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ORIGINAL ARTICLE

Efficacy of profound versus moderate neuromuscular blockade in enhancing postoperative recovery after laparoscopic donor nephrectomy

A randomised controlled trial

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BACKGROUND Profound neuromuscular blockade (NMB) during anaesthesia has been shown to reduce postoperative pain scores, when compared with a moderate block. We hypothesised that profound NMB during laparoscopic donor nephrectomy (LDN) could also improve the early quality of recovery after surgery.

OBJECTIVES To compare the effectiveness of profound versus moderate NMB during LDN in enhancing postoperative recovery.

DESIGN A phase IV, double-blinded, randomised controlled trial.

SETTING Multicentre trial, from November 2016 to December 2017.

PATIENTS A total of 101 living kidney donors scheduled for LDN were enrolled, and 96 patients were included in the analyses.

INTERVENTIONS Patients were randomised to receive profound (posttetanic count 1 to 3) or moderate (train-of-four count 1 to 3) neuromuscular block.

MAIN OUTCOME MEASURES The primary outcome was the early quality of recovery at postoperative day 1, measured by the Quality of Recovery-40 Questionnaire. Secondary outcomes were adverse events, postoperative pain, analgesic consumption and length-of-stay.

RESULTS The intention-to-treat analysis did not show a difference with regard to the quality of recovery, pain scores, analgesic consumption and length-of-stay. Less intra-operative adverse events occurred in patients allocated to profound NMB (1/48 versus 6/48). Five patients allocated to a profound NMB received a moderate block and in two patients neuromuscular monitoring failed. The as-treated analysis revealed that pain scores were significantly lower at 6, 24 and 48 h after surgery. Moreover, the quality of recovery was significantly better at postoperative day 2 in patients receiving a profound versus moderate block (179.5 ± 13.6 versus 172.3 ± 19.2).

CONCLUSION Secondary analysis indicates that an adequately maintained profound neuromuscular block improves postoperative pain scores and quality of recovery. As the intention-to-treat analysis did not reveal a difference regarding the primary endpoint, future studies should pursue whether a thoroughly maintained profound NMB during laparoscopy improves relevant patient outcomes.

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Introduction

The use of low-pressure pneumoperitoneum (PNP) during laparoscopic donor nephrectomy (LDN) has been shown to reduce deep intra-abdominal pain and shoulder pain in a previous trial by our group.[1] However, the use of low-pressure PNP was also associated with prolonged operation time and possibly with compromised intra-operative safety. In an additional study, we showed that the use of low-pressure PNP is facilitated by deep neuromuscular blockade (NMB).[2] Nowadays, deep NMB is an emerging innovation in anaesthesiology and surgery. Many studies are published on its beneficial effects during surgery when compared with moderate NMB, including a reduction of postoperative pain,[3–6] reduced intra-operative adverse events,[7,8] and improved surgical space conditions.[3,4,6,9,10] Recently, we performed a systematic review and meta-analysis on the clinical benefits of deep NMB versus moderate NMB during laparoscopy, in which we revealed that deep NMB improves the surgical space conditions and reduces postoperative pain scores, when compared with moderate NMB.[11] Nevertheless, the need for and clinical benefit of routine use of deep NMB during laparoscopy is still under debate. Opponents of deep NMB argue that routine use of deep NMB leads to unnecessary risks of residual paralysis and additional costs of reversal of NMB with sugammadex, and state that clinical significant differences between deep and moderate NMB in relevant patient outcome are missing.[12] For example, a study by Kim *et al.*[13] found no effect of deep NMB on the quality of recovery after robotic gastrectomy, when compared with moderate NMB. A part of the controversy is based on a disagreement on the definition of the different levels of NMB. Biro *et al.*[14] recently suggested a revision of the classification of the depth of NMB, in which they added the level 'profound' NMB, defined as posttetanic count (PTC) 1 to 3. They point out that it might be favourable to distinguish between deep [train-of-four (TOF) count 0, PTC ≥ 4] and profound NMB (PTC 1 to 3), as in certain procedures, a PTC of 1 to 3 is required to prevent minor patient movements or diaphragm contractions.

The aim of this study is to assess the effectiveness of profound versus moderate NMB during standard pressure LDN in enhancing postoperative recovery.

Methods

Study design and patients

This randomised controlled clinical trial was performed between November 2016 and December 2017 at the Radboud University Medical Center (Nijmegen, The Netherlands) and the Leiden University Medical Center (Leiden, The Netherlands). All adult patients eligible for LDN were approached at least 2 weeks before surgery. The study protocol was published[15] and the trial was registered at ClinicalTrials.gov (NCT02838134).

Ethics

The study protocol was approved for both centres by the local ethics committee, the Central Committee on Research involving Human Subjects, Arnhem-Nijmegen, The Netherlands, reference number NL58160.091.16, (Chairperson Prof E van Leeuwen) on 27 October 2016. Oral and written informed consent was obtained from all patients before inclusion.

Randomisation and blinding

A total of 96 patients were randomised, based on a computer-generated list, to either profound or moderate neuromuscular blockade with stratification for centre. Surgeons, scrub nurses and researchers were blinded to treatment allocation. Treatment allocation was concealed in sealed opaque envelopes. The attending anaesthetic staff were not blinded because they had to maintain the adequate level of NMB according to the allocation of treatment.

