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Short communication

Deep neuromuscular block with pipecuronium in patients undergoing laparoscopic surgery — A prospective case series

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ABSTRACT

Introduction: We tested the feasibility of maintaining low intraabdominal pressures during pipecuronium-induced deep block (post-tetanic count ≥1, train-of-four count = 0) in patients undergoing laparoscopic surgery.
Methods: Ten adult patients awaiting cardiac surgery or heart transplantation and requiring non-elective abdominal surgery were included. Pipecuronium bromide 0.09 mg/kg was used for muscle relaxation and maintenance of deep block. Top-up doses of pipecuronium (0.01–0.02 mg/kg) were administered when post-tetanic count was 4–8. Intraabdominal pressures were kept below 10 mmHg. Mean arterial pressure was measured intra-arterially. Surgical field view was rated on a 5-point scale (1 = extremely poor, 5 = optimal).
Results: Induction dose of 0.09 mg/kg pipecuronium had an onset time of 5.3 (2.3–6.3, 25–75% IQR) min. Deep block was maintained for 51.2 ± 19.7 min. Top-up pipecuronium doses were necessary in 5 patients, 56.0 ± 28.1 min after the first dose. At the end of surgery, neuromuscular block was deep (post-tetanic count 0–6). Administration of 2 mg/kg of sugammadex induced recovery to train-of-four ratio ≥0.9 in 3.5 ± 1.6 min, and to train-of-four ratio = 1.0 in 4.3 ± 1.2 min. Mean intraabdominal pressure was 8.1 ± 1.1 mmHg during pneumoperitoneum. There was no significant change in heart rate (0.0, −2.6 to 0) beats/min.
Discussion: Pipecuronium is a rational alternative when deep neuromuscular block is necessary, because of its long-acting neuromuscular blocking effect that may be antagonized quickly and safely with sugammadex.
Registration: European Clinical Trials Database registration number: 2022-004114-11, Clinical Trials Database registration number: NCT06517524.

Introduction

Several studies and meta-analyses have demonstrated the potential benefits of deep neuromuscular block for laparoscopic surgery compared to moderate neuromuscular block [1,2]. Although the advantages of deep block in certain laparoscopic procedures seem obvious, its routine use is limited by the prolonged and variable antagonism with neostigmine and the risk of postoperative pulmonary complications due to residual neuromuscular block [3]. Relatedly, the use of long-acting agents such as pancuronium and pipecuronium has also decreased markedly in the past decade [4]. The widespread use of sugammadex guided by quantitative neuromuscular monitoring has the potential to overcome these limitations [5], and deep neuromuscular block should be maintained safely during daily practice when clinical circumstances require its use. Importantly, sugammadex only has binding affinity for steroidal neuromuscular agents (rocuronium, vecuronium and pipecuronium) [6,7]. The safe and cost-effective reversal of pipecuronium-induced moderate to deep neuromuscular block with sugammadex has been demonstrated in previous studies [7].

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Rocuronium, the most commonly used agent for achieving deep block, has pharmacological limitations: its intermediate duration of action requires repeated bolus administrations (and attendant extremes of block), while surgical procedures requiring deep levels of neuromuscular block for extended durations are best managed by the more labour-intensive continuous infusion to maintain the desired depth of neuromuscular block. We present a prospective case series of surgeries requiring variable durations of deep block for laparoscopic surgery in patients with very low cardiac ejection fraction. The main purpose of this report is to highlight the feasibility of achieving and maintaining pipecuronium-induced deep neuromuscular block for surgery requiring low intraabdominal pressures, and to demonstrate pipecuronium's rapid and complete antagonism with sugammadex 2 mg/kg from a deep level of block.

Methods

This single-centre, prospective, observational case-series study was approved by the local ethics committee of the University of Debrecen and the National Institute of Pharmacy (OGYÉI/3968-1/2023); written informed consent was obtained from all participating patients. The study was first registered prior to patient enrolment in the European Clinical Trials Database (registration number 2022-004114-11), and later also in the Clinical Trials Database (registration number NCT06517524, Principal investigator: Béla Fülesdi). The study and data collection were performed at the Clinical Centre of the University of Debrecen (Debrecen, Hungary) between March 2023 and December 2023. We included 10 adult New York Heart Association (NYHA) Functional Classification 3–4 surgical patients (high cardiovascular risk) who were awaiting cardiac surgery or heart transplantation, before which they underwent non-elective abdominal surgery either for tumour removal or for cholecystectomy.

