Original Article

Epidural administration of ropivacaine and its effects on the pharmacodynamics of rocuronium: Randomized controlled trial. Interaction between ropivacaine and rocuronium

ABSTRACT

Background: Potentiation of neuromuscular blocking agents by local anesthetics has been described in various clinical and experimental studies. This study assessed the influence of epidural ropivacaine on pharmacodynamic characteristics of rocuronium.

Design: This was a prospective randomized clinical trial at the women's hospital, an university tertiary hospital in Brazil. Sixty-two patients underwent elective abdominal surgeries requiring general anesthesia.

Intervention: Patients were distributed into two groups: Group 1 (general anesthesia and epidural anesthesia) and Group 2 (general anesthesia). In Group 1, 0.2% ropivacaine at a dose of 40 mg (20 ml) was associated with 2 mg (2 ml) of morphine in a single epidural injection. The following parameters were assessed: clinical duration (DC_{25}) and time for recovery of the train-of-four (TOF) 0.9 ratio (T4/T1 = 90%) after an initial 0.6 mg/kg dose of rocuronium. The primary outcomes were DC_{25} and TOF 0.9 ratio (T4/T1 = 90%). Secondary outcomes were total propofol and remifentanil consumption.

Results: Values were presented as median and interquartile range. The results for DC_{25} and TOF 0.9 of rocuronium were, respectively, 41.5 35.0–55.0 (25.0–63.0) in Group 1 and 44.0 37.0-51.0 (20.0–67.0) in Group 2 ($P = 0.88$); 88.0 67.0–99.0 (43.0–137.0) in Group 1; and 80.0 71.0-86.0 (38.0–155.0) in Group 2 ($P = 0.83$). There was no significant difference between the groups, in terms of pharmacodynamic characteristics of rocuronium. Propofol consumption did not show any difference between the groups. However, remifentanil consumption was significantly lower in Group 1 ($P < 0.01$).

Conclusion: Epidural ropivacaine, in the dose studied, did not prolong the duration of rocuronium-induced neuromuscular blockade.

Trial Registry Number: ReBEC (ref: RBR-7cyp6t).

Key words: Anaesthesia; epidural; local anaesthetics; neuromuscular blocking agentes; rocuronium; ropivacaine

Introduction

The interaction between local anaesthetics (AL) and nondepolarizing neuromuscular blocking agents has been studied both experimentally and in clinical trials.[1-14] The currently common combination of general and regional

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anesthesia is aimed at improving the quality of intra- and postoperative analgesia. This interaction is further emphasized since the influence of local anesthetics on the pharmacokinetic and pharmacodynamic properties of neuromuscular blocking drugs has already been described in the literature with consequent clinical relevance.[5-9]

Nevertheless, none of these studies have assessed the interaction between ropivacaine, a local anesthetic known for its favorable cardiotoxic profile, and rocuronium, a neuromuscular blocking agent commonly used because of its short latency and specific antagonist available.[15,16] The purpose of the current study was to assess the influence of epidural ropivacaine on the duration of neuromuscular block produced by rocuronium.

Methods

The current study was approved (Ref: CAAE 50852714.7.0000.5404) by the Research Ethics Committee of the State University of Campinas School of Medicine, Campinas, São Paulo, Brazil (Chairperson: Prof R. M. S. Celeghini) on December 21, 2015. This is an open and randomized clinical trial [Figure 1 for study profile according to the Consolidated Standards of Reporting Trials. After a written informed consent term was obtained, 60 female patients, ASA I and II physical status, undergoing abdominal gynecological surgeries under general anesthesia associated or not with epidural block were included in the study. Exclusion criteria were prediction of difficult airway, neuromuscular, renal, and hepatic disorders; body mass index (BMI) higher than 30.0 or lower than 20.0 kg/m^2; fluid and electrolyte imbalance and acid–base disorders; use of drugs that interact with neuromuscular blocking agents; contraindication to epidural anesthesia; and history of hypersensitivity reaction to drugs used.

