J Anesth (2011) 25:716–720
DOI 10.1007/s00540-011-1209-1

ORIGINAL ARTICLE

Intraoperative reversal of neuromuscular block with sugammadex or neostigmine during extreme lateral interbody fusion, a novel technique for spine surgery

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Received: 7 June 2011 / Accepted: 29 July 2011 / Published online: 13 August 2011

Abstract
Purpose Extreme lateral interbody fusion (XLIF) is a method for stabilization of the lumbar spine. Intraoperatively, the surgeon identifies the lumbar nerve roots with a stimulator to prevent their injury. The objective of this study was to determine the extent to which shallow rocuronium-induced neuromuscular block must be intraoperatively reversed for reliable identification of nerve roots.
Methods General anesthesia (midazolam–propofol–sufentanil–oxygen/air/sevoflurane–rocuronium) was administered to all patients. Train-of-four (TOF) stimulation of the ulnar nerve at 15-s intervals and electromyographic response of the adductor pollicis muscle were used. During operation, the surgeon stimulated the lumbar nerve roots (5–10 mA) to identify their course. At the appearance of two twitches to the TOF stimuli, sugammadex (2 mg/kg) or neostigmine (0.04 mg/kg) was administered. When the response to nerve root stimulation appeared, the TOF ratio was recorded.
Results When the response to nerve root stimulation with 10 mA became detectable, the median (range) TOF ratios were 0.67 (0.50–0.81) and 0.65 (0.42–0.71) after sugammadex and neostigmine, respectively. Similarly, TOF ratios at the first detectable response to stimulation with 5 mA were 0.88 (0.67–0.93) and 0.83 (0.61–0.93). After sugammadex and neostigmine, the respective intervals until TOF ratio $\geq$0.90 were 2.0 (0.8–3.3) and 15.9 (7.3–28.8) min.
Conclusion Intraoperative reversal of shallow rocuronium-induced block with either sugammadex or neostigmine is an efficient method. For reliable detection of lumbar nerve roots with a stimulating current of 10 mA, the block should be reversed to a TOF ratio of at least 0.70. For a current intensity of 5 mA, the TOF ratio should reach 0.90.

Keywords XLIF · Rocuronium · Sugammadex · Neostigmine · Reversal · Neuromuscular block

Preliminary results were presented at the meeting: Euroanaesthesia 2011, Amsterdam, The Netherlands, June 11–14, 2011.

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Introduction

Traditionally, acetylcholinesterase inhibitors, for example neostigmine, are used for reversal of non-depolarizing neuromuscular block (NMB). However, neostigmine has numerous adverse effects and its action is not always reliable [1]. Compared with neostigmine, sugammadex offers faster and very consistent effects and, until now, very few adverse effects have been reported after its administration [2, 3]. Most often, reversal agents are administered at the end of anesthesia to prevent or treat

residual neuromuscular block. However, their use may also be warranted during some operations when the requirements for the depth of NMB markedly change with the phase of surgery.

Extreme lateral interbody fusion (XLIF) is a new method for operative stabilization of the lumbar spine [4, 5]. This type of surgery is performed retroperitoneally under general anesthesia in the lateral decubitus position and adequate neuromuscular block for good surgical access is obligatory. When adequate exposure of the lumbar spine is achieved, the surgeon identifies the course of lumbar nerve roots with a stimulator to minimize the risk of their injury. If the stimulating electrode is close to the nerve root, the triggered electromyographic (tEMG) response from the respective muscle can be recorded. During this phase of surgery, NMB must be minimal.

The main objective of the study was to determine the extent to which the NMB must be reversed for reliable identification of lumbar nerve roots. As a secondary objective, the time course of reversal after sugammadex or neostigmine was compared.

Materials and methods

After local ethics committee approval and obtaining informed consent, patients scheduled for XLIF under general anesthesia with tracheal intubation were studied. The exclusion criteria were ASA physical status more than 2, expected difficult tracheal intubation [6], and contraindication to the drugs used in the study. Patients using medication known to interfere with neuromuscular blocking agents (NMBAs) and those with severe renal, hepatic, metabolic, or neuromuscular diseases were also excluded.

Patients were randomly assigned to receive either sugammadex (SUG group) or neostigmine (NEOST group) during surgery for reversal of rocuronium block. A method of computer-generated random numbers with blockwise randomization was used to obtain balanced sample sizes in both groups.

