INTUBATING CONDITIONS AND INJECTION PAIN

- Cisatracurium or Rocuronium versus Rocuronium-Cisatracurium Combination -

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Summary

The present report evaluates the incidence of pain on intravenous injection and the condition of tracheal intubation at one minute following the administration of cisatracurium or rocuronium versus rocuronium-cisatracurium combination.

We studied 60 patients, ASA 1, aged 18-60 years, undergoing elective surgical procedures. The patients were randomly assigned to 3 groups who received intravenously either 0.15 mg/kg cisatracurium [2**ED**$_{95}$], 0,6 mg rocuronium [2**ED**$_{95}$] or a combination of 0.075 mg/kg cisatracurium [1**ED**$_{95}$], plus 0.3 mg rocuronium [1**ED**$_{95}$]. In the awake patients, the pain on injection of muscle relaxant was assessed on a four point scale (none, mild, moderate, severe). Administration of the relaxant was followed by 1-2 mg/kg of lidocaine and 2 mg/kg propofol. Oro-tracheal intubation was performed 60 seconds following the administration of the relaxant. The intubating conditions were assessed and rated as excellent, good, fair or poor.

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The administration of 2**ED**$_{95}$ cisatracurium resulted in poor intubating conditions at 60s, without pain on injection. In contrast, the administration of 2**ED**$_{95}$ rocuronium resulted in excellent or good intubating conditions at 60s associated with high incidence of pain on injection in most of the patients. However, the combination of 1**ED**$_{95}$ cisatracurium with 1**ED**$_{95}$ rocuronium provided similar intubating conditions to the 2**ED**$_{95}$ rocuronium alone, associated with a significantly less pain on injection.

Keywords: Rocuronium, cisatracurium, pain on injection, intubation.

Introduction

Rocuronium is a steroidal non-depolarizing muscle relaxant with a rapid onset of action which facilitates early tracheal intubation. However, it has a high incidence of severe pain following intravenous administration in the awake patients. In contrast, cisatracurium is a benzylisoquinolinium diester non-depolarizing muscle relaxant which does not induce pain on injection; however it has a slow onset of action.

The present report evaluates the incidence of pain on injection and the condition of tracheal intubation at one minute following the administration of cisatracurium or rocuronium versus rocuronium-cisatracurium combination.

Methods

After obtaining Hospital Ethics Committee approval and informed consent, we studied 60 patients, ASA 1, aged 18-60 years, undergoing elective surgical procedures at Sahel General Hospital (Beirut). No patient had any disease or metabolic abnormality known to alter neuromuscular transmission, or was receiving any drug that might interfere with neuromuscular function.

The patients were randomly assigned to 3 groups who received intravenously, before induction of general anesthesia, either 0.15 mg/kg^{-1} cisatracurium [2**ED**$_{95}$], 0.6 mg rocuronium [2**ED**$_{95}$] or a combination of 0.07 mg/kg^{-1} cisatracurium [1**ED**$_{95}$], plus 0.3 mg rocuronium [1**ED**$_{95}$]. The study was designed to be randomized and double-blinded. A randomization list was generated, and identical syringes containing each drug were prepared according to the list, by one personnel blinded to the study.

No premedication was given. ECG, pulse oximetry and noninvasive blood pressure were monitored in all patients. In the awake patient, 1-2 μg/kg^{-1} of fentanyl were administered intravenously, to be followed after 60s by the injection of the muscle relaxant over 20 seconds. The patients were observed and asked if they had pain at the injection site and were assessed on a four point scale (none, mild, moderate, severe), as showed in Table 1.

Table 1
Degree of pain: Assessment of pain during injection of muscle relaxant

Degree of pain	**Response**	**Pain score**
None	Negative response to questioning	0
Mild	Pain reported in response to questioning only, without any behavioral signs	1
Moderate	Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning	2
Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears	3

Administration of the relaxant was immediately followed by 1-2 mg/kg^{-1} of lidocaine and 2 mg/kg^{-1} propofol. Direct laryngoscopy and oro-tracheal intubation was performed 60 seconds following the administration of the relaxant. The intubating conditions were assessed by an anesthesiologist who was blinded to the study, and were rated as excellent, good, fair or poor as shown in Table 2.

Table 2
Assessment of intubating conditions

Intubating conditions laryngoscopy	
1- Excellent	vocal cords open, no coughing, easy laryngoscopy
2- Good	vocal cords moving, coughing with diaphragm, fair laryngoscopy
3- Poor	vocal cords closing clear coughing, diffilut laryngoscopy
4- Inadequate	vocal cords closed, severe coughing, laryngoscopy impossible

Statistical Analysis

Considering a 50% improvement in the intubating conditions and pain score to be clinically significant and with type I and type II errors of 5% and 10% respectively, a power analysis revealed that at least 20 patients are needed in each group. The student's t-test and Chi-square analysis were used for statistical analysis. Statistical significance was considered at $p < 0.05$.

Results

1. Demographic data

The demographic characteristics (age, weight, and sex distribution) were not statistically different among the three groups (Table 3).

