Effects of 2 mg.kg\(^{-1}\) of Intravenous Lidocaine on the Latency of Two Different Doses of Rocuronium and on the Hemodynamic Response to Orotracheal Intubation

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Summary: Vivancos GG, Klamt JG, Garcia LV – Effects of 2 mg.kg\(^{-1}\) of Intravenous Lidocaine on the Latency of Two Different Doses of Rocuronium and on the Hemodynamic Response of Orotracheal Intubation.

Background and objectives: Lidocaine potentiates the effects of neuromuscular blockers and attenuates the hemodynamic response to orotracheal intubation. The objective of the present study was to test the effects of lidocaine on the latency of two different doses of rocuronium and on the hemodynamic response to intubation.

Methods: Eighty patients were distributed in 4 groups: Groups 1 and 2 received 0.6 mg.kg\(^{-1}\) of rocuronium; patients in Group 2 also received 2 mg.kg\(^{-1}\) of lidocaine before intubation. Patients in Groups 3 and 4 received 1.2 mg.kg\(^{-1}\) of rocuronium; patients in Group 4 received additional 2 mg.kg\(^{-1}\) of lidocaine. The latency of the neuromuscular blockade was measured by acceleromyography. Hemodynamic evaluation was performed at baseline, immediately before, and 1 minute after orotracheal intubation (Oi).

Results: Statistically significant differences were not observed between the latency from 0.6 mg.kg\(^{-1}\) and 1.2 mg.kg\(^{-1}\) of rocuronium in patients who received lidocaine before intubation and those who did not. The latency in patients who received 0.6 mg.kg\(^{-1}\) of rocuronium with lidocaine was statistically similar to that of those who received 1.2 mg.kg\(^{-1}\) rocuronium independently of whether lidocaine was administered or not. Patients who did not receive lidocaine before induction showed the same increases in systolic, diastolic, and mean arterial pressure and heart rate after Oi, which was not observed in those patients who received lidocaine.

Conclusions: Intravenous lidocaine before anesthetic induction was capable of attenuating the hemodynamic response associated to Oi maneuvers, but it did not reduce the latency of the neuromuscular blockade produced by two different doses of rocuronium.

Keywords: Lidocaine; Neuromuscular Blockade, Neuromuscular Nondepolarizing Agents; Intubation, Intratracheal.

INTRODUCTION

Intravenous local anesthetics have been used during induction of general anesthesia to decrease hypertension and tachycardia secondary to orotracheal intubation (Oi) 1-4. Several authors demonstrated this protective effect of lidocaine when used alone or in association with beta-blockers 5,6, calcium channel blockers 7, and inhalational anesthetics 8. Attenuation of the hemodynamic response can be beneficial and prevent complications, especially in those with coronary ischemic disease 9. When systemic lidocaine is used it decreases airways reactivity being useful in patients with asthma 10-12, it decreases intraoperative anesthetic consumption 13,14, the blockade of the systemic inflammatory response secondary to surgery 15,16, postoperative pain 13,14,17, and favors early hospital discharge 18.

Systemic and epidural use of local anesthetics decreases the latency and increases the duration of neuromuscular blockers 19,21. The interaction of local anesthetics with preand post-synaptic nicotinic receptors in the neuromuscular junction explains this phenomenon 22-24. Rocuronium, a short-latency non-depolarizing neuromuscular blocker has been used for rapid-sequence intubation of patients as an alternative to succinylcholine 25. Even when used in high doses its latency is greater than that of succinylcholine 26.

High doses of rocuronium are recommended to shorten its latency, although it increases its duration. The objective of the present study was to test the effects of 2 mg.kg\(^{-1}\) of lidocaine on the latency of two doses of rocuronium and to determine whether the use of high doses of rocuronium is necessary when using lidocaine. This study also intended to confirm the protective effects of lidocaine regarding the hemodynamic response to Oi.