Anesthesia

The patients were premedicated with diazepam 10 mg orally 1 h before the beginning of anesthesia. After 3-min preoxygenation, the anesthesia was induced with midazolam (1–2 mg), sufentanil (0.2–0.3 μg/kg), and propofol (2 mg/kg). Rocuronium (0.6 mg/kg) was used to facilitate endotracheal intubation. The endotracheal tube was connected to a closed "low-flow" anesthetic breathing circuit. The lungs were mechanically ventilated with 40% oxygen maintaining end-tidal carbon dioxide tension between 4.7–5.0 kPa and sevoflurane concentration at 1.7%, corresponding to 1.0 times the minimum alveolar anesthetic concentration. Boluses of sufentanil 5–10 μg were administered when necessary.

Neuromuscular block monitoring

This study complied with good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents [7]. The neuromuscular transmission (NMT) module of the AS/3^{TM} Anesthesia Monitor (Datex-Ohmeda, Helsinki, Finland) was used, with the NMT monitoring system connected to the patient before induction of anesthesia. After careful skin preparation of the right distal forearm, five skin EMG monitoring electrodes (H124, Kendall) were applied over the ulnar nerve and adductor pollicis muscle as appropriate. The forearm was immobilized in supination on a splint. The skin temperature was maintained above 34°C throughout the study period by wrapping the arm in cotton wool. After induction of anesthesia, but before administration of rocuronium, the NMT monitor was calibrated using the automatic start-up-procedure. We used train-of-four (TOF) assessed at 15-s intervals by stimulation of the ulnar nerve with four rectangular impulses at 2 Hz, duration 0.2 ms, and supramaximal current. The evoked electromyographic response of the adductor pollicis muscle was monitored and the following NMB values were measured for all patients:

1. TOF ratio at which the first reliable response to lumbar nerve root stimulation with 10 and 5 mA could be detected; and
2. time interval from injection of the reversal agent (at TOF count = 2) to TOF ratio $\geq$ 0.9.

Surgery

After induction of anesthesia and setting-up the NMT monitoring, the patient was turned into the right lateral decubitus position with a wedge under the lumbar region (jack-knife position). The surgeon introduced recording needle electrodes into the respective muscles of the left lower extremity. The adductor magnus and brevis (root L2), adductor longus (root L3), rectus femoris (root L4), and tibialis anterior (root L5) muscles were used to record the evoked (triggered) electromyographic response (tEMG) to intraoperative lumbar nerve stimulation. The grounding and backward stimulating electrodes were placed into the subcutaneous tissue caudally from the ipsilateral iliac crest. An NIM-3 device (Medtronic, Sofamor Danek, Memphis, TN, USA) was used for neuromonitoring.

During the initial phase of surgery, sufficiently deep neuromuscular block was maintained with small top-ups of

rocuronium (2.5 mg) as necessary. When exposure of the lumbar spine was sufficient, the surgeon inserted a special retractor with firm fixation to the operating table. He started searching the course of the lumbar nerve roots with a stimulation electrode and current intensity 10 mA at 20-s intervals; the tEMG from the respective muscles was sought.

Spontaneous recovery from the NMB was allowed until two responses to TOF stimulation (TOF count = 2); at this point the reversal drug was injected. Sugammadex (2 mg/kg) was used in the SUG group; in the NEOST group, 0.04 mg/kg neostigmine with 0.02 mg/kg atropine was administered. The surgeon, but not the anesthesiologist, was initially blinded to the drug (sugammadex or neostigmine) used for reversal. When the TOF ratio recovered to at least 0.1 after administration of the reversal agent, the surgeon changed the interval of lumbar nerve stimulation from 20 to 5 s. When the first tEMG response to lumbar nerve stimulation was detected, the TOF ratio was noted and the stimulation current was reduced from 10 to 5 mA. Depending on the reversal drug, the anesthesiologist notified the surgeon either to maintain the 5-s interval (for sugammadex) or to switch over back to 20-s after 5 min from reversal administration (for neostigmine). Stimulation of the lumbar nerve roots was stopped when the tEMG response to 5 mA was detected. To determine the times when the TOF ratio was 0.7 and 0.9, respectively, the time trend of reversal was constructed; the relevant values were read from the graph.