Table 3
Patients characteristic, (mean ± SD)

	Cisatracurium (n = 20)	Rocuronium (n = 20)	Combinations (n = 20)
Age (yr)	41 ± 13	34 ± 13	35 ± 13
Sex: male/female	11/9	10/10	11/9
Weight (kg)	67.8 ± 8.3	64.5 ± 16.5	68.2 ± 8.1

2. Pain on injection

As shown in Table 4, cisatracurium produced no pain on injection in all patients. In contrast, rocuronium produced the highest reported pain

response; 90% of patients reported either moderate or severe pain. The administration of the mixture of cisatracurium and rocuronium was associated with a significant decrease of moderate and severe pain down to 25%.

Table 4

Assessment of pain during injection of muscle relaxant

Pain on injection	None	Mild	Moderate	Severe
Cisatracurium	20/20 (100%)			
Rocuronium		2/20 (10%)	8/20 (40%)	10/20 (5%)
Combination	12/20 (60%)	3/20 (15%)	4/20 (20%)	1/20 (5%)

3. Intubating conditions

Intubating conditions (IC) at 60s were all poor or inadequate in 18 out of 20 patients in the cisatracurium group. In contrast, when using rocuronium or the combination mixture (rocuronium/cisatracurium) the IC at 60s were recorded to be excellent or good in all patients (Table 5).

Table 5

Assessment of intubating conditions during 60s after muscles relaxant administration

Intubating conditions score	Excellent	Good	Poor	Inadequate
Cisatracurium	---	2/20 (10%)	8/20 (40%)	10/20 (5%)
Rocuronium	11/20 (55%)	9/20 (45%)	---	---
Combination	10/20 (50%)	10/20 (50%)	---	---

4. pH and osmolality

Measuring the pH of cisatracurium, rocuronium and the combination showed that the pH of rocuronium was 4.05 ± 0.02, cisatracurium 5.37 ± 0.03 and rocuronium – cisatracurium mixture 4.08 ± 0.03 (Table 6).

Table 6

Values of pH of the three groups

Groups	pH
Cisatracurium	5.37 ± 0.03
Rocuronium	4.05 ± 0.02
Combination	4.08 ± 0.03

Discussion

Our study shows that iv administration of cisatracurium 0.15 mg/kg^{-1} resulted after 60s in poor or inadequate intubating conditions in 90% of patients. In contrast, 0.6 mg/kg^{-1} rocuronium provided excellent or good intubations conditions in all patients. According to the "law of mass action", potency is a major determinant of the speed of action. The onset of neuromuscular block following the intravenous administration of muscle relaxants is inversely proportional to its potency[1]. This can explain the slow onset of cisatracurium whose ED_{95} is 0.3 mg/kg^{-1}.

Our study has also shown that in the awake state pain did not follow the intravenous administration of cisatracurium in any of the patients. In contrast, our report, as well as previous reports, have shown that the incidence of pain following the intravenous injection of rocuronium is very common. Incidence of pain-related withdrawal reactions up to 80% have been observed[2]. The intense pain caused by rocuronium has restricted its use before induction of anesthesia. The pathophysiological mechanisms that lead to this adverse effect are still unclear. Possible explanations include activation of nociceptors by the unphysiological osmolality or pH of the solution, or by the release of endogenous mediators, such as histamine or bradykinin[3-4].

Our study shows, that the mixture of one ED_{95} (0.075 mg/kg^{-1}) cisatracurium and one ED_{95} (0.3 mg/kg^{-1}) rocuronium provides intubating conditions after 60s comparable to those associated with the administration of $2ED_{95}$ of rocuronium. Also, the administration of the mixture was associated with a significant decrease of pain; 75% of patients reported none or mild pain. The mechanisms of the low incidence of pain on injection following the administration of the combination are unclear. It seems unlikely that pH is responsible for the pain on IV rocuronium injection since the rocuronium and the mixture have the same pH. Tuncali B et al.[4] showed that dilution of rocuronium up to 0.5 mg/mL with 0.9% NaCl, while conserving the same pH, was an effective method to prevent pain on injection. Peripheral veins are innervated with polymodal nociceptors that mediate the response to intravenous injection

of certain anesthetics that cause pain[5]. It is possible that rocuronium may stimulate these polymodal nociceptors, while adding cisatracurium may counteract the stimulation of these nociceptors. Our study showed that, the combinations of one ED_{95} (0.3 mg/kg^{-1}) of rocuronium with one ED_{95} (0.075 mg/kg^{-1}) of cisatracurium resulted in a significant decrease of pain on injection associated with significant improvement of intubating conditions.

A previous study showed that combinations of rocuronium and cisatracurium were synergistic[6]. In the same study, the results support the contention that combinations of structurally dissimilar neuromuscular-blocking drugs resulted in a potentiating effect. Naguib[7] and Meretoja et al.[8] showed respectively, that rocuronium-mivacurium and vecuronium-atracurium combinations produced synergistic effects. On the other hand, combinations of structurally similar neuromuscular-blocking drugs produce an additive response in humans[9-11].

In conclusion, the administration of $2ED_{95}$ cisatracurium, which is a benzylisoquinolinium diester non-depolarizing muscle relaxant, resulted in poor intubating conditions at 60s, without pain on injection. In contrast, the administration of $2ED_{95}$ rocuronium, which is a steroidal non-depolarizing muscle relaxant, resulted in excellent or good intubating conditions intubation at 60s associated with a high incidence of pain on injection in most patients. However, the combination of $1ED_{95}$ cisatracurium with $1ED_{95}$ rocuronium provided intubating conditions similar to the achieved by the $2ED_{95}$ rocuronium alone, associated with a significant decrease of pain on injection.

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