METHODS

After analysis and approval by the Ethics Committee of Hospital das Clínicas of Faculdade de Medicina de Ribeirão Preto, patients signed an informed consent. Eighty patients were selected for this study. Patients were randomly divided into four groups, according to the method described by Doig and Simp-
The following inclusion criteria were used: ages between 18 and 50 years, physical status ASA I or II, body mass index (BMI) between 18 and 27 kg.m⁻², absence of medication that could interfere with the neuromuscular blockade, absence of hepatic or renal dysfunction, and absence of neuromuscular disease. Patients in Groups 1 (Roc 0.6) and 2 (Lido + Roc 0.6) received 0.6 mg.kg⁻¹ of rocuronium and lidocaine was only administered in Group 2. In Groups 3 (Roc 1.2) and 4 (Lido + Roc 1.2), 1.2 mg.kg⁻¹ of rocuronium was used and lidocaine was administered only to patients in Group 4. When used, 2 mg.kg⁻¹ of 2% lidocaine was administered during 5 minutes before anesthetic induction. The standard technique of total intravenous anesthesia was used for general anesthesia. Midazolam 0.05 mg.kg⁻¹ was administered upon arrival to the operating room. Target-controlled infusion of propofol and continuous infusion of remifentanil were used. Anesthetic induction was achieved with a target dose of 4 µg.ml⁻¹ of propofol and infusion of 0.5 µg.kg⁻¹.min⁻¹ of remifentanil, both in 5 minutes. Rocuronium, whose dose varied according to the group, was the neuromuscular blocker used. Neuromuscular function was evaluated by a TOF Watch SX (Organon) monitor by accelerometry. Supramaximal stimulation of the ulnar nerve (60 mA) was performed, and contraction of the adductor pollicis muscle was evaluated in the contralateral arm to the venous cannulation. The monitor was installed upon arrival of the patient to the operating room. After induction and loss of consciousness, the device was calibrated via the automatic system of the monitor for detection of the supramaximal stimulus. After calibration, a simple stimulus was applied every second for 5 minutes until the signal stabilized. Whenever necessary, this time was prolonged. The signal was considered to be stable when the variation was smaller than 5% during 1 minute. The blocker was administered over 5 seconds and the time to determine latency was marked from the beginning of the injection on. Monitoring was through a simple 0.1-Hz stimulus until the answer of adductor pollicis was 5% of the initial response, at which time the latency time was recorded.

Patients were also evaluated through a parametric Dixtal 2010 monitor with a 5-lead electrocardiogram, non-invasive blood pressure through oscilometry, oxygen saturation through pletismography, capnography, and esophageal temperature. Hemodynamic variables, systolic, diastolic, and mean arterial pressure (mmHg), as well as heart rate (beats/min) were recorded on three moments: 2 minutes after the administration of midazolam (Baseline), immediately before intubation (before OI), and 1 minute after tracheal intubation (after OI).

The software Graphpad Prism 3.0 was used for the statistical analysis. Categorical variables (gender and physical status ASA) were described as proportions, and the Chi-square test was used for independent samples for intergroup analysis. Quantitative variables were described as mean ± standard deviation. The normality of distribution was tested for all variables in each group by the non-parametric Kolmogorov-Smirnov test. Analysis of variance (ANOVA) was used for intergroup comparisons with Newman-Keuls post-test for multiple comparisons. For intragroup comparisons of mean, systolic, and diastolic arterial pressure and heart rate, analysis of variance for repeated measurements with Newman-Keuls post-test for multiple comparisons was used. The level of critical significance was 5%.

### RESULTS

Regarding the demographic data, statistically significant differences were not observed among groups. Statistical significant differences were not observed for tenar temperature (Table I).

Figure 1 shows the mean and distribution of the latency values for all four groups. Significant differences were not observed between Groups 1 and 2 and Groups 3 and 4, i.e., addition of lidocaine did not decrease the latency of 0.6 mg.kg⁻¹ and 1.2 mg.kg⁻¹ of rocuronium. A statistical significant difference was observed when Group 1 was compared to Groups 3 and 4, i.e., the increase in dose from 0.6 mg.kg⁻¹ to 1.2 mg.kg⁻¹ decreased the latency time of rocuronium. A significant difference was not observed between Group 2 and Groups 3 and 4, i.e., the association of lidocaine and rocuronium at a dose of 0.6 mg.kg⁻¹

