Deep neuromuscular blockade and neuromuscular reversal : applications and implications

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Chapter 8

Summary and conclusions

The introduction of sugammadex brought new opportunities in perioperative neuromuscular management. Sugammadex enables the application of deep neuromuscular block (NMB) and may help to reduce the incidence of postoperative residual curarization (PORC). This thesis investigated the effect of deep NMB on surgical conditions in laparoscopic retroperitoneal surgery using the Leiden - surgical rating scale. In addition, outcome data of neuromuscular reversal with sugammadex *versus* neostigmine and of everyday use of deep NMB is presented.

In *Section 1*, two randomized controlled trials are presented that investigated the effect of deep neuromuscular block on surgical working conditions in laparoscopic urologic surgery. **Chapter 2** presents data of a randomized controlled trial, which assessed the effect of moderate (train-of-four count of 1-2 twitches) vs. deep NMB (post-tetanic-count of 1-2 twitches) on surgical conditions during laparoscopic retroperitoneal prostatic and kidney surgery. These procedures take place in a limited space and it was hypothesized that surgical conditions in especially in these procedures may largely depend on adequate muscle relaxation. The primary outcome was the quality of the surgical working conditions as rated by the surgeon. For this purpose, the five-point Leiden - surgical rating scale was developed (L-SRS: 1. *extremely poor conditions* to 5. *optimal conditions*). Surgical conditions were rated by the surgeon every 15 minutes after installation of the pneumoperitoneum. The main finding of this study was that a deep NMB resulted in a higher L-SRS than a moderate NMB (mean L-SRS 4.0 vs. 4.7, $p<0.001$). In addition, L-SRS scores of 3 or lower occurred in 1% in deep NMB vs. 18% in the moderate NMB group. This indicates that deep NMB produced superior surgical conditions and significantly reduced the incidence of sudden deterioration of the surgical working field.

Although a deep NMB improved surgical conditions over a moderate NMB, the quality of the surgical working field varied considerably (*e.g.* L-SRS scores <5 were noted even during a deep NMB). It was hypothesized that variation this could be due to involuntary diaphragmic contractions that are triggered by elevated arterial CO_2 levels (*i.e.* hypercapnia) induced by CO_2 pneumoperitoneum. **Chapter 3** presents a study that investigated the effect of arterial CO_2 levels on surgical conditions in laparoscopic retroperitoneal surgery during deep NMB. In this study, patients were randomized to have arterial CO_2 levels maintained at a low level (hypocapnia, pCO_2 3.5 – 4.5 kPa) or at a high level (hypercapnia, pCO_2 6.5 – 7.5 kPa). Primary outcome parameter was the quality of surgical field rated on the L-SRS at 15 minutes intervals. The mean L-SRS scores during hypo- and hypercapnia were 4.84 vs. 4.77 respectively ($p >0.05$). Again, 99% of the ratings were good (L-SRS score 4) or excellent (L-SRS score 5), irrespective of the randomisation. This study confirmed the results of the previous study that deep NMB overall yields good surgical working conditions, but the hypothesis suggesting an influence of arterial CO_2 levels on surgical conditions during deep NMB was rejected.

In *Section 2,* two outcome studies are presented. **Chapter 4** presents retrospective data about the everyday use of deep neuromuscular block in laparoscopic retroperitoneal surgery. Electronic charts of patients who had received general anaesthesia between January 2014 and December 2016 were searched for anaesthetics with the use of high dose rocuronium to achieve deep NMB. These cases were matched with respect to sex, age and ASA class to patients that had received anaesthesia with low dose rocuronium. The primary postoperative outcome was 30-day readmission rate; secondary outcomes included duration of surgery and anaesthesia, and postoperative pain. 130 Patients were included in each cohort. All patients of the high dose of rocuronium cohort were reversed with sugammadex (mean) 267 mg at the end of anaesthesia. In the low dose rocuronium cohort 33% of the patients were reversed with sugammadex 212 mg, 20% were reversed with neostigmine 1.6 mg. The remainder of the patients were not reversed. Postoperative respiratory and pain outcomes, as well as hospital length of stay did not differ between the two groups. Unplanned readmission rate was significantly lower in the high dose rocuronium cohort compared to the low dose cohort (3.8% *vs.* 12.7%, OR = 0.33, p =0.03). This was primarily due to fewer infectious complications at the site of surgery in patients who had received a high dose rocuronium. Prospective studies are needed to confirm these findings and to study the effects of a high dose rocuronium/ sugammadex reversal anaesthetic technique on the pharmaco-economic variables.

