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Epidurally administered mepivacaine delays recovery of train-of-four ratio from vecuronium-induced neuromuscular block

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Background. The aim of this study was to examine the efficacy of epidurally administered mepivacaine on recovery from vecuronium-induced neuromuscular block.

Methods. Eighty patients were randomly assigned to one of two study groups. They were either given epidurally a bolus of 0.15 ml kg^{-1} of mepivacaine 2%, followed by repetitive injections of 0.1 ml kg^{-1} h^{-1} throughout the study, or were not given epidurally. General anaesthesia was induced and maintained with fentanyl, propofol and nitrous oxide. Neuromuscular block was induced with vecuronium 0.1 mg kg^{-1} and monitored using acceleromyographic train-of-four (TOF) at the adductor pollicis. Patients in each treatment group were randomized to receive neostigmine 0.04 mg kg^{-1} at 25% recovery of the first twitch of TOF or to recover spontaneously to a TOF ratio of 0.9. The effect of epidural mepivacaine on speed of spontaneous and facilitated recovery of neuromuscular function was evaluated.

Results. The time from administration of vecuronium to spontaneous recovery to a TOF ratio of 0.9 was significantly longer in the epidural mepivacaine group [105.4 (14.2) min] as compared with the control group [78.5 (9.1) min, $P<0.01$]. Neostigmine administered at 25% of control in T1 shortened recovery from neuromuscular block, however the time required for facilitated recovery to a TOF ratio of 0.9 in the epidural group was significantly longer than that in the control group [7.6 (1.6) min *vs* 5.8 (2.1) min, $P<0.01$].

Conclusions. In clinical anaesthesia, it should be recognized that epidurally administered mepivacaine delays considerably the TOF recovery from neuromuscular block.

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Local anaesthetics impair neuromuscular transmission[1–6] and augment the effect of neuromuscular blocking agents.[7 8] However, the effect of local anaesthetics injected into the epidural space and absorbed into the systemic circulation on neuromuscular function has not fully been elucidated. Only two clinical trials evaluating neuromuscular effects of epidurally administered local anaesthetic are reported with inconsistent results. Toft and colleagues[9] reported that epidural bupivacaine prolonged clinical duration of atracurium in adult patients, whereas Taivainen and colleagues[10] showed that epidural bupivacaine had no effect on recovery time from vecuronium-induced neuromuscular block in children. Therefore, this study was designed to determine the influence of mepivacaine administered into the lower thoracic epidural space on spontaneous and pharmacologically augmented recovery from vecuronium-induced neuromuscular block at the thenar muscle. In particular, we questioned whether the effect of mepivacaine would differ between recovery of T1 height and that of the train-of-four (TOF) ratio or not.

Methods

After approval of the protocol by the Hospital Ethics Committee, 80 adult female patients consented to

participate in this study. Patients were ASA physical status I or II, 27–57 yr of age undergoing elective gynaecological surgery with combined epidural and general anaesthesia. None of the patients had neuromuscular, hepatic and renal disorders, or were taking any drug known to interact with neuromuscular blocking agents. Patients whose BMI was $\geq$25 or $<$18.5 were also excluded from the study.

Patients were assigned based on computer-generated randomization numbers into one of four study groups. They were either given epidurally repetitive injections of mepivacaine throughout the study (epidural group, n=40), or were not given (control group, n=40). Moreover, patients in each treatment group were randomized to receive neostigmine during recovery (facilitated recovery group, n=20) or to recover spontaneously to a TOF ratio of 0.9 (spontaneous recovery group, n=20).