### Table I – Demographic Characteristics and Temperature in the Tenar Region

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.80 ± 9.76</td>
<td>31.55 ± 11.55</td>
<td>30.20 ± 9.74</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.00 ± 13.90</td>
<td>65.20 ± 14.72</td>
<td>61.10 ± 9.98</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 ± 0.11</td>
<td>1.68 ± 0.11</td>
<td>1.63 ± 0.08</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>22.98 ± 2.86</td>
<td>22.80 ± 2.60</td>
<td>22.65 ± 2.54</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (30%)</td>
<td>8 (40%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (70%)</td>
<td>12 (60%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Physical status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA I</td>
<td>20 (100%)</td>
<td>18 (90%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>ASA II</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral Temperature (°C)</td>
<td>34.22 ± 1.36</td>
<td>33.95 ± 1.02</td>
<td>34.54 ± 0.95</td>
</tr>
</tbody>
</table>

Group 1: 0.6 mg.kg⁻¹ of rocuronium; Group 2: 0.6 mg.kg⁻¹ of rocuronium + 2 mg.kg⁻¹ of lidocaine; Group 3: 1.2 mg.kg⁻¹ of rocuronium; Group 4: 1.2 mg.kg⁻¹ of rocuronium + 2 mg.kg⁻¹ of lidocaine.
produced a latency similar to that of the higher dose of rocuronium.

Figure 2 shows systolic (A), diastolic (B), and mean (C) arterial pressure and heart rate (D) of patients who did not receive lidocaine (Groups 1 and 3) and patients who received lidocaine before anesthetic induction (Groups 2 and 4). Intragroup comparison showed a statistically significant difference in mean values of the four variables before and after intubation (without lidocaine), with an increase in mean pressure and heart rate levels. In patients who received lidocaine (with lido), the levels of all variables before and after OI were statistically similar.

DISCUSSION

The systemic injection of lidocaine before OI is used in clinical practice in an attempt to reduce the cardiovascular response to manipulation of the airways. Hamaya and Dohi 28 demonstrated that the use of intravenous lidocaine is capable of attenuating the increases in heart rate and blood pressure after tactile stimulation of the airways. Yorumu et al. 1 demonstrated the prevention of the increase in heart rate after OI in patients who received systemic lidocaine. In the present study, an intragroup analysis was performed to detect differences in the mean levels of hemodynamic variables in three phases (baseline, before OI, and after OI). For this analysis, 80 patients were divided into two groups independently of the dose of rocuronium used, since rocuronium did not cause important hemodynamic changes, even in high doses 20. Patients who received lidocaine presented significant attenuation of tachycardia and they did not show increases in blood pressure after OI. In those patients the mean values of heart rate were statistically similar before and after OI. In patients who did not receive lidocaine, a significant increase in blood pressure levels and heart rate were observed. This effect was demonstrated even with the use of high doses of propofol and remifentanil in anesthetic induction which by themselves are capable of partially blocking this response 30,31. The degree of the blockade of coughing reflexes is associated with the plasma concentration of lidocaine. It is known that lidocaine has sedative and analgesic actions in the central nervous system 32-34, being used as an anesthetic adjunct during general anesthesia 13,14,17,18. Thus, central mechanisms of lidocaine are responsible for this blocking effect on coughing reflexes and attenuation of the hemodynamic response to OI.

To study the latency of rocuronium, we followed the principles described in “Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents ii: the Stockholm revision” 35. This review is a guide of the main care to guarantee the trustworthiness of the results in the study of neuromuscular blockers. Through these recommendations, the homogenous distribution of the patients in the study groups was possible.