After intravenous (iv) midazolam (0.05 mg/kg, maximum 2 mg) premedication, anaesthetic induction was accomplished with etomidate (0.3 mg/kg), followed by intravenous administration of 2 μg/kg fentanyl and pipecuronium bromide (Arduan®, Richter Gedeon Ltd. Budapest, Hungary) in a dose of 0.09 mg/kg (2 x ED95). After tracheal intubation, sevoflurane maintenance was age-adjusted for target minimum alveolar concentration of 1–1.5%. Bolus iv fentanyl (1 mcg/kg) was used for analgesia. Additional doses of pipecuronium bromide 0.01–0.02 mg/kg were given iv when a post-tetanic count (PTC) of 4–8 was determined by a TOF-Watch SX® acceleromyograph (Organon Ireland Ltd., Dublin, Ireland). During surgery, the patient's hemodynamic parameters such as heart rate and mean intra-arterial pressure (MAP) were recorded continuously. While the upper pressure limit of intraabdominal pressure was set at 15 mm Hg, as per institutional routine, the surgeon aimed to perform the procedure using low-pressure pneumoperitoneum, defined as an intra-abdominal pressure value below 10 mm Hg.

A calibrated TOF-Watch SX® acceleromyograph was used for neuromuscular monitoring according to good clinical research standards [8], and all train-of-four (TOF) data were normalized. When the muscle response stabilized, pipecuronium was administered and the trachea was intubated once the train-of-four (TOF) count was 0. A post-tetanic count (PTC) stimulation was evaluated every 5 min throughout surgery and was used to guide administration of additional pipecuronium (0.01–0.02 mg/kg) once PTC was 4–8. Administration of sevoflurane was discontinued after deflation of pneumoperitoneum, and neuromuscular block was antagonized with 2 mg/kg iv sugammadex. Neuromuscular recovery was documented as a normalized TOF ratio $\geq$0.9, and the endotracheal tube was removed when the patient responded to verbal commands.

Primary endpoints of the study

Maintenance of low-pressure pneumoperitoneum during laparoscopic surgery using deep neuromuscular block with pipecuronium and reversal of neuromuscular block to TOF ratio $\geq$0.9 within 3 min after administration of 2 mg/kg sugammadex.

Results

Ten patients were included. Five patients underwent cholecystectomies, 3 underwent laparoscopic rectal or colon resections, and 2 underwent laparoscopic appendectomy and adrenalectomy. Surgical duration was 35–170 min, while pneumoperitoneum duration was 35–125 min.

A single dose of 0.09 mg/kg pipecuronium resulted in an onset time of 5.3 (25–75% interquartile range, IQR, of 2.3–6.3) min. A top-up dose of pipecuronium (0.01–0.02 mg/kg) was administered when recovery to PTC 4–8, TOF count = 0 was documented. This was necessary in 5 patients, 56.0 ± 28.1 min (range: 25–90 min) after the first pipecuronium dose. At administration of the top-up dose, the PTC was a median of 5.0 (range: 5–15). In these cases, the duration of pneumoperitoneum was 125, 75, 75, 35, and 45 min, respectively. After administration of the first top-up dose, deep block was maintained for 51.2 ± 19.7 min (median: 45 min, range: 45–80 min). An additional, second top-up was necessary in 4 cases because of the surgical need for longer duration of pneumoperitoneum. The administration of a third top-up dose of pipecuronium was necessary in a single patient. The duration between pipecuronium administrations was 45 min. Data on intraoperative neuromuscular monitoring are summarized in Table 1.

Using this neuromuscular blocking strategy, the depth of the neuromuscular block at the end of surgery was PTC = 0 in 5 cases, PTC = 1 in 3 cases, and PTC = 6 in 2 cases. Administration of 2 mg/kg actual body weight (ABW) of sugammadex antagonized this block in 3.5 ± 1.6 min to TOFR $\geq$ 0.9, and in 4.3 ± 1.2 min to TOFR = 1.0. No re-onset of block (“recurarization”) was observed 15 min after reversal. Data on sugammadex antagonism are summarized in Table 2.

Feasibility of low-pressure peritoneum during the procedure: deep neuromuscular block with pipecuronium facilitated maintenance of low-pressure pneumoperitoneum in all cases. The average intraabdominal pressure was 8.1 ± 1.1 (median: 8.0, min: 6; max: 9) mmHg during the procedure. The highest mean intraabdominal

Table 1
Data on neuromuscular blocking agent administration and intraoperative neuromuscular monitoring. Means and standard deviations and medians (25–75% interquartile ranges) are presented, as appropriate.

