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Original contribution

Neostigmine injected 5 minutes after low-dose rocuronium accelerates the recovery of neuromuscular function

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Abstract

Study Objective: To determine whether neostigmine 5 minutes after 0.4 mg/kg rocuronium accelerates reversal.

Design: Prospective, randomized, comparative open-label study.

Setting: Operating room.

Patients: 60 ASA physical status I and II patients, aged 18 to 65 years.

Interventions: Patients received 0.4 mg/kg rocuronium during nitrous oxide (N_2O)-propofol-opioid anesthesia. Reversal of neuromuscular blockade was achieved with neostigmine, either at 0.03 mg/kg or 0.05 mg/kg intravenously (IV), together with glycopyrrolate administered 5 minutes after relaxant and compared with spontaneous recovery. Onset, depth, and duration of neuromuscular block, as well as recovery of train-of-four (TOF) to 0.8 and 0.9 were evaluated.

Main Results: Times to achieve TOF ratios of 0.8 and 0.9 were significantly shorter when 0.03 mg/kg or 0.05 mg/kg neostigmine was administered 5 minutes after administration of rocuronium (20.2 ± 5 min and 22.6 ± 5.9 min or 17.8 ± 4.8 min and 19.4 ± 5.1 min, respectively) compared with controls (36.2 ± 8.5 min and 39.0 ± 8.7 min; $P < 0.01$). Duration to spontaneous T1 25% recovery after rocuronium was 15.5 ± 6.5 min versus 9.3 ± 2.3 min and 7.7 ± 1.6 min in the treatment groups ($P < 0.01$). Recovery index (T1 from 25% to 75%) was significantly shorter after neostigmine (7.1 ± 2.4 min and 5.7 ± 4.0 min) versus controls (13.3 ± 8.3 min; $P < 0.01$). Speed of reversal did not differ significantly between IV neostigmine doses of 0.03 mg/kg or 0.05 mg/kg.

Conclusion: Neostigmine accelerates recovery when administered 5 minutes after injection of IV rocuronium 0.4 mg/kg.

1. Introduction

Muscle relaxants are routinously administered at induction of anesthesia to achieve smooth intubation of the trachea. Schlaich et al. reported that without muscle

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relaxants after remifentanil/propofol administration, intubating conditions were poor in 40% of patients; adding reduced doses of rocuronium to this regimen improved intubating conditions significantly [1]. Although the rapid onset and short effect of the depolarizing neuromuscular blocking agent, succinylcholine, is still unmatched, anesthesiologists are concerned about its side effects. Cardiovascular side effects, myalgia, masseter rigidity, and possibly hyperkalemia render it less preferable [2-4]. High-dose rocuronium has a reasonably short onset and sugammadex allows the timely termination of neuromuscular blockade [5,6]. As an alternative, low-dose rocuronium and early reversal with anticholinesterases such as neostigmine may help to shorten the duration of relaxation suitable for short surgical procedures [1,7].

The purpose of the study was to investigate rocuronium-induced neuromuscular block and determine its duration to complete recovery when neostigmine is given soon after injection of muscle relaxant.

2. Materials and methods

The Ethics Committee of the Innsbruck Medical University granted approval of the study. Written, informed consent was obtained from all patients, and the study was conducted according to the guidelines for "good clinical research practice" [8]. Sixty patients undergoing surgical intervention in general anesthesia were investigated. Tracheal intubation was achieved with intravenous (IV) rocuronium 0.4 mg/kg according to the manufacturer's recommendations for most patients undergoing intubation within two minutes. Patients were randomly allocated to three equal groups using Microsoft Excel hazard function (Microsoft, Redmond, WA, USA). In Group 1 (n = 20), reversal of neuromuscular block was achieved with neostigmine 0.03 mg/kg + glycopyrrolate 0.007 mg/kg IV; in Group 2 (n = 20) it was achieved with neostigmine 0.05 mg/kg + glycopyrrolate 0.01 mg/kg IV. Group 3 (n = 20) was used as the control group, with spontaneous recovery from neuromuscular block. Doses of neostigmine 0.03 mg/kg and 0.05 mg/kg were reported to safely antagonize rocuronium block [9].

Patients who were ASA physical status I or II, age 18 to 65 years, with a body mass index (BMI) of between 18 and 28 kg/m^2, and scheduled for elective surgery with the need for tracheal intubation were enrolled in the study. Exclusion criteria included emergency surgery, patients with neuromuscular diseases or known allergy to muscle relaxant, those taking medication interfering with muscle relaxant action, or those with a history of renal or liver impairment. In case of discontinued intervention, the next consecutive patient was enrolled according to study protocol.

During anesthesia, end-tidal CO_2 ($ETCO_2$) was measured by infrared spectroscopy using the side stream sampling method (F-CU5 Anesthesia Monitor; GE Healthcare, Ltd., Little Chalfont, UK) and maintained between 30 and 40 mmHg. Body temperature was measured with a thermistor thermometer module (F-CU5 Anesthesia Monitor; GE Healthcare, Ltd.) as part of routine care and kept between 36.5°C and 37°C using Bair Hugger warming devices (Arizant, Inc., Eden Prairie, MN, USA).

For neuromuscular monitoring, the Datex electromyograph (EMG; Relaxograph; GE Healthcare, Ltd.) was used to obtain the evoked compound EMG of the adductor pollicis muscle. Neuromuscular block was assessed by train-of-four (TOF) stimulation of the ulnar nerve at the wrist (two Hz every 20 sec, 200 microsec duration). Five Ag/AgCl electrodes were placed: two for ulnar nerve stimulation two cm apart, two for measurement of adductor pollicis muscle activity (thenar) two cm apart, and one for reference (hypothenar).

Calibration was performed after induction of anesthesia but prior to administration of the muscle relaxant. For each patient, onset time for maximal twitch depression of T1 (first twitch of TOF), clinical duration until 25% recovery of T1, recovery index (T1 from 25% to 75%), and time from injection of rocuronium to TOF-ratio of 0.8 and 0.9 were determined, allowing either spontaneous or induced recovery.

Premedication consisted either of midazolam 7.5 mg orally or piritramide 7.5 to 15 mg combined with atropine 0.5 mg intramuscularly (IM) 30 to 60 minutes before the patient was brought to the operating room. Anesthesia was induced by fentanyl one to two μg/kg and propofol two to three mg/kg and maintained with propofol infusion at 4 to 6 mg/kg/hr and 60% to 70% nitrous oxide (N_2O) in oxygen (O_2). Additional doses of fentanyl one μg/kg were given if indicated. Normothermia and normocarbia were maintained throughout the operation.

After induction of anesthesia and calibration of the Datex Relaxograph, 0.4 mg/kg rocuronium was given IV as a bolus over 5 seconds followed by neostigmine, either 0.03 mg/kg or 0.05 mg/kg, 5 minutes later. The third group was allowed to recover spontaneously. Neuromuscular response was recorded until recovery from block to a TOF ratio of 0.9.

2.1. Statistical analysis

Statistical analysis was performed with the SPSS for Windows 12.0 statistical software program (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used for screening of normal distribution. Mean values were compared using either analysis of variance (ANOVA) with Bonferroni correction at the 5% significance level or Kruskal-Wallis test in the three groups. Differences between two groups were calculated using the Least Significant Difference Method and the Mann-Whitney-U test. Results were deemed significant at a P-value < 0.05.