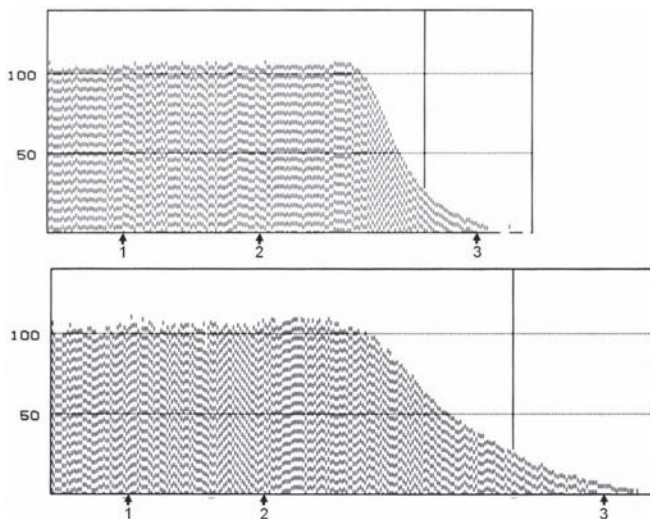


Figure 1 Adductor Pollicis Response. Group I propofol (upper tracing); Group II - etomidate (lower tracing). 1 -hypnotic injection; 2 - cisatracurium injection; 3 - cisatracurium onset of action (tracheal intubation time).

Table 1 Assessment of Tracheal Intubation Conditions.²

Variable	Acceptable		Unacceptable
	Excellent	Good	
Laryngoscopy	Easy	Reasonable	Difficult
Vocal cords	Open	With motion	Closed
Cough	Absent	Mild	Vigorous

Acceptable: all variables are excellent or good; unacceptable: at least one of the variables is poor.

Table 2 Patients' Demographic Characteristics.

	Group I (propofol)	Group II	p
Age (years)*	44.6 ± 7.1	43.6 ± 7.7	0.627
Weight (kg)*	62.9 ± 8.6	62.6 ± 5.6	0.684
Physical status (ASA I/II)**	20/10	20/10	

* Data expressed as mean ± SD; ** number of patients; Student's t-test.

Table 3 Cardiovascular Parameters (Mean ± SD).

	MAP (mm Hg)			HR (bpm)		
	M0	M1	M2	M0	M1	M2
Group I	86.0 ± 9.4	78.9 ± 9.6	83.8 ± 11.1	78.5 ± 11.8	74.8 ± 11.8	75.4 ± 10.2
Group II	83.5 ± 8.5	78.7 ± 7.6	86.4 ± 8.6	79.3 ± 13.0	75.0 ± 12.0	80.1 ± 13.4
p	0.13	0.92	0.17	0.78	0.93	0.13

MANOVA and Mann-Whitney tests.

vocal cord with movement). Vigorous cough occurred in 14 patients in Group II and mild cough in five patients in Group I, with a significant difference between groups ($p < 0.0001$).

Mean values and standard deviations of cardiovascular parameters (MAP and HR) in both groups are shown in Table 3. There was significant difference between groups at different time points. In both groups, the changes in MAP and HR over time showed no significant difference ($p = 0.98$ and 0.50 , respectively).

Discussion

In clinical practice, the desirable characteristics in selecting a neuromuscular blocker are hemodynamic stability, rapid onset of action, and ability to provide adequate muscle relaxation to enable laryngoscopy and tracheal intubation¹¹. Cisatracurium is one of the 10 isomers of atracurium, with ED_{95} of 0.05 mg.kg^{-1} in balanced anesthesia, without cardiovascular effects due to histamine release, which is an important advantage over atracurium^{11,12}.

This study evaluated the onset of action, tracheal intubation conditions, and hemodynamic repercussions of cisatracurium with a dose corresponding to two ED_{95} , using propofol or etomidate as hypnotic agents during anesthesia induction, as installation of neuromuscular block and tracheal intubation conditions are influenced by effects intrinsic to the hypnotic agent used in anesthesia.

Etomidate, due to its hemodynamic profile and ability to maintain the degree of muscle perfusion, may contribute to a shorter latency of NDNMB⁵. Our data showed that in all patients of both groups, the dose of atracurium (0.1 mg.kg^{-1}) provided excellent laryngoscopy, with vocal cords completely relaxed. However, regarding clinical conditions for intubation, statistical analysis showed significant difference between groups, which may be attributed to the occurrence of vigorous cough in 47% of patients in Group II.