We stopped the NMT monitoring after obtaining a TOF ratio above 0.9 in three consecutive measurements. At this point, it was clear that tEMG monitoring became reliable and if nerve roots were far from the blades of the retractor and intervertebral disc, the surgeon completely removed and replaced the disc using the Oracle cage (Synthes, Oberdorf, Switzerland). Until completion of the surgery, anesthesia was maintained without muscle relaxation. Before extubation at the end of anesthesia, TOF control measurement was done to confirm full recovery from the block.

Statistical analysis

For calculations, we used the statistical software package InStat v. 3.10 (GraphPad Software, San Diego, CA, USA). The required size of the SUG and NEOST groups was determined by performing a power analysis based on a previous study [8, 9]. As relevant condition, the time interval from injection of sugammadex or neostigmine to TOF ratio $\geq$0.9 was used. From the data (sugammadex 1.7 $\pm$ 0.7 min, neostigmine 13.3 $\pm$ 5.7 min), it was calculated that 10 patients in each group would be sufficient to find a significant difference of 6 min or more in the above described recovery time (0.05 two-sided significance level, 90% power).

The respective groups (NEOST vs. SUG) were compared by use of the unpaired Student *t* test, the Mann–Whitney test, or Fisher's exact test, as appropriate. The results were expressed as mean $\pm$ SD (95% CI) or median (range), or frequencies; *P* values less than 0.05 were considered statistically significant.

Results

Twenty-two patients were enrolled in the study and reliable NMT monitoring was set up for all of them. However, for one patient in the NEOST group, the appropriate lumbar nerve roots were not identified despite full recovery from NMB (TOF ratio = 0.99). This patient was excluded from the study. The resulting groups consisted of 11 and 10 patients in the SUG and NEOST groups, respectively. The patient characteristics are summarized in Table 1.

TOF ratios when the first tEMG response to stimulation of lumbar nerve roots was detected were similar in the SUG and NEOST groups (Table 2). Times from reversal

Table 1 Patient characteristics

	SUG group	NEOST group	*P* value
No (M/F)	11 (4/7)	10 (2/8)	0.635[a]
Age (year)	49 $\pm$ 8 (44–55)	52 $\pm$ 10 (45–59)	0.519[b]
Weight (kg)	76 $\pm$ 14 (67–85)	79 $\pm$ 11 (71–86)	0.659[b]
Height (cm)	172 $\pm$ 10 (165–179)	170 $\pm$ 7 (165–175)	0.582[b]
BMI (kg/m^2)	25.7 $\pm$ 3.8 (23.1–28.3)	27.3 $\pm$ 4.2 (24.3–30.3)	0.373[b]
ASA (1/2)	1/10	4/6	0.149[a]

Data are presented as mean $\pm$ SD (95% CI), or frequencies

BMI body mass index, *ASA* American Society of Anesthesiologists' Physical Status Classification

[a] Fisher's exact test

[b] Unpaired Student *t* test

Table 2 Variables describing use of sugammadex or neostigmine for intraoperative reversal of shallow rocuronium-induced neuromuscular block

	SUG group	NEOST group	*P* value[a]
Supramaximal current of TOF measurements (mA)	46 (29–70)	35 (23–70)	0.210
Duration of anesthesia (min)	120 (70–170)	135 (90–170)	0.203
Duration of surgery (min)	85 (50–160)	103 (65–160)	0.306
Difference in duration of anesthesia and surgery (min)	20 (10–35)	25 (10–50)	0.498
Intubation dose of rocuronium (mg)	45 (30–60)	45 (40–60)	1.000
Total dose of rocuronium (mg)	50 (30–75)	53 (40–70)	0.776
TOF ratio when first EMG response to 10-mA stimulation of lumbar nerve roots was detected	0.67 (0.50–0.81)	0.65 (0.42–0.71)	0.359
TOF ratio when first EMG response to 5-mA stimulation of lumbar nerve roots was detected	0.88 (0.67–0.93)	0.83 (0.61–0.93)	0.621
Interval from administration of the reversal drug to TOF ratio = 0.70 (min)	1.3 (0.5–2.0)	6.9 (4.3–20.5)	**<0.001**
Interval from administration of the reversal drug to TOF ratio ≥0.90 (min)	2.0 (0.8–3.3)	15.9 (7.3–28.8)	**<0.001**
TOF ratio before extubation	0.97 (0.92–0.99)	0.98 (0.91–0.99)	0.711

Data are presented as median (range)

Bold values indicate significant differences

[a] Mann–Whitney test

until return of TOF ratio to 0.70 and 0.90 were shorter in the SUG group. After intraoperative reversal of the NMB with either sugammadex or neostigmine, the remaining course of surgery and anesthesia were uneventful for all patients. No clinical events because of residual block or reappearance of the block occurred. Two patients in the NEOST group and one in the SUG group suffered from postoperative nausea at the time of transfer from the operating room.