Study protocol

From a list of random computer-generated numbers, patients were distributed into two groups of 30 patients per group, according to anesthetic technique: Group 1 (epidural and general anesthesia) and Group 2 (general anesthesia).

The anesthetic procedures were performed by one of the anesthesiologists participating in the study, and data were collected by the main researchers.

All patients were fasted and premedicated with intravenous midazolam (2–3 mg), 5 min before the beginning of the

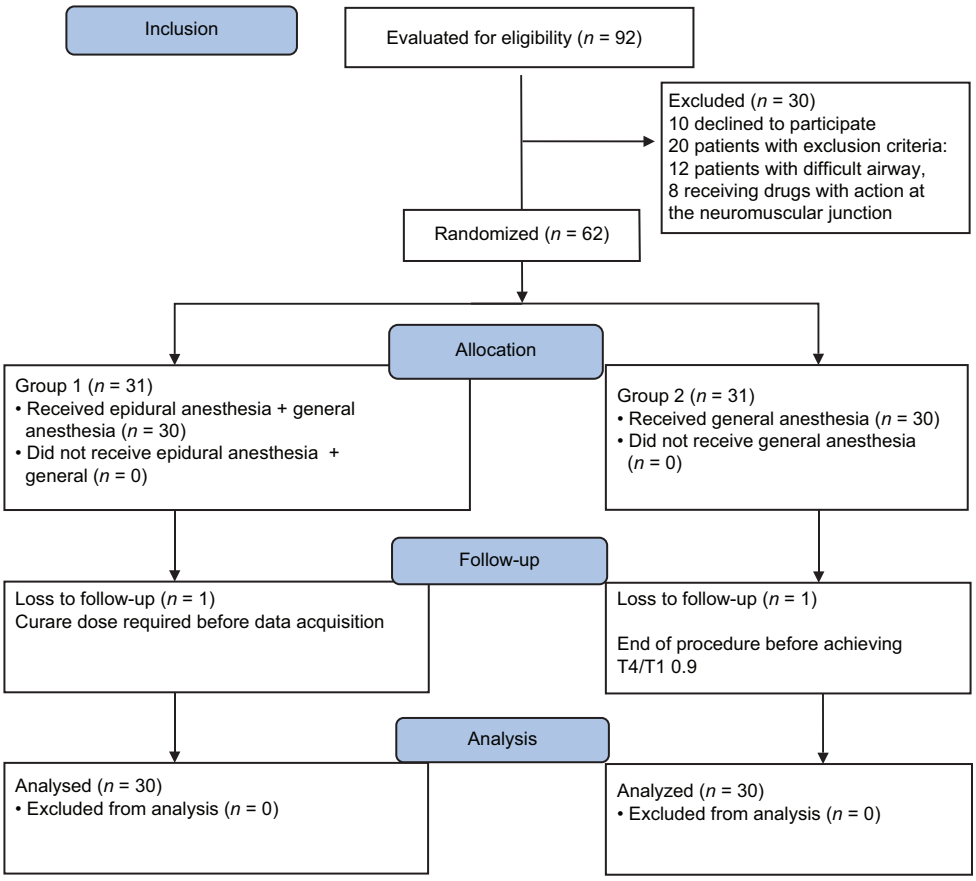


Figure 1: Flowchart of study steps

procedure. Continuous monitoring with cardioscopy in DII, pulse oximetry, noninvasive arterial pressure, capnography, and gas analyzer was performed. To evaluate neuromuscular block, a neuromuscular transmission monitor (Acceleromyographic train-of-four [TOF]-GUARD) was employed. Surface electrodes were placed over the course of the ulnar nerve at the wrist contralateral to the dominant hand of the patient; the acceleration transducer (piezoelectric) was fixed on the distal phalange of the thumb of the index limb and a temperature probe over the skin of the thenar region. A "control" muscle response was obtained using isolated supramaximal stimuli (1 Hz) during 3 min, for stabilization of the response. After the induction of anesthesia and administration of rocuronium, neuromuscular function was monitored continuously, with a train-of-four sequence–TOF. This study was based on the guidelines proposed by Fuchs-Buder, aimed at avoiding other factors that could interfere in the pharmacodynamics of neuromuscular blocking agents.[17]

In Group 1 patients, the epidural block was performed with the patients in the sitting position. After local infiltration with 2% lidocaine (2–3 mL), an 18-gauge Tuohy needle was introduced at the L3-4 interspace, using the midline approach and loss of resistance to air technique for identification of the epidural space, followed by an injection of 20 ml 0.2% ropivacaine (40 mg) associated with morphine (2 mg).