Propofol has been widely used as inducing agent, with some advantages over other hypnotics, such as etomidate and thiopental¹³⁻¹⁶. The lower incidence of cough seen in the propofol group (two patients with mild cough) compared to the etomidate group (vigorous cough in 14 patients) may be due to the greater depressant action of propofol on pharyngeal-laryngeal reflexes^{15,17-18}.

Propofol is able to decrease the reactivity of larynx and pharynx muscle tone and enable tracheal intubation without neuromuscular blockers^{8,13,16-20}. However, there are no reports in literature concerning its direct action on vocal cords. In vitro experiments showed that propofol at doses similar to those clinically used acts on the neuromuscular junction and reduces the channel open time of the muscle nicotinic receptors^{6,7}.

Excellent and good scores are considered indicative of clinically acceptable conditions for tracheal intubation, but it depends on the skill of the professional performing tracheal intubation, depth of anesthesia, and degree of neuromuscular block^{1,11}. Thus, it is difficult to assess the pharmacodynamic properties of neuromuscular blockers considering only the intubation conditions. Furthermore, it is important to note that when evaluating tracheal intubation, monitoring the adductor pollicis is questioned, as this muscle sensitivity to NDNMB is not parallel to that of muscles involved in laryngoscopy and tracheal intubation²¹. Therefore, in this study we adopted the guidelines recommended by Fuchs-Buder et al.¹ to avoid factors that might interfere with neuromuscular block and to allow the adequate assessment of cisatracurium pharmacodynamic characteristics.

We assessed onset of action using acceleromyography, considering a reduction of $\geq 95\%$ in the response amplitude of the adductor pollicis to isolated stimuli, time at which we performed laryngoscopy and tracheal intubation maneuvers.

Factors related to neuromuscular block monitoring also interfere with the blockade time^{1,22}. Experimental studies have shown that the onset of action of NDNMB is inversely proportional to the times for muscle response stabilization and stimulus frequency, as both periods are shorter and greater during stabilization and stimulus frequency is applied to achieve the response prior to NMB administration^{1,23,24}. The most likely explanation is that the series of contractions induced by nerve stimulation when maintained for a prolonged time increases muscle blood flow and results in higher drug amount in the stimulated muscle. Another explanation is that the high frequency stimulation may lead to neurotransmitter depletion at the stimulation site, with consequent shortening of latency and increased degree of neuromuscular block^{25,26}.

In this study, the onset of action of cisatracurium was significantly lower in the propofol group than in the etomidate group (86.6 ± 14.3 vs $116, 9 \pm 11.6$ s). These results differ from those described by Bluestein et al.¹¹, who evaluated the effects of propofol as a hypnotic agent and cisatracurium at varying doses and different times for tracheal intubation. The authors reported that cisatracurium (0.1 mg.kg^{-1}) had an onset of action of 4.6 minutes, and tracheal intubation conditions after 2 minutes of injection of NMB were good or excellent in 89% of patients. The use of higher doses of cisatracurium (equal to 3 or 4 ED_{95}) increased this percentage to 100% 1.5 min after NMB, and the onset of action was also shortened to 3.4 and 2.8 minutes with 3-4 ED_{95} , respectively.

Large doses of NMB ($>2\text{ED}_{95}$) may be used to reduce the time of onset of neuromuscular blockers and obtain rapid muscle relaxation for tracheal intubation. However, it has drawbacks, such as a greater risk of cardiovascular effects, besides prolonged blockade^{11,27,28}.

Although one of the adverse effects of propofol is reduced cardiac index and systemic vascular resistance with consequent hypotension²⁹, there were no significant changes in the hemodynamic parameters of both groups in the present study that could have influenced the neuromuscular block.

We conclude that the neuromuscular block with cisatracurium was faster and tracheal intubation conditions were better in patients receiving propofol compared to those receiving etomidate.