During 6-week follow-up after surgery, one patient suffered from numbness of the left groin at the dermatome of the ilioinguinal nerve, probably because of injury of this nerve at the abdominal wall. No other signs of neurological deficit, including monitored nerve roots, were discovered.

Discussion

The requirement for a variable depth of NMB during XLIF surgery is a challenge for the anesthesiologist. From induction of anesthesia until obtaining adequate exposure of the lumbar spine, the NMB has to be deep enough to allow retroperitoneal access. Surgical exposure is then facilitated by insertion of a special retractor so that the operation field is clearly visible. At this point, the surgeon has to identify the course of lumbar nerve roots. This is done by searching for the nerve with a stimulation electrode and registering the tEMG response of the respective muscles of the lower limb. If the neuromuscular transmission is blocked by rocuronium, there is no muscle response even if the stimulating electrode is in the proximity of the nerve root.

On the basis of our results, recovery from the rocuronium block as high as TOF ratio 0.70 was necessary for identification of lumbar nerve roots with a stimulating current of 10 mA (Table 2). If an intensity of 5 mA was used, the triggered muscle response was detected at a TOF ratio of at least 0.90. When these TOF ratios were achieved, the ability to detect the lumbar nerves was identical irrespective of the reversal agent used. In general, tEMG thresholds for response below 5 mA indicate direct contact, between 5 and 10 mA they indicate close proximity (little but some soft tissue between the instrumentation and the nerve), and more than 11 mA indicates further distance from the intrapsoas nerves [10].

At the beginning of the study, the surgeon was blinded to the reversal drug used for a particular patient. However, because there was a substantial difference in the onset of effect between sugammadex and neostigmine, he gradually learned to guess which was injected.

There are alternatives to our technique. Adequate intubation conditions and surgical access can be achieved without administration of NMBA [11, 12]. However, the combination of deep anesthesia and placing the patient into a jack-knife position during XLIF can compromise the circulation seriously. Short-acting suxamethonium is not recommended in elective cases without increased risk of aspiration. Mivacurium or a lower dose of intermediate-acting relaxant may also be used. However, all NMBAs generally have variable effects and it is usually difficult to predict their clinical duration [13]. Without reversal, waiting for a spontaneous recovery may be time-consuming and can potentially prolong the surgery.

In contrast, when the reversal drug (either neostigmine or sugammadex) is administered with correct timing and dosage, recovery is accelerated. We observed no serious adverse effects after neostigmine but the variability of its action was substantial. Although TOF ratio 0.90 was reached during surgery for all patients in the NEOST group, for one patient the time interval from administration of neostigmine until TOF ratio 0.90 was as long as 28.8 min. The reversal of shallow rocuronium-induced block with 2 mg/kg sugammadex was rapid and consistent. For all SUG group patients, TOF ratio 0.90 was achieved within 3.3 min.

In conclusion, during XLIF surgery, the intraoperative reversal of rocuronium-induced shallow block with either sugammadex or neostigmine is a safe and efficient method. For reliable intraoperative detection of lumbar nerve roots with a stimulating current of 10 mA, the NMB should be reversed to a TOF ratio of at least 0.70. For a current intensity of 5 mA, the respective TOF ratio should reach 0.90. These target TOF ratios can be achieved with both 2 mg/kg sugammadex and 0.04 mg/kg neostigmine.

Acknowledgments The authors gratefully acknowledge financial support from the Czech Ministry of Health Internal Grant Agency, project no. NS 9618–4/2008.

Conflict of interest Milan Adamus is a member of the advisory board of MSD (Schering-Plough, s.r.o., a subsidiary of Merck & Co., Inc.) and has received lecture honoraria from MSD. However, no financial support from MSD was received for this study.

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