

## 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<sup>-1</sup> of mepivacaine 2%, followed by repetitive injections of 0.1 ml kg<sup>-1</sup> h<sup>-1</sup> 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<sup>-1</sup> 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<sup>-1</sup> 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.

*Br J Anaesth* 2007; **99**: 721–5

**Keywords:** anaesthetic techniques, epidural; anaesthetics local, mepivacaine; monitoring, neuromuscular function; neuromuscular block, vecuronium; neuromuscular transmission

Accepted for publication: July 10, 2007

Local anaesthetics impair neuromuscular transmission<sup>1–6</sup> and augment the effect of neuromuscular blocking agents.<sup>7–8</sup> 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<sup>9</sup> reported that epidural bupivacaine prolonged clinical duration of atracurium in adult patients, whereas Taivainen and colleagues<sup>10</sup> 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  $0.04\text{--}0.06\text{ mg kg}^{-1}$  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  $8\text{--}10\text{ ml kg}^{-1}\text{ h}^{-1}$  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  $0.15\text{ ml kg}^{-1}$  of mepivacaine 2% for epidural anaesthesia, followed by  $0.1\text{ ml kg}^{-1}$  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  $2\text{--}4\text{ }\mu\text{g kg}^{-1}$  and propofol  $2.5\text{ mg kg}^{-1}$  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  $4\text{--}8\text{ mg kg}^{-1}\text{ h}^{-1}$  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  $>36^{\circ}\text{C}$  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  $>32^{\circ}\text{C}$ .

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  $0.1\text{ mg kg}^{-1}$  i.v. When T1 recovered to 25% of baseline, patients of the facilitated recovery group received neostigmine  $0.04\text{ mg kg}^{-1}$  and atropine  $0.02\text{ mg kg}^{-1}$  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<sup>11</sup> 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 administration of vecuronium did not differ between the groups (Table 2), and in all patients the complete

**Table 1** Patients' characteristics. Data are shown as mean (SD). Spontaneous: spontaneous recovery, facilitated: facilitated recovery. No significant differences were seen between the groups

	Control group (n=36)		Epidural group (n=34)	
	Spontaneous (n=20)	Facilitated (n=16)	Spontaneous (n=16)	Facilitated (n=18)
Age (yr)	44.0 (9.1)	40.3 (6.2)	47.6 (9.3)	38.9 (7.1)
Weight (kg)	56.9 (9.5)	53.3 (4.8)	55.8 (6.6)	53.0 (6.7)
Height (cm)	156.8 (7.2)	156.3 (7.7)	157.0 (6.7)	161.0 (5.6)

**Table 2** Onset and duration of vecuronium-induced neuromuscular block. Data are shown as mean (SD) [range]. No significant differences were seen between the groups

	Lag (s)	Onset (min)	DUR25% (min)
Control group (n=36)	50.8 (14.5) [30–90]	2.0 (0.5) [2.0–3.3]	42.7 (6.1) [33.0–53.5]
Epidural group (n=34)	45.4 (13.0) [30–90]	2.0 (0.3) [2.0–3.0]	45.3 (11.9) [28.0–74.0]

neuromuscular block was obtained. The DUR25% did not differ between the groups (Table 2). Likewise, no significant difference was seen in the time until spontaneous and facilitated recovery of T1 from 25 to 75% between the groups (Table 3). However, the times until spontaneous and facilitated recovery from 25% of control in T1 to TOF ratios of 0.7 and 0.9 were significantly longer in the epidural than in the control group ( $P<0.01$ , Table 3). Therefore, an averaged total time from the administration of vecuronium until spontaneous recovery to a TOF ratio of 0.9 was significantly longer in the epidural mepivacaine group [105.4 (14.2) min,  $P<0.01$ ] compared with the control group [78.5 (9.1) min]. The TOF ratios, measured when T1 spontaneously recovered to 25, 50, 75 and 90% of control, were significantly lower in the epidural group than those in the control group ( $P<0.01$ , Table 4). The upper levels of postoperative epidural analgesia ranged between Th6 and Th10 in all patients.