TOF% at start (before muscle relaxation)	108.2 ± 5.6
T1 at start (before muscle relaxation)	98 (93–102)
T4 at start (before muscle relaxation)	107.2 ± 10.7
Intubating dose of pipecuronium (mg)	7 (7–8)
Top-up dose necessary (number of cases)	5
1 st top-up dose of pipecuronium (mg)	2 (1–2)
Time until the first top-up dose (min)	56.0 ± 28.1
PTC at first top-up dose	8.6 ± 4.6
Second top-up dose necessary (number of cases)	4
2nd top-up dose of pipecuronium (mg)	1 (1–1,5)
Time from 1st until 2nd top-up dose (min)	51.2 ± 19.7
PTC at 2nd top-up dose	2.25 ± 1.26
3rd top-up dose necessary (number of cases)	1
3rd top-up dose of pipecuronium (mg)	0.5
Time from 2nd until 3rd top-up dose (min)	45
PTC at 3rd top-up dose	3 (3–3)
Total pipecuronium dose (mg)	8.4 ± 1.7
Pipecuronium dose in mg/kg	0.1 (0.09–0.11)
Number of pipecuronium vials used	2 (2–3)

TOF, train-of-four ratio; T1, first twitch in the train-of-four sequence; T4, fourth twitch in the train-of-four sequence; PTC, post-tetanic count.

Table 2
Data on reversal of pipecuronium block with sugammadex. Means and standard deviations and medians (25–75% interquartile ranges) are presented, as appropriate.

Time from the last pipecuronium dose until reversal (min)	49.1 ± 23.8
TOFC at reversal with sugammadex	0 in all cases
PTC at reversal with sugammadex	PTC = 0 in 5 cases PTC = 1 in 3 cases PTC = 6 in 2 cases
Time from reversal with sugammadex until TOFR 0.9 (min)	3.45 ± 1.6
Time from reversal with sugammadex until TOFR 1.0 (min)	4.3 ± 1.2
Final normalized TOF%	104.1 ± 5.7
Time between sugammadex and returned normalized TOF100 %	4.46 ± 0.9
Total dose of sugammadex (mg)	158.0 ± 28.1
Number of sugammadex vials/patient	1 (1–1)

TOFC, train-of-four count; PTC, post-tetanic count; TOF, train-of-four.

pressure during the cases that was necessary to achieve proper surgical visualization was 9.7 ± 1.1 mmHg. This highest mean intraabdominal pressure was maintained for an average duration of 6.6 ± 4.7 min. The lowest mean intraabdominal pressure was 7.2 ± 1.2 mmHg.

Discussion

Deep neuromuscular block (PTC ≥ 1, TOF count = 0) and total block (PTC = 0, TOF count = 0) (9) achieved with pipecuronium enabled maintenance of low-pressure pneumoperitoneum without negatively affecting the surgical field. At the end of the laparoscopic procedure, both total and deep blocks were effectively antagonized with sugammadex 2 mg/kg ABW within 5 min. A single dose of 0.09 mg/kg ABW (2 x ED95) pipecuronium resulted in maintenance of deep block for 56 ± 28.1 min. A top-up dose of pipecuronium was necessary only when the duration of surgery exceeded 35 min. After a second top-up dose, the deep block lasted for 51.2 ± 19.7 min. Thus, administration of pipecuronium facilitated long periods of deep neuromuscular block, allowing maintenance of low-pressure pneumoperitoneum.

Most previous studies used rocuronium for laparoscopic surgeries to achieve deep neuromuscular block. Using the shorter-acting rocuronium requires repeated doses and may risk fluctuations in the level of block during bolus administrations; alternatively, a longer-acting neuromuscular agent like pipecuronium may maintain a more consistent level of block. Additionally, the duration of pneumoperitoneum may not be predictable in some cases and the necessary dose of the reversal agent may be higher during rocuronium neuromuscular block. The dosing guidelines for sugammadex antagonism of deep block (PTC ≥ 1, TOF count = 0) recommend a dose of 4 mg/kg ABW, but are silent on the appropriate dose when the block is total (PTC = 0). Deep block may necessitate the administration of 4–16 mg/kg of sugammadex for effective antagonism [9]. Recent experimental and clinical studies indicated that the affinity of sugammadex for pipecuronium is four times higher than for rocuronium [10] and a pipecuronium-induced deep block can be antagonized effectively by a lower, 2 mg/kg sugammadex dose [7]. Considering the effective reversal dose of sugammadex is 2 mg/kg ABW for pipecuronium-induced block, its use may be reconsidered.

There are also limitations to this brief report; the small number of patients (n = 10) suggests that pipecuronium is indeed effectively antagonized with sugammadex 2 mg/kg despite the absence of twitches (TOF count = 0) or post-tetanic counts. However, this sugammadex effectiveness cannot be universally extrapolated to all patients receiving pipecuronium, and larger studies are needed to establish its efficacy. Our results, however, are congruent with previous reports [7]. Second, the notion that a fixed dose of sugammadex (2 mg/kg) is adequate in all patients regardless of the level of neuromuscular block (including total block, when PTC = 0) is fundamentally wrong and unsafe, since a massive overdose may well be present when PTC = 0, and significantly more sugammadex might be necessary to bind all free (unbound) rocuronium molecules. This underscores the importance of ensuring adequate recovery by quantitative monitoring before extubation, especially in cases with complete neuromuscular block.