All patients were premedicated with midazolam 0.04–0.06 mg kg^{-1} i.m. 45 min before the induction of anaesthesia. On arrival at the operating room, all patients were monitored with ECG, non-invasive blood pressure and pulse oximetry. An i.v. infusion of acetated Ringer's solution 8–10 ml kg^{-1} h^{-1}was started via a cannula in the right forearm. With the patients in right lateral decubitus position, epidural punctures were performed at the Th12–L1 intervertebral space after local infiltration of 2–3 ml of mepivacaine 0.5% using a median approach with 17-gauge Tuohy needle and the loss-of-resistance technique with saline. After identification of the epidural space, a 19-gauge epidural catheter was inserted through the needle and introduced 5 cm cephalad. Immediately after placement of the catheter, all patients were given 1 ml of mepivacaine 1% epidurally as a test dose. Two minutes later, the patients of the epidural group received a bolus of 0.15 ml kg^{-1} of mepivacaine 2% for epidural anaesthesia, followed by 0.1 ml kg^{-1} of mepivacaine 2% every hour. The patients of the control group received no drugs into the epidural space throughout the study.

General anaesthesia was induced with fentanyl 2–4 μg kg^{-1} and propofol 2.5 mg kg^{-1} while patients received 100% oxygen through an anaesthesia facemask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was maintained with nitrous oxide 67% in oxygen, a propofol infusion 4–8 mg kg^{-1} h^{-1} and supplemental fentanyl as clinically indicated. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R™ (Nihon Kohden, Tokyo, Japan). Rectal temperature was monitored using Mon-a-Therm™ (Mallinckrodt, Anesthesia Products Inc., St Louis, USA) and patients' temperature was maintained at $>$36°C using a warming mattress, blanket (Thermacare™ and Medi-Therm II™, Gaymer Industries, Inc., NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded every 15 s throughout the experiment using a surface probe attached in acceleromyographic unit and kept at $>$32°C.

After having obtained stable depth of anaesthesia, the ulnar nerve was stimulated at the wrist with square-wave, automatically detected supramaximal stimuli of 0.2 ms duration, delivered in a TOF mode at 2 Hz every 15 s and contraction of the ipsilateral adductor pollicis muscle was measured using acceleromyography (TOF Guard™, Organon NV, Turnhout, Belgium). After the control TOF stimuli were administered for at least 20 min and evoked responses had been stable, the first twitch (T1) of TOF and TOF ratio measured at the end of control stimulation was regarded as the baseline value. All patients received vecuronium 0.1 mg kg^{-1} i.v. When T1 recovered to 25% of baseline, patients of the facilitated recovery group received neostigmine 0.04 mg kg^{-1} and atropine 0.02 mg kg^{-1} for reversal. Patients of the spontaneous recovery group were allowed to recover spontaneously. A TOF ratio of 0.9 normalized by the baseline TOF ratio[11] was monitored.

The following variables were measured or calculated: lag time (s) from the time of bolus injection of vecuronium to the beginning of depression of T1; onset time (min) from the injection of vecuronium to maximum depression of T1; maximum depression (%) of T1; duration (min) from the injection of vecuronium to spontaneous recovery of T1 to 25% of control (DUR25%); times (min) required for spontaneous and facilitated recovery of T1 from 25% to 75%; time (min) required for spontaneous and facilitated recovery to TOF ratios of 0.7 and 0.9 from T1 of 25% of control. All data were collected on a memory card and analysed on a desktop computer offline.

Even after the neuromuscular monitoring had been accomplished, epidural injection of mepivacaine was continued every hour in the epidural group and similarly, epidural analgesia was commenced in the control group. Immediately after the patients had awakened from general anaesthesia, the levels of epidural analgesia were assessed by the pinprick method.

Data are presented as mean (SD) [range]. Statistical analysis was performed using StatView software™ for Windows (SAS Institute, Cary, NC, USA). The unpaired Student's t-test was used for two group comparisons. A P-value of $<$0.05 was considered statistically significant.

Results

Ten patients (four patients in the control group and six patients in the epidural group) were excluded from analysis of results because the TOF ratio did not recover to 0.9, or T1 did not recover above 90% of control or exceeded 110% of control as a result of the baseline shift. Data of 70 patients were analysed in this study. Similar patients' demographics were found between the control group and the epidural group (Table 1). Lag and onset time after an administration of vecuronium did not differ between the groups (Table 2), and in all patients the complete