## Discussion

The results of the present study show that epidurally administered mepivacaine significantly delayed not only spontaneous recovery but also facilitated recovery of the TOF ratio from vecuronium-induced neuromuscular block, while it did not influence the T1 recovery. In the epidural group, more TOF fade was observed at the same degree of the T1 recovery.

Non-depolarizing neuromuscular blocking agents-induced fade in muscular contraction under repetitive nerve stimulation is caused by a gradual reduction of acetylcholine release from the motor nerve terminals,<sup>12 13</sup> while depression of the twitch (e.g. T1) height is caused by block of postsynaptic acetylcholine receptors. Based on our results, it is likely that the clinical dose of epidurally administered mepivacaine may act primarily on the motor nerve terminals to gradually decrease presynaptic acetylcholine release during a TOF nerve stimulation and delay recovery of the TOF ratios. Local anaesthetics theoretically may interfere with neuromuscular transmission by inhibiting acetylcholine release<sup>1–3</sup> blockade<sup>4</sup> or modification<sup>5</sup> of acetylcholine receptor, or direct depression of muscle excitability.<sup>6</sup> Certainly, high concentrations of local anaesthetics can affect both pre- and postsynaptic functions in the neuromuscular junction.<sup>1 2</sup> Lidocaine can block the twitch tension in the concentration over 200  $\mu\text{g ml}^{-1}$ .<sup>14</sup> Even if 20 ml of lidocaine 2% is injected into the epidural space, peak plasma concentration of lidocaine reaches only 2.65  $\mu\text{g ml}^{-1}$ .<sup>15</sup> There are no available data that show the effective concentration of mepivacaine for neuromuscular blockade, however, it is likely that the clinical dose of mepivacaine cannot physically block postsynaptic transmission in the neuromuscular junction, although in low and clinical concentrations the primary site of action of local anaesthetics is at the motor nerve terminal.<sup>3</sup> Tapering in acetylcholine release from nerve terminals causes tetanic fade of muscle contraction without producing neuromuscular block in single twitches.<sup>1</sup> Therefore,

**Table 3** Comparative times for spontaneous and facilitated recovery. Data are shown as mean (SD) [range]. \* $P<0.05$  compared with the control group

	Spontaneous recovery		Facilitated recovery	
	Control group (n=20)	Epidural group (n=16)	Control group (n=16)	Epidural group (n=18)
T1 25–75%	22.1 (5.8) [14.0–30.0]	22.0 (6.8) [13.0–33.0]	2.8 (1.0) [2.0–4.5]	3.3 (1.7) [2.0–7.0]
T1 25%-TOF ratio 0.7	25.3 (8.2) [9.0–37.5]	37.4 (8.9) [27.0–63.2]*	2.6 (0.5) [2.0–3.0]	3.5 (0.9) [2.0–4.8]*
T1 25%-TOF ratio 0.9	35.9 (9.6) [19.0–53.2]	59.2 (12.5) [41.0–77.0]*	5.8 (2.1) [3.0–8.0]	7.6 (1.6) [5.0–10.7]*

**Table 4** The TOF ratios measured when the T1 spontaneously recovered to 25, 50, 75 and 90% of control. Data are shown as mean (SD) [range]. \* $P<0.05$  compared with the control group

%T1 of control	25%	50%	75%	90%
Control group (n=20)	0.18 (0.08) [0.10–0.39]	0.36 (0.10) [0.18–0.52]	0.57 (0.14) [0.30–0.74]	0.75 (0.12) [0.49–0.86]
Epidural group (n=16)	0.04 (0.08) [0–0.30]*	0.20 (0.08) [0.10–0.44]*	0.43 (0.09) [0.22–0.64]*	0.61 (0.07) [0.39–0.74]*

it seems reasonable to believe that the delayed recovery of the TOF ratio without delay in the T1 recovery observed in the present study was caused by a gradual decrease in the amount of transmitter release from nerve terminals during a TOF stimulation. Neuromuscular block caused by the combinations of local anaesthetics and neuromuscular blocking agents is only partially reversed by neostigmine, but effectively antagonized by 4-aminopyridine which is a selective  $K^+$  channel blocker and increases acetylcholine release from the motor nerve endings.<sup>8</sup> This supports the idea that local anesthetics primarily inhibit the presynaptic function in the neuromuscular junction. Open channel block of postsynaptic acetylcholine receptor by mepivacaine molecules may prolong recovery times of the TOF ratio.<sup>4</sup> If its mechanism would be mainly involved in the fading phenomenon of the present study, however, antagonism with neostigmine should open the channel frequently and augment the TOF fade irreversibly.

