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Abstract: Purpose During pneumoperitoneum (PP) for robot-assisted prostatectomy, a deep neuromuscular block (NMB) is necessary. New relaxometry equipment permits maintenance of profound NMB in order to improve patient safety and surgical conditions. Methods Twenty adult patients undergoing robot-assisted prostatectomy were included. Under automated quantitative relaxometry with the TOFcuffTM device, rocuronium dosing was adapted with the aim to keep NMB at deep levels. The time fractions with intense block (PTC 0), adequately deep block (PTC 1 to 3) and a not sufficiently deep block (PTC > 3) were quantified. Results An optimally deep block (PTC 1–3) was achieved during 110 ± 38 min (50 ± 15%). Intense block was found during 60 ± 45 min (27 ± 18%) of total PP time. Values of PTC > 3 lasted 60 ± 45 min (23 ± 17%). Median PTC always remained between 1 and 3. Inadvertent movements during PP were never encountered, and operation conditions as reported by the surgeons were excellent. Conclusion Our technique of controlled profound NMB by repetitive bolus doses achieved its goal in 77% of PP time. Under automated quantitative relaxometry, an optimized rocuronium dosing strategy should be applied to maintain a high level of safety and adequate operation conditions without risking an unnecessary prolongation of NMB into the post-pneumoperitoneum period.

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AUTOMATED QUANTITATIVE RELAXOMETRY FOR DEEP NEUROMUSCULAR BLOCKADE IN ROBOT-ASSISTED PROSTATECTOMY

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Abstract

Purpose: During pneumoperitoneum (PP) for robot-assisted prostatectomy, a deep neuromuscular block (NMB) is necessary. New relaxometry equipment permits maintenance of profound NMB in order to improve patient safety and surgical conditions. Methods: Twenty adult patients undergoing robot-assisted prostatectomy were included. Under automated quantitative relaxometry with the TOFcuffTM device, rocuronium dosing was adapted with the aim to keep NMB at deep levels. The time fractions with intense block (PTC 0), adequately deep block (PTC 1 to 3) and a not sufficiently deep block (PTC > 3) were quantified. Results: An optimally deep block (PTC 1-3) was achieved during 110 ± 38 min (50 ± 15%). Intense block was found during 60 ± 45 min (27 ± 18%) of total PP time. Values of PTC > 3 lasted 60 ± 45 min (23 ± 17%). Median PTC always remained between 1 and 3. Inadvertent movements during PP were never encountered, and operation conditions as reported by the surgeons were excellent. Conclusion: Our technique of controlled profound NMB by repetitive bolus doses achieved its goal in 77% of PP time. Under automated quantitative relaxometry, an optimized rocuronium dosing strategy should be applied to maintain a high level of safety and adequate operation conditions without risking an unnecessary prolongation of NMB into the post-pneumoperitoneum period.

Keywords

Neuromuscular monitoring • robot-assisted prostatectomy • deep neuromuscular block • relaxometry • rocuronium

Introduction

Robot-assisted urological interventions are characterized by multiple actuators inserted into the abdominal cavity. If a patient does inadvertent moves during pneumoperitoneum (PP), these instruments may injure large blood vessels and abdominal organs. To avoid such life-threatening complications by movements and to improve operating conditions, it is necessary to administer an adequate level of anesthesia and even more so to maintain a deep neuromuscular (NM) block.[1,2] Surveillance and maintenance of a deep NMB is achieved by continuous or repeated administration of a non-depolarizing NMB agent. The actual level and course of NMB has to be monitored with quantitative relaxometry. [3] Problems with conventional relaxometry result from the inaccessibility of the patient's arms to employ visual or tactile assessment of finger movements. Some devices may indicate train of four (TOF) or post tetanic count (PTC) values on their display,[4,5] but their mode of action is solely based on the motor response of the adductor pollicis muscle, which is very much dependent on the location of the stimulation electrodes and the pre-existing tension in the fingers’ spread.[6–8] These circumstances may cause a variability in the motor response, thus reducing the accuracy and reliability of the measurements. Inaccuracies with relaxometry and the inability to measure the exact status of neuromuscular transmission may lead to inappropriate decisions, in particular, if the NMB is not deep enough during PP or if towards end of surgery a residual block remains unrecognized.[9–11] Novel relaxometry equipment such as the TOFcuffTM (RGB Medical, E-28037 Madrid, Spain) intends to provide reliable quantitative relaxometric values independent of the position of arm and hand. The accuracy and reliability of the TOFcuffTM has been tested and found to be sufficient[12,13] However, a conclusive clinical validation of the technique is not yet available. Naguib et al.[14] recently defined the spectrum of NMB levels as: intense (complete) block if PTC = 0, deep block if PTC ≥ 1 and TOF-count = 0, moderate block if TOF-count = 1–3, and finally, shallow block if TOF-ratio < 0.4. According to this list, a deep block is present with any positive PTC value, as long as the TOF count remains 0. This might be sufficient for several types of surgery, but many authors state that in endoscopic and robot-assisted interventions, the suitable block range has to be