In both the groups, general anesthesia technique was induced with sufentanil (0.5 μg/kg) and propofol (2.0 mg/kg), followed by a dose of rocuronium (0.6 mg/kg) injected within 5 s. Patients received bag-mask ventilation with 100% oxygen until the performance of laryngoscopy and tracheal intubation. Anesthesia was maintained with continuous infusions of propofol (5–7 mg/kg/h) and remifentanil (0.05–0.15 μg/kg/min), titrated according to each 5% variation on the cardiac frequency and mean blood pressures values. Furthermore, an oxygen and nitrous oxide gas mixture (50%) was administered, and the expired fraction of N_2O was monitored, to provide amnesia since no monitor of anesthesia depth is available at our institution. Ventilatory parameters were adjusted to maintain expired CO_2 ($P_{ET}CO_2$) between 30 and 33 mmHg. Skin temperature on the tenar region was maintained between 30°C and 32°C.

Evaluation of neuromuscular block

The primary outcomes assessed were $DC_{25\%}$ (clinical duration in minutes) – the time interval between rocuronium injection and spontaneous recovery of 25% of the amplitude of the first TOF-evoked response (T1); time in minutes for spontaneous recovery of the TOF ratio (T4/T1 = 0.9). Secondary outcomes were total propofol consumption and total remifentanil consumption.

Statistical analysis

The sample size was estimated considering data from a previous study conducted by Suzuki *et al*.[7] Those authors observed that the time between the administration of neuromuscular blocking agent and spontaneous recovery of the T4/T1 ratio = 0.9 was significantly longer ($P < 0.01$) in patients receiving local anesthetics by the epidural route, in comparison to those receiving only general anesthesia. Considering it clinically significant, a beta error = 20% (power = 80%) and alpha error = 5%, it was determined that sample size would be at least 28 patients per group.

For the data analysis, the Statistical Analysis System for Windows program version 9.2 was used. A comparison between categorical variables between both the groups was made with the Chi-square test. Numerical variables were described using minimum and maximum values and median and quartiles and were analyzed using the Mann–Whitney U-test. The level of significance adopted was 5% ($P < 0.05$).

Results

Of the 67 patients included and randomized for this study, five were excluded (two declined and three had some exclusion criterion) and 62 were enrolled and randomized between March 2015 and October 2017. One patient from each group was discontinued and excluded from the analysis (need of an additional dose of rocuronium before the data acquisition and end of the surgery prior to obtaining T4/T1 = 0.9); therefore, 60 patients were analyzed according to the protocol.

No significant differences in age, height, weight, and BMI were found between the groups [Table 1].

There was no significant difference between the groups in patient distribution relative to physical status (ASA) ($P = 0.42$), values of expired CO_2 ($P = 0.47$), and temperature ($P = 0.14$).

Surgical duration and propofol consumption did not show any difference between groups. However, remifentanil consumption was significantly lower in Group 1 ($P < 0.01$) [Table 2].

A comparative analysis also did not show a statistically significant difference between the groups regarding DC25 ($P = 0.88$) and TOF = 0.9 ($P = 0.83$) [Table 3]. Graphs 1 and 2 (boxplots) illustrates the analysis of values observed for these variables.