The highest level of epidural analgesia evaluated post-operatively was Th6. Therefore, there may be no direct blocking action of mepivacaine on the cervical and the upper thoracic spinal nerves in the epidural space. It is likely that mepivacaine, absorbed from the epidural space into systemic circulation and transferred to the neuromuscular junction of the forearm may act on the motor nerve terminals. Moreover, it is known that i.v. mepivacaine produces a marked decrease in tidal volume. The respiratory depression may be partly due to neuromuscular blocking action of mepivacaine; however, the major cause of respiratory depression is thought to be depressant action of mepivacaine on the central nervous system.<sup>7</sup> This central effect may influence activity in the nerves supplying skeletal muscle of the monitored arm.

The time to recover spontaneously to a TOF ratio of 0.9 was significantly longer in the epidural group than in the control group. Above a TOF ratio of 0.8, we cannot detect visually fade even in tetanic responses at the adductor pollicis muscle.<sup>16</sup> It is therefore recommended that neuromuscular function should be monitored objectively during combined general and epidural anaesthesia. Although there is a statistically significant difference in the time for antagonism to a TOF ratio of 0.9 between the epidural group and the control group, the difference is only 1–2 min and has only limited clinical significance. It is therefore reasonable that vecuronium-induced neuromuscular block should always be antagonized with neostigmine if no objective evaluation of residual curarization is undertaken.

We could not find the effect of mepivacaine on T1 recovery. However, Toft and colleagues demonstrated that epidural block with bupivacaine slowed down T1 recovery to 15% of control after an intubating dose of 0.5 mg kg<sup>-1</sup> atracurium (40 min in the control vs 46 min in the epidural group). Although bupivacaine was repeatedly administered every hour, the durations of action induced by supplemental doses of atracurium 0.15 mg kg<sup>-1</sup> were comparable between the control and the epidural group ( $\approx$  30 min).

The different effect of epidural bupivacaine between the initial dose and supplemental doses of atracurium was not explained in their article. In their study, a 50 Hz tetanic stimulation was given once at 20–30 min after the initial dose for measuring post-tetanic counts. It is known that tetanus-induced acetylcholine release from the motor nerve terminals displaces neuromuscular relaxant from the endplate and shortens the time of T1 recovery.<sup>17</sup> If the nerve terminals are inhibited by bupivacaine, even the tetanic stimulus may not cause sufficient acetylcholine release and accelerate T1 recovery. It was possible that T1 recovery was hastened only in the control patients after this tetanic stimulation and thus a difference in duration of action after the initial dose of atracurium could be seen between the control and the epidural groups. If the tetanic stimulation had not been applied, such a difference should not be observed like our present result. The fact that there was no difference in durations of action induced by supplemental doses of atracurium supports the idea. In another report, Taivainen and colleagues<sup>10</sup> investigated the effects of epidural bupivacaine on vecuronium-induced neuromuscular block in paediatric patients, however they found no significant difference in recovery time to a TOF ratio of 0.95, when compared with the control patients. It is well known that sensitivity to non-depolarizing neuromuscular block is much lower in children than adults because children have more muscle tissue and acetylcholine receptors in relation to their body weight than any other age group of patients.<sup>18</sup> Therefore, neuromuscular function in children may be also resistant to an interaction between non-depolarizing neuromuscular blocking agent and local anaesthetic.

In conclusion, epidurally administered mepivacaine delays significantly both spontaneous and facilitated TOF recovery from vecuronium-induced block. Anaesthesiologists should be aware of the interaction during combined general and epidural anaesthesia.

## Acknowledgement

This study was performed using the institutional fund.

## Funding

This study was funded by the Department of Anaesthesiology, Surugadai Nihon University Hospital, Tokyo, Japan.

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