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restricted to a narrow spectrum of PTC 1 to 3,[15–20]. Keeping in mind the most important “safety argument” of avoiding inadvertent moves, it is plausible to require this narrowing of the relaxometric values spectrum to its deeper end. Therefore, recently we have adopted in our department a titrated mode of NMB agent application under continuous, automatically timed relaxometry with the intention to maintain profound neuromuscular block in the range of 1 to 3 PTC during PP. We apply this method in all robot-assisted prostatectomies since a TOFcuffTM relaxometer became available. This study intends to describe how far we succeeded in this task, and to propose how to improve the methodology in the future.

**Methods**

**Study design**

We selected 20 adult patients undergoing elective robot-assisted prostatectomy in general anesthesia, a number we considered sufficient to obtain suitable results to be analyzed with descriptive statistics about the feasibility of our standardized procedure to maintain an adequate NMB level of PTC 1-3 during PP. The trial was approved by the local Ethics Committee (No. 2016-01781, chaired by Prof. Peter Meier-Abt) on 1 February 2017. Study participants were consecutively recruited from the surgical program of the clinic of urology, thus resulting in a prospective, non-randomized, unblinded, single-center study design. All patients who met the inclusion criteria gave their informed consent. The methodology for this investigation was identical to our locally adopted standard anesthesia procedure for robot-assisted urological surgery. General anesthesia was initiated with a bolus of propofol 2 mg/kg, fentanyl 0.3 mg/kg and rocuronium 0.6 mg/kg, followed by tracheal intubation and controlled ventilation. Maintenance of anesthesia was performed with desflurane, repetitive doses of fentanyl and an infusion of remifentanil according to clinical needs. Hemodynamics were monitored with a 5-lead EKG and invasive blood pressure measurement in the patients' radial artery.

**Relaxometry with the TOFcuffTM**

Neuromuscular block was continuously monitored with a TOFcuffTM device mounted on the right upper arm, which – during surgery – remained adducted to the body and was not accessible to the anesthetist. The TOFcuffTM is a novel technique that combines non-invasive blood pressure measurement (NIBP) with relaxometry. Two stimulation electrodes are integrated into the cuff, which is wrapped around the upper arm of the patient. The resulting muscular contractions are registered by pressure variations in the slightly pre-inflated cuff. The electric stimulation with 40 mA affects all motor nerves passing through the upper arm underneath the electrodes. This feature has the consequence that not only one specific nerve is aimed at (like the ulnar nerve at the wrist with conventional relaxometry), but one obtains a cumulative response from the upper arm musculature via their respective motor nerves, independent of their specific anatomical location. The resulting contractions are distributed over the entire arm (from the upper arm down to the fingers), but only the contractions registered as pressure variations in the cuff are used to calculate the neuromuscular transmission level. The uniform positioning of the cuff on the upper arm leaves far less room for user caused inaccuracies than the separate electrodes at the wrist (as is the case in conventional relaxometry). We assume that the cuff related technique offers a better reproducibility of measurements, by eliminating the intra- and inter-individual variability in the positioning of wrist electrodes. The inbuilt “autopilot” feature automatically applies suitable stimulation patterns that match the actual depth of NMB. When the desired level of a deep NMB is achieved, the inbuilt algorithm of the device elicits TOF measurements in 2 min intervals, which in turn enables PTC measurements every 6 min, under the condition that the preceding TOF measurements resulted in 0 counts. In contrast, a positive TOF count permits only further TOF but no PTC measurements anymore. This algorithm ensures a continuous surveillance of the NMB status by applying the suitable stimulation pattern according to the actual status of the NMB, the prevailing clinical situation and the individual patient’s need. Digital values are displayed both ways, as numerals and as a graphic course over time.