References

1. Fuchs-Buder T, Claudius C, Skovgaard LT et al. - Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand.* 2007;51:789-808.
2. Viby-Mogensen J, Engbaek J, Eriksson LI et al. - Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. *Acta Anaesthesiol Scand.* 1996;40:59-74.
3. Viby-Mogensen J, Ostergaard D, Donati F et al. - Pharmacokinetic studies of neuromuscular blocking agents: good clinical research practice (GCRP). *Acta Anaesthesiol Scand.* 2000;44:1169-1190.
4. Muir AW, Anderson KA, POW E - Interaction between rocuronium bromide and some drugs, used during anaesthesia. *Eur J Anaesthesiol.* 1994;11(Suppl 9):93-98.
5. Gill RS, Scott RPF - Etomidate short the onset time of neuromuscular block. *Br J Anaesth.* 1992;69:444-446.
6. Dilger JP, Liu Y, Vidal AM - Interactions of general anaesthetics with single acetylcholine receptor channels. *Eur J Anaesthesiol.* 1995;12:31-39.
7. Abdel-Zaher AO, Askar FG - The myoneural effects of propofol emulsion (Diprivan) on the nerve-muscle preparations of rats. *Pharmacol Res.* 1997;36(4):323-332.
8. Braga AFA, Braga FSB, Potério GMB et al. - The effect of different doses of propofol on tracheal intubating conditions without muscle relaxant in children. *Eur J Anaesthesiol.* 2001;18:384-388.
9. Savarese JJ, Lien CA, Belmont MR et al. - The clinical pharmacology of new benzyloisoquinoline-diester compounds, with special consideration of cisatracurium and mivacurium. *Anaesthesist.* 1997;46:840-849.
10. Munhoz DC, Braga AFA, Potério GMB - Influência do propofol e do etomidato no bloqueio neuromuscular produzido pelo rocurônio. Avaliação pela aceleromiografia. *Rev Bras Anestesiol.* 2002;52:673-680.
11. Bluestein LS, Stinson LW Jr, Lennon RL et al. - Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. *Can J Anaesth.* 1996;43:925-931.
12. Kirov K, Motamed C, Decailliot F et al. - Comparison of the neuromuscular blocking effect of cisatracurium and atracurium on the larynx and adductor pollicis. *Acta Anaesthesiol Scand.* 2004;48:577-581.
13. Taha SK, Siddik-Sayyid SM, Alameddine M et al. - Propofol is superior to thiopental for intubation without muscle relaxants. *Can J Anaesth.* 2005;52:249-253.
14. Erhan E, Ugur G, Gunusen I et al. - Propofol - not thiopental or etomidate - with remifentanyl provides adequate intubating conditions in the absence of neuromuscular blockade. *Can J Anaesth.* 2003;50:108-115.
15. Barker P, Langton JA, Wilson IG et al. - Movements of the vocal cords on induction of anaesthesia with thiopentone or propofol. *Br J Anaesth.* 1992;69:23-25.
16. Brown GW, Patel, Ellis FR - Comparison of propofol and thiopentone for laryngeal mask insertion. *Anaesthesia.* 1991;46:771-772.
17. Kallar MD - Propofol allows intubation without relaxants. *Anesthesiology.* 1990;73:A21.

18. Woods AW, Allam S - Tracheal intubation without the use neuromuscular blocking agents. *Br J Anaesth.* 2005;94:151-158.
19. Sneyd R, O' Sullivan E - Tracheal intubation without neuromuscular blocking agents: is there any point? *Br J Anaesth.* 2010;104:535-537.
20. Siddik-Sayyid SM, Taha SK, Aouad MT et al. - Propofol 2m/kg is superior to propofol 2mg/kg for tracheal intubation in children during sevoflurane induction. *Acta Anaesthesiol Scand.* 2011;55:535-538.
21. De Mey JC, De Baerdemaeker L, De Laat M et al. - The onset of neuromuscular block at the masseter muscle as a predictor of optimal intubating conditions with rocuronium. *Eur J Anaesthesiol.* 1999;16:387-389.
22. Braga Ade F, Munoz DC, Braga FS et al. - Influence of stimulus frequency on blockade induced by pancuronium and rocuronium: study on rats phrenic nerve-diaphragm preparation. *Acta Cir Bras.* 2007;22:446-450.
23. Curran MJ, Donati F, Bevan DR - Onset and recovery of atracurium and suxamethonium - induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. *Br J Anaesth.* 1987;59:989-994.
24. Girling KJ, Mahajan RP - The effect of stabilization on the onset of neuromuscular block when assessed using accelerometry. *Anesth Analg.* 1996;82:1257-1260.
25. McCoy EP, Mirakhur RK, Maddineni VR et al. - Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia. *Br J Anaesth.* 1995;76:29-33.
26. Saxena PR, Dhasmana KM, Prakash O - A comparison of systemic and regional haemodynamic effects of d-tubocurarine, pancuronium. and vecuronium. *Anesthesiology.* 1983;59:102-108.
27. Scott RPF, Savarese JJ, Basta SJ et al. - Clinical pharmacology of atracurium given high dose. *Br J Anaesth.* 1986;58:834-838.
28. Tullock WC, Diana P, Cook DR et al. - Neuromuscular and cardiovascular effects of high-dose vecuronium. *Anesth Analg.* 1990;70: 86-90.
29. Aun CST, Sung RYT, O'Meara ME et al. - Cardiovascular effects of intravenous induction in children: comparison between propofol and thiopentone. *Br J Anaesth.* 1993;70:647-653.