The idea of reducing the latency of a neuromuscular blocker is clearly important when the anesthesiologist is facing the need of rapid-sequence intubation 36-37. The main indication of this procedure is the prevention of bronchoaspiration in patients in a full stomach, the so-called Mendelson Syndrome 18. Neuromuscular blockers more indicated for rapid sequence intubation are succinylcholine and rocuronium due to their lower latency 28. The interaction between local anesthetics and neuromuscular blockers is known and demonstrated in different models 19,23,24,39,40. Local anesthetics have a strong capability of inhibiting several subtypes of nicotinic receptors of acetylcholine, including muscular 22,41-43. The hypothesis that lidocaine could potentiate the neuromuscular blockade of rocuronium, decreasing its latency, was not demonstrated in the present study. The results were able to demonstrate statistical significance of the comparison among the latencies of two different doses of rocuronium, 0.6 mg.kg⁻¹ and 1.2 mg.kg⁻¹, which has been widely divulaged in the literature 39,44. Using the dose of 1.2 mg.kg⁻¹, indicated for rapid-sequence intubation, the latencies obtained were 47.40 seconds in the group that did not receive lidocaine, and 48.60 seconds in the group that received lidocaine, i.e., nearly identical. For the dose of 0.6 mg.kg⁻¹, despite the mean differences between Groups 1 (Roc 0.6) and 2 (Lido + Roc 0.6) of 59.30 and 55.30 seconds, respectively, statistically significant differences were not observed. Cardoso et al. 19 also did not observe differences in the latency of rocuronium 0.6 mg.kg⁻¹ when it was administered after lidocaine. Those results go against the results of Nonaka et al. 20 who demonstrated a 35%-reduction in the latency of vecuronium, from 174 to 115 seconds, after pre-treatment intravenous lidocaine, 1.5 mg.kg⁻¹. The explanation for the difference in the latencies of vecuronium and rocuronium has not been established. It is believed that the lower latency of rocuronium is related to its lower potency; therefore, when it is used in high doses an important gradient between the plasma and the biophase is generated leading to more rapid diffusion of rocuronium molecules for the neuromuscular junction 45,46. Pharmacokinetic differences between both blockers with a lower volume of distribution, decreased protein binding, and greater $K_{\text{w}}$ of rocuronium in relation to...
Figure 2

Lido: lidocaine; OI: orotracheal intubation.
Effects of 2 mg.kg\(^{-1}\) of intravenous lidocaine on the latency of two different doses of rocuronium and on the hemodynamic response to orotracheal intubation

Vecuronium could also explain the lower latency for the same reason above. It has been speculated that the lower latency of rocuronium is associated to the rapid occupation of 100% of nicotinic receptors due to the rapid diffusion of a large number of molecules of the anesthetic due to the excessively high gradient.\(^{45,46}\) This mechanism could hinder a greater reduction of the already low latency. The use of lower doses of rocuronium could detect a significant difference, since the gradient would be lower. In the present study, the latency of 0.6 mg.kg\(^{-1}\) of rocuronium (lower dose) associated with lidocaine (Group 2) was statistically similar to 1.2 mg.kg\(^{-1}\) with and without lidocaine (Groups 3 and 4, respectively). This result shows that the latency of the lower dose could be closer to that of the higher dose when using lidocaine, which does not demonstrate, but it could indicate a potentiation of the neuromuscular blocker by lidocaine. Another factor associated to this difference could be the muscle group involved. The adductor pollicis muscle is more sensitive to neuromuscular blockers than the diaphragm and laryngeal muscles.\(^{47-49}\) For example, in this more resistance musculature a larger absolute amount of nicotinic receptors needs to be blocked, and it is possible that in those muscle groups the reduction in latency with the administration of lidocaine could be detected due to the need of greater diffusion of anesthetic molecules. Yorukoglu et al. \(^1\) without monitoring the muscular blockade, compared intubation conditions of patients who received 0.6 mg.kg\(^{-1}\) of rocuronium with and without lidocaine with those who received succinylcholine. He demonstrated that conditions for OI after the use of lidocaine before rocuronium were comparable to those of succinylcholine over 60 seconds, which was not observed in patients who did not receive lidocaine.\(^1\) Although the neuromuscular blocker is not the only factor responsible for good intubation conditions, more adequate muscle relaxation in other muscles other than adductor pollicis could have contributed for this result. Intubation conditions after a low dose of rocuronium (0.3 mg.kg\(^{-1}\)) associated with lidocaine was compared to the conditions obtained after the administration of succinylcholine with similar results; however, intubation was performed in 90 seconds with the combination rocuronium-lidocaine, and 60 seconds with succinylcholine.\(^{50}\)

The present study has some limitations. Intubation and laryngoscopy conditions were not tested. It is possible that the use of lidocaine could have facilitated OI independently of the latency of rocuronium in the adductor pollicis. The latency of the neuromuscular blocker was not evaluated in other groups of muscles more resistant to neuromuscular blockers and whose relaxation could be involved in facilitating OI maneuvers is another limiting factor.