**Neuromuscular block strategy**

Application and maintenance of the NMB was performed by the same, well-trained anesthetist (MSu), thus ensuring a standardized procedure in all cases. Incremental rocuronium boluses of 10 mg were administered as soon as PTC surpassed the value of 3, thus using the time to the next bolus as the variable that depended on the patients’ individual response. We classified the resulting relaxometric values during PP and applied the following rocuronium dosing regimen: at a PTC = 0, no repetition dose was given. If PTC was 1-3, no repetition dose was yet given, but the next dose was expected to follow soon. If PTC resulted at 4 and higher, a repetition dose of 10 mg rocuronium was given.

The main objective was to calculate the percentage of PP time that was present under these conditions. Towards the end of PP, no more NMB agent was administered until the termination of surgery. The return of a TOF ratio ≥ 0.9 had to be confirmed before extubation and awakening the patient [16,20]. If spontaneous recovery from deep block arrived at a TOF count > 2, we reversed with neostigmine/glycopyrrolate, while at TOF count ≤ 2, sugammadex was administered.
**Clinical assessments**

During PP, CO2 was insufflated into the abdominal cavity with gas flows at the surgeons’ discretion, with an upper pressure limit set at 13 mmHg. Most of the time, the actual insufflation pressure fluctuated between 5 and 10 mmHg. After surgery, the surgeon was asked about his overall subjective satisfaction with the patient’s abdominal relaxation level during PP by using a verbal rating scale (VRS) ranging from 0 (very poor) to 4 (excellent).

On the 1st post-operative day, an examination and interview of the patient was conducted by the involved anesthesiologist. This encompassed the review of entries into the patient’s record for side effects or complications related to the NMB or its reversal, for skin lesions at the site of the relaxometry cuff, as well as for abdominal gas insufflation related effects such as shoulder pain.

**Statistical analysis**

Descriptive statistical analysis was performed for the key data from the administered NMB and the adopted reversal technique, as well as the satisfaction level of the involved surgeons. For calculations, we used Microsoft Excel for Mac 16.9 (Microsoft. Redmond, WA) and GraphPad Prism 7.0 for Mac (GraphPad, La Jolla, CA). Mean and standard deviation (for normally distributed data) or median, quartiles and range (for non-normally distributed data) were calculated.

**Results**

All 20 patients experienced uneventful surgery and anesthesia. The biometric and clinical data reflecting the patient population for this kind of surgery are summarized in Table 1.

The duration of PP lasted 223 ± 40 min (mean ± SD), which corresponded to 84% of surgery duration and 63% of total anesthesia time. An ideally deep (profound) NMB (PTC 1-3) during PP was achieved for 50 ± 15% of PP time (110 ± 38 min). An unnecessarily intense block occurred in 27 ± 18% (60 ± 45 min) of PP time. A still deep, but for this kind of surgery as not sufficiently deep deemed block at a PTC ≥ 4 and TOFc 0 was present in 23 ± 17% (60 ± 45 min) of PP time (Figure 1).

The median PTC was always in the aimed range of 1 to 3, but due to the rule of giving a repetition dose of rocuronium only when PTC was above 3, for short periods higher values occurred too. The cumulative rocuronium dose was 205 ± 61 mg. During PP, the maintenance of a deep NMB was achieved with 0.35 ± 0.11 mg/kg/h (mean ± SD). The total rocuronium consumption was 28% higher than it used to be before the implementation of this technique (based on unpublished internal calculations). In our study population, the average rocuronium consumption was found to be 0.4 mg/kg/h over the entire anesthesia period, including the initial intubation dose. In 8 (40%) patients, the reversal could be achieved with neostigmine/glycopyrrolate to safely extubate the patients at a TOF ratio of 0.9 or higher. Twelve (60%) patients were reversed with sugammadex. The average time from the last rocuronium administration to the end of surgery lasted 58 ± 17 min.

The viewing conditions and the accessibility to the operation field as reported by the surgeons resulted unanimously at level 4 in all cases (VRS ranging from 0 (very poor) to 4 (excellent)). The visit during the 1st post-operative day didn’t reveal any method-related adverse events in the investigated patients. There were no symptoms related to NMB and its reversal and no signs due to the mechanical effect of the relaxometry cuff. None of the patients complained of shoulder pain.