In **Chapter 5**, the effect of sugammadex vs. neostigmine reversal on postoperative oxygenation was studied. In this randomized controlled trial, 100 patients were randomized for reversal of a moderate NMB with sugammadex 2 $mg.kg^{-1}$ or neostigmine 2.5 mg. To mimic real world conditions, neuromuscular monitoring was not allowed. Instead, timing of extubation was based on clinical signs of adequate muscle strength. In the recovery ward, the use of supplemental oxygen was not allowed unless saturation dropped to values below 94%. Patients who had received sugammadex had a mean (95% confidence interval) Train-of-four (TOF) ratio at extubation of 0.99 (0.98-1.00) compared to a TOF ratio of 0.74 (0.68-0.80) for patients who had received neostigmine. This translated to a mean lowest arterial oxygen saturation of 96.8% (96.1 – 97.4) vs. 93.3% (91.9-94.7) in the recovery ward for sugammadex and neostigmine reversed patients respectively. Following reversal with sugammadex, 90% of patients had a TOF ratio of > 0.9 at extubation *and* a lowest saturation > 94% at the PACU, compared to 16% of neostigmine reversed patients. It was concluded that, in a setting were neuromuscular monitoring is not used, reversal of a moderate NMB with sugammadex leads to less postoperative residual curarization (TOF ratio <0.9) and less postoperative hypoxemia.

In *Section 3,* **Chapter 6** presents a systematic review of the use of surgical rating scales in laparoscopic surgery. After a systematic search in Pubmed, Embase and Web of Science, 17 reports were eligible for inclusion. A total of 10 unique surgical rating scales were identified. These scales were judged for their quality with the use of a quality

score. This score delivered points for optimal length of the scale, description of the scale items, validation procedures and correlation with other variables. The overall score of the rating scales was low and most scales lacked a validation procedure. In addition, the methodology of rating and the reporting of the results differed significantly between studies. The only fully validated surgical rating scale for laparoscopic surgery was the Leiden - surgical rating scale. A guideline about the construction and use of surgical rating scales, as well as for methodology and results reporting was proposed for future research.

In the final section, **Chapter 7** gives a broad overview about current management of neuromuscular relaxation during surgery. Literature was systematically reviewed for the latest evidence concerning the effect of sugammadex reversal and the use of deep neuromuscular block during surgery on outcome. Increasing evidence shows beneficial effects of reversal of NMB with sugammadex over neostigmine and the application of deep NMB during certain procedures. If and to what extend this improves outcomes is not yet fully determined. Good quality research in this scientific field is scarce, which leaves opportunities for the future.

Conclusions

From the data presented in this thesis, the following conclusions can be drawn:

1. Deep neuromuscular block results in superior surgical working conditions compared to a moderate neuromuscular block, during laparoscopic retroperitoneal surgery.

2. Superior surgical working conditions during laparoscopic retroperitoneal surgery are independent of arterial CO_2 levels during deep neuromuscular block.

3. The application of deep NMB is safe and associated with less unplanned postoperative 30-day readmission rates when applied in laparoscopic urologic surgery.

4. Reversal of a moderate NMB with sugammadex results in less postoperative residual curarization and less postoperative hypoxemia compared to reversal with neostigmine, in a setting were intraoperative neuromuscular monitoring and postoperative supplemental oxygen are not allowed.

5. The Leiden - surgical rating scale is a high quality rating scale for assessment of surgical working conditions in laparoscopic surgery.