In conclusion, deep neuromuscular block with pipecuronium is feasible and enables administration of low-pressure pneumoperitoneum for an extended period (50–60 min). The use of pipecuronium may be a rational alternative to rocuronium if a deep neuromuscular block is necessary because its long-acting neuromuscular blocking effect may be antagonized quickly and safely with a relatively low dose of sugammadex at the end of surgery.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Disclosure of interest

SJB has intellectual property assigned to Mayo Clinic; was a consultant for Merck & Co., Inc.; is a principal, shareholder and Chief Medical Officer in Senzime AB (Sweden); an unpaid member of Scientific Advisory Boards for NMD Pharma (Denmark) and Takeda Pharmaceuticals (Japan); and Member of the Editorial Boards for *Anesthesiology*; *Journal of Clinical Anesthesia*; *Anaesthesia Critical Care & Pain Medicine;* and *Journal of Clinical Medicine*.

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Author contributions

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Substantial contribution to conception and design: LA, ZS-M, BF.
Data acquisition: LA, ZS-M, MB, ZK, GN, AP, RN.
Data interpretation: LA, ZS-M, SJB, BF.
Drafting of paper: LA, ZS-M, MB, ZK, GN, AP, RN, SJB, BF.
Revising paper critically for important intellectual content: LA, ZS-M, SJB, BF.

References

[1] Liu S, He B, Deng L, Li Q, Wang X. Does deep neuromuscular blockade provide improved perioperative outcomes in adult patients? A systematic review and meta-analysis of randomized controlled trials. PLoS One 2023;18(3):e0282790. http://dx.doi.org/10.1371/journal.pone.0282790.
[2] Fuchs-Buder T, DE Robertis E, Brunaud L. Neuromuscular block in laparoscopic surgery. Minerva Anestesiol 2018;8:509–14. http://dx.doi.org/10.23736/S0375-9393.17.12330-8.
[3] Fuchs-Buder T, Romero CS, Lewald H, Lamperti M, Afshari A, Hristovska AM, et al. Peri-operative management of neuromuscular blockade: a guideline from the European Society of Anaesthesiology and Intensive Care. Eur J Anaesthesiol 2023;40:82–94. http://dx.doi.org/10.1097/EJA.0000000000001769.

[4] Brull SJ, Fulesdi B. Residual neuromuscular block in vulnerable patients: obesity, obstructive sleep apnea and postoperative pulmonary complications. Rev Esp Anestesiol Reanim (Engl Ed) 2019;66:237–40. http://dx.doi.org/10.1016/j.redar.2019.03.005.
[5] Brull SJ, Naguib M. Selective reversal of muscle relaxation in general anesthesia: focus on sugammadex. Drug Des Devel Ther 2009;3:119–29. http://dx.doi.org/10.2147/dddt.s3868.
[6] Asztalos L, Szabó-Maák Z, Gajdos A, Nemes R, Pongrácz A, Lengyel S, et al. Reversal of vecuronium-induced neuromuscular blockade with low-dose sugammadex at train-of-four count of four: a randomized controlled trial. Anesthesiology 2017;127:441–9. http://dx.doi.org/10.1097/ALN.0000000000001744.
[7] Tassonyi E, Asztalos L, Szabó-Maák Z, Nemes R, Pongrácz A, Lengyel S, et al. Reversal of deep pipecuronium-induced neuromuscular block with moderate versus standard dose of sugammadex: a randomized, double-blind, noninferiority trial. Anesth Analg 2018;127:1344–50. http://dx.doi.org/10.1213/ANE.0000000000003719.
[8] Fuchs-Buder T, Brull SJ, Fagerlund MJ, Renew JR, Cammu G, Murphy GS, et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents III: the 2023 Geneva revision. Acta Anaesthesiol Scand 2023;67:994–1017. http://dx.doi.org/10.1111/aas.14279.
[9] Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring: challenges and opportunities. Anesthesiology 2017;126:173–90. http://dx.doi.org/10.1097/ALN.0000000000001409.
[10] Fábián AI, Tassonyi E, Csernoch V, Fedor M, Sohajda T, Szente L, et al. Carboxymethyl-γ-cyclodextrin, a novel selective relaxant binding agent for the reversal of neuromuscular block induced by aminosteroid neuromuscular blockers: an ex vivo laboratory study. BMC Anesthesiol 2021;21:206. http://dx.doi.org/10.1186/s12871-021-01424-4.