Table 1: Physical characteristics of patients: Weight, height, and body mass index in Groups 1 and 2

Variables	Groups	Means	SD	Median	IQR [xx-yy]	*P*
Age (years)	1	40.9	7.7	43.0	35.0-46.0 [26.0-58.0]	0.70
	2	40.6	11	40.0	32.0-48.0 [17.0-63.0]	
Weight (kg)	1	73.1	10.5	72.0	66.0-81.0 [52.0-90.0]	0.139
	2	69.1	11.2	79.0	58.0-79.0 [52.0-89.0]	
Height (cm)	1	161.4	6.0	161.0	158.0-165.0 [151.0-176.0]	0.428
	2	160.2	6.8	160.0	154.0-165.0 [152.0-178.0]	
BMI (kg/m^2)	1	27.0	3.7	28.0	25.9-30.0 [20.0-30.0]	0.209
	2	28.0	5.0	25.9	23.0-30.0 [20.0-30.0]	

*Mann-Whitney U-test. SD: Standard deviaton; IQR: Interquartile range; BMI: Body mass index

Table 2: Patient characteristics in relation to the variables surgical duration, total dose of propofol and remifentanil in Groups 1 and 2

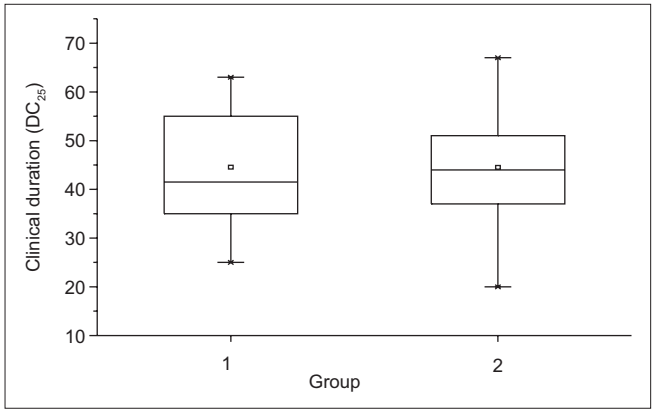
Variables	Groups	Means	SD	Median	IQR [xx-yy]	*P*
Surgical duration (min)	1	128.5	29.4	128.0	102.0-150.0 [73.0-200.0]	0.15
	2	116.4	32.8	118.5	90.0-138.0 [60.0-195.0]	
Propofol dose (mg)	1	927.7	301.9	954.5	700.0-1100.0 [330.0-1893.0]	0.83
	2	930.3	386.4	829.9	1206.0-356.3 [356.3-1698.0]	
Remifentanil dose (μg)	1	574.0	367.3	550.5	300.0-760.0 [0.0-1300.0]	<0.001
	2	972.6	479.7	160.0	660.0-1340.0 [27.0-2000.0]	

*Mann-Whitney U-test. SD: Standard deviaton; IQR: Interquartile range

Table 3: Clinical duration and time for recovery of TOF=90% in Groups 1 and 2

Variables	Groups	Means	SD	Median	IQR [xx-yy]	*P*
DC_{25} (min)	1	44.6	11.3	41.5	35.0-55.0 [25.0-63.0]	0.88
	2	44.5	10.7	44.0	37.0-51.0 [20.0-67.0]	
T4/T1 0.9 (min)	1	87.4	23.6	88.0	67.0-99.0 [43.0-137.0]	0.83
	2	82.3	21.2	80.0	71.0-86.0 [38.0-155.0]	

*Mann-Whitney U-test. SD: Standard deviaton; IQR: Interquartile range; DC: Clinical duration; TOF: train-of-four



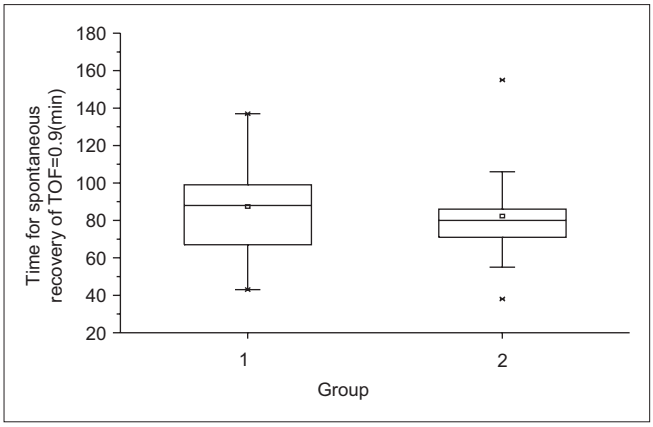
Graph 1: Boxplots – Clinical duration in Groups 1 and 2. (x-axis: Group; y-axis: Clinical duration DC25)