Thus, the results obtained allow the conclusion that 2 mg.kg\(^{-1}\) of lidocaine IV before anesthetic induction is capable of attenuating the hemodynamic response, i.e., tachycardia and hypertension associated with OI maneuvers. However, this dose of lidocaine is not capable of potentiating the effects of 0.6 mg.kg\(^{-1}\) and 1.2 mg.kg\(^{-1}\) of rocuronium neither decrease its latency, despite the latency of patients who received 0.6 mg.kg\(^{-1}\) being similar to that of patients who received 1.2 mg.kg\(^{-1}\) of rocuronium with or without lidocaine.
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EFEITO DA UTILIZAÇÃO DE 2 MG.KG\(^{-1}\) DE LIDOCAÍNA ENDOVENOSA NA LATÊNCIA DE DUAS DOSES DIFERENTES DE ROCURÔNIO E NA RESPONSA HEMODINÂMICA À INTUBAÇÃO TRAQUEAL

more effectively than lidocaine or salbutamol alone. Anesthesiology, 1998;89:862-868.


Resumen: Vivancos GG, Klamt JG, Garcia LV – Efecto de la Utilización de 2 mg.kg\(^{-1}\) de Lidocaína Endovenosa en la Latencia de dos Dosis Diferentes de Rocuronio y en la Resposta Hemodinámica a la Intubação Traqueal.

Justificativa y objetivos: La lidocaína potencia el efecto de los bloqueantes neuromusculares y atenua la respuesta hemodinámica a la intubación. El objetivo del presente estudio fue comprobar el efecto de la lidocaína sobre la latencia de dos dosis diferentes del rocuronio y sobre la respuesta hemodinámica a la intubación.

Método: 80 pacientes fueron distribuidos en 4 grupos: los dos Grupos 1 y 2 recibieron 0,6 mg.kg\(^{-1}\) de rocuronio, siendo que los del...
Grupo 2 recibieron también 2 mg.kg-1 de lidocaína antes de la inducción; los dos Grupos 3 y 4 recibieron 1,2 mg.kg-1 de rocuronio siendo que los del Grupo 4 recibieron 2 mg.kg-1 de lidocaína. La latencia del bloqueo neuromuscular se midió por medio de la aceleromiografía. La evaluación hemodinámica se hizo en el momento basal, inmediatamente antes y un minuto después de la IOT.

Resultados: No se encontró diferencia estadística significativa entre la latencia del rocuronio en las dosis de 0,6 mg.kg-1 y 1,2 mg.kg-1 en los pacientes que recibieron o no la lidocaína antes de la inducción. La latencia de los pacientes que recibieron rocuronio 0,6 mg.kg-1 con lidocaína fue estadísticamente igual a la de los pacientes que recibieron 1,2 mg.kg-1 de rocuronio, independientemente de la administración o no de lidocaína. Los pacientes que no recibieron lidocaína antes de la inducción, presentaron aumentos de los valores de presión arterial sistólica, diastólica y promedio, y de la frecuencia cardíaca después de la IOT, pero eso no se dio en los que recibieron la lidocaína.

Conclusiones: Así, la lidocaína por vía venosa antes de la inducción anestésica fue capaz de atenuar la respuesta hemodinámica asociada a las maniobras de IOT, pero no de reducir la latencia del bloqueo neuromuscular producido por dosis diferentes de rocuronio.

Descriptores: ANESTESICO, Local: lidocaína; COMPLICACIONES, Bloqueo neuromuscular, Intubación endotraqueal; FISIOLOGÍA, Transmisión neuromusculares.