![Figure 1. Distribution of achieved neuromuscular block levels during the pneumoperitoneum period. Train of four counts (TOFc) were always 0, and the median of post-tetanic counts (PTC) was at 3.](image)

*Table 1. Biometric and clinical data of the investigated patient population*

| Age (years) | Weight (kg) | Height (cm) | Anesthesia duration (min) | Surgery duration (min) | Pneumoperitoneum duration (min) |
|-------------|-------------|-------------|---------------------------|------------------------|-------------------------------|
| 61 ± 7      | 85 ± 13     | 177 ± 8     | 338 (275-445)             | 263 (195-330)          | 223 (165-285)                 |

Data are presented as mean ± SD for biometric data and as median (range) for clinical data (n = 20).
Discussion

Instalment and maintenance of profound NMB during the PP period in abdominal endoscopic procedures in general and in robot-assisted surgery in particular is a widely advocated method.[15,19,21,22] The rationale behind this opinion is based on 3 considerations: 1) improved safety level by preventing inadvertent movements by the patient in case of insufficiently deep anesthesia and analgesia,[1,18] 2) improved visibility and accessibility conditions for the surgeon due to lower muscular tone in the abdominal wall,[19,21] and 3) less side effects of intra-abdominal gas insufflation during PP under limited pressure (such as hemodynamic instability, respiratory problems and postoperative shoulder pain).[23–25]

However, some authors contested the necessity for a profound NMB in a robot-assisted surgery,[26–28] so that this issue still has to be considered as disputed. A very deep NMB may also have disadvantages: higher drug consumption for NMB agent and reversal agents and the necessity for accurate relaxometry. The latter might be difficult to achieve because of the technical limitations and sensitivity to artefacts of conventional relaxometry devices. In particular, the adductor pollicis dependent techniques may be considered less reliable due to multiple reasons such as user-caused variability in electrode positioning, and the inevitable circumstance of the adducted arm and inaccessible hand.[16] We view modern relaxometric equipment such as the TOFcuffTM as an important step to improve reliability and handling of NMB monitoring.

The main finding in our 20 cases series is that automated quantitative relaxometry and repetitive rocuronium bolus doses partially enable the maintenance of an optimally profound NMB status of PTC 1-3. The occurrence of 27% intense block is from the safety point of view acceptable, but an unnecessarily intense block may prolong emergence from anesthesia. Of a bigger concern was the 23% remainder of unsatisfactory, still deep but not ideally profound NMB. Although this was an undesired state, it did not automatically represent an imminent danger because of the concomitant application of desflurane and opioids in sufficient dosing. Due to this, only partially achieved ideal depth of NMB, we consider our repetitive bolus technique to be not yet satisfactory. Instead, we would recommend a continuous infusion technique of rocuronium during PP with manual adaptation of the infusion rate according to relaxometry.

Our results underline the benefit of automated quantitative relaxometry. Under successfully maintained profound neuromuscular block, surgery might become easier (and maybe even faster) due to better viewing and operating conditions.[23–25]. Additionally, the lower insufflation pressures might have advantages for the patients’ postoperative outcome, which appear to be associated with a lower incidence of shoulder pain.[29]

Limitations of the study

The employed relaxometry with the TOFcuffTM still needs a more validation. The resulting higher consumption of NMB agents accounts for more costs, in particular, if reversal with sugammadex is indicated. We did not compare our procedure to continuous rocuronium infusion regimens, for which, larger randomized comparative trials are necessary.

Conclusions

A sufficiently deep NMB during pneumoperitoneum for robot-assisted surgery has to be titrated under close meshed quantitative relaxometric surveillance. Even under thorough relaxometric control, repetitive rocuronium bolus doses fail to provide ideal conditions during the entire pneumoperitoneum period, for which a continuous rocuronium infusion might be necessary.

Compliance with ethical standards

Conflicts of interest MSu declares to have no conflicts of interests. PB has received travel allowances by Merck Sharp & Dohme and by Acutronic Medical Systems. MS has received travel support from Baxter, Switzerland.

Informed consent The study protocol complied with the Declaration of Helsinki of the World Medical Association, and all participants gave written informed consent before participating in the study.

Research involving human and animal rights The study was approved by the Cantonal Ethics Committee (Approval No. 2016-01781) chaired by Prof. Peter Meier-Abt) on 1 February 2017. This is a “Sex-Inclusive Biomedical & Clinical Research” that has been performed on males only because it deals with prostatectomy as the investigated surgical condition.

Authors’ contributions: P. Biro initiated and designed the study, M. Sunnen and M. Schlaepfer contributed equally to the collection and interpretation of data and with writing the manuscript. M. Schlaepfer additionally performed data presentation and statistical analysis. This work represents the dissertation thesis of M. Sunnen.

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