Discussion

Although an interaction between local anesthetics and neuromuscular blocking agents has been described in the literature,[1-14] the results of the current study have shown that epidural administration of ropivacaine did not significantly alter the clinical duration and time for spontaneous 90% recovery in the T4/T1 ratio of rocuronium-induced neuromuscular block. These results are contrary to the findings of other authors who described potentiation of neuromuscular block produced by different neuromuscular blocking agents in patients.[5-8]

In contrast to findings observed in our study, the results of other studies may be attributed to the use of higher local anesthetic concentrations than those used in this study, in which ropivacaine was administered in analgesic concentrations (0.2%), implying a lower total mass of ropivacaine, and consequently, a lower plasma concentration of local anesthetic. Thus, the concentration of ropivacaine at the NMJ may have been insufficient and might explain the lack of influence on pharmacodynamic variables of rocuronium.

Furthermore, characteristics inherent to drugs studied may justify these differences. In a series of experimental studies, it was observed that different local anesthetics, including racemic bupivacaine, levobupivacaine, and lidocaine, interact with neuromuscular blocking agents at the neuromuscular junction and may have a pre- and postsynaptic action.[2,3,11-13] Nevertheless, this interaction and potentiation of rocuronium-induced neuromuscular block in diaphragm preparations of rats exposed to ropivacaine may be explained only by a presynaptic action of local anesthetics, shown by a decrease in the amplitude and frequency of miniature end-plate potentials.[2] In addition, ropivacaine has stereoselective properties, characterized by the predominance of sensory fibers in relation to motor fibers.[15]



Graph 2: Boxplots –Time for spontaneous recovery of train-of-four = 0.9 in Groups 1 and 2. (x-axis: Group; y-axis: Recovery time (train-of-four 0)

Mechanisms of this interaction and its clinical implications, however, have still not been fully investigated. It has been described that local anesthetics have a multifactorial action at the neuromuscular junction that may involve depressed conduction of the presynaptic motor fiber, inhibiting ACh release during nerve stimulation, binding to different specific ACh sites, resulting in desensitization of receptors, temporary occlusion of nicotine receptors, stabilization of the postjunctional membrane, and interference with the excitation-contraction coupling mechanism of the skeletal muscle fiber.[2,13,18]

This mechanism may convey an interaction of lower clinical relevance, with the use of analgesic concentrations in particular. Even in those studies that had statistically significant results,[5-7] the increase in rocuronium-induced neuromuscular block found may be of limited clinical relevance. Nevertheless, it is likely that we will be challenged by clinical settings where many clinical conditions and drugs used in the perioperative period, such as calcium blocking channels or halogenated agents, interact simultaneously compromising the neuromuscular transmission.

In addition, we observed that remifentanil consumption in Group 1 was shown to be significantly lower than in the group that did not receive epidural anesthesia. Thus, epidural ropivacaine, in the concentration and dose used, might be effective at increasing the quality of surgical analgesia, although our study was not powered to assess this finding.

It is also known that opioids have no activity at the neuromuscular junction and do not interact with neuromuscular blocking agents. It may be inferred that this finding had no influence on the pharmacodynamic characteristics of rocuronium.

In this study, although epidural ropivacaine did not increase the duration of rocuronium-induced neuromuscular block in the 2 DE95 dose, the interaction between local anesthetics and neuromuscular blocking drugs is described. Confirmation of this interaction is of the utmost importance. Therefore, more frequent monitoring of the effects of neuromuscular blocking agents is recommended, particularly when these drugs are used simultaneously or in any situation in which the margin of safety of neuromuscular junction is compromised. In those situations, patients undergoing general anesthesia combined with epidural block may have more common complications that are related to a higher degree and duration of neuromuscular blockade, with a higher risk of postoperative residual block (curarization).

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Nil.

Conflicts of interest
There are no conflicts of interest.

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