Anaesthesia and surgery

All laparoscopic procedures were performed by two surgeons with at least one experienced transplant surgeon (>30 LDNs). In all patients, anaesthesia was induced and maintained with remifentanil and propofol. Neuromuscular function was monitored by the Philips IntelliVue NMT module (connected to Philips IntelliVue MP70/MX800 patient monitor, software version J.10.52; Philips, Amsterdam, the Netherlands) or TOF-Cuff NMT monitor (RGB Medical Devices S.A., Madrid, Spain). Both groups received an initial bolus dose of rocuronium 0.6 mg kg^{-1}. Before administration of rocuronium 0.6 mg kg^{-1}, the NMT module or TOF-Cuff was calibrated.

In the profound NMB group, an infusion of rocuronium (0.3 to 0.4 mg kg^{-1}) was started after intubation and titrated towards a PTC of 1 to 3. In the moderate NMB group, patients received no additional rocuronium after tracheal intubation and the neuromuscular function was allowed to recover spontaneously. After skin closure, the NMB was reversed with sugammadex, using 4 mg kg^{-1} in the profound NMB group and 2 mg kg^{-1} in the moderate NMB group. Extubation was performed when the patients had a stable TOF ratio of more than 0.9 for 2 min.

Postoperative protocol

Postoperative pain management was achieved by paracetamol (1000 mg every 6 h) and patient-controlled intravenous analgesia (1 mg morphine per bolus). On postoperative day 1, patient-controlled analgesia was replaced by oral analgesics. In case of postoperative nausea and/or vomiting, ondansetron 4 mg intravenously (maximum 12 mg day^{-1}) was administered or, second choice, metoclopramide 10 mg intravenously (maximum 30 mg day^{-1}). On day 1 the urinary catheter was removed

and patients were encouraged to start immediately with a normal diet and mobilisation.

Evaluation of peri-operative conditions

The primary surgeon was asked to evaluate the Leiden surgical rating scale (L-SRS)[9] every 15 min after introduction of trocars. In case of insufficient surgical conditions (SRS 1 or 2) with violation of the safety of the patient, the surgeon could increase the intra-abdominal pressure (IAP) or convert to a hand-assisted procedure or laparotomy. In case of insufficient surgical conditions due to (severe) muscle contractions (SRS 1 to 2), the surgeon could request for an additional 0.6 mg kg^{-1} bolus of rocuronium. The blinded research physician registered the intra-operative parameters.

Outcome measures

The primary outcome measure was the total score of the Quality of Recovery-40 Questionnaire (QoR-40) at 24 h after extubation. The QoR-40 is a validated tool to measure a patient's self-assessed quality of recovery after surgery.[16] It comprises 40 questions regarding five dimensions: patient support, comfort, emotions, physical independence and pain. Each item is rated on a scale of 1 to 5, giving a minimum score of 40 and a maximum score of 200. A baseline measurement was performed the day before surgery. Secondary outcome measures were intra-operative parameters and intra-operative complications requiring corrective action. Intra-operative blood loss of greater than 200 ml in the collection bottle from the suction device was regarded as significant and reported. Other secondary outcomes included total score of the QoR-40 at 48 h after extubation, postoperative pain scores [numerical rating scale (NRS)], postoperative nausea (NRS), the cumulative use of analgesics and anti-emetics, time to reach discharge criteria and length of hospital stay. Follow-up was performed after 30 and 60 days with registration of postoperative complications, graded according to the Clavien–Dindo classification,[17,18] readmissions and return to daily activity and work.

Sample size calculation and data analysis

Generally it is assumed that a 10-point difference in the total QoR-40 score represents a clinically relevant improvement in quality of recovery, based on previously reported values on the mean and range of the QoR-40 score in patients after anaesthesia and surgery.[16] Based upon our previous studies, we used a SD of 15 points for the QoR score the first day after surgery.[19] A sample size of 48 patients per group was required to provide 90% power to detect a 10-point difference in the quality of recovery score at 1 day after extubation (alpha 5%).

Data were analysed on an intention-to-treat basis. After unblinding, the depth of neuromuscular blockade was analysed to assess the need for an as-treated analysis, as was mentioned in our previously published trial protocol.[15] For all analyses, statistical significance was defined as P less than 0.05. All analyses were performed using SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, New York, USA).

Results

Patient characteristics

The process of patient enrolment is depicted in Fig. 1. A total of 127 living kidney donors were screened for enrolment, 18 patients refused consent, seven patients were excluded because of insufficient command of the Dutch language and one patient was excluded because of chronic use of psychotropic drugs. A total of 50 patients were allocated to profound NMB and 51 patients to moderate NMB. Five patients were excluded because of withdrawal of consent or logistical reasons. Therefore, in both groups 48 patients remained for analysis, Patient baseline characteristics are shown in Table 1. There were no significant differences at baseline.

Level of neuromuscular blockade

After unblinding, the actual level of neuromuscular blockade was analysed for each individual patient, from start of surgery until 90 min. Within the profound group, a profound NMB (PTC 1 to 3) was achieved in 27 patients, and 14 patients achieved a deep NMB (TOF count 0, PTC $\geq$ 4). In five patients we failed to achieve a deep NMB, despite a continuous rocuronium infusion. In two patients from the profound NMB group, the data on the level of neuromuscular blockade were missing, due to failure of NMB level registration. Within the moderate NMB group, failure of NMB registration occurred in five patients. Overall, it appeared that in the profound NMB group, in 56% of the time an adequate depth of NMB was achieved. Therefore, we performed both an intention-to-treat analysis and an as-treated analysis, as described in our study protocol.[10] In the as-treated analysis, we combined the patients with PTC 1 to 3 and patients with TOF count 0 and PTC at least 4 in the profound NMB group. The five patients (10.4%) in which a TOF count 0 wasn't achieved, were analysed as moderate NMB. The two patients in the profound NMB group with missing data on their level of NMB were excluded from the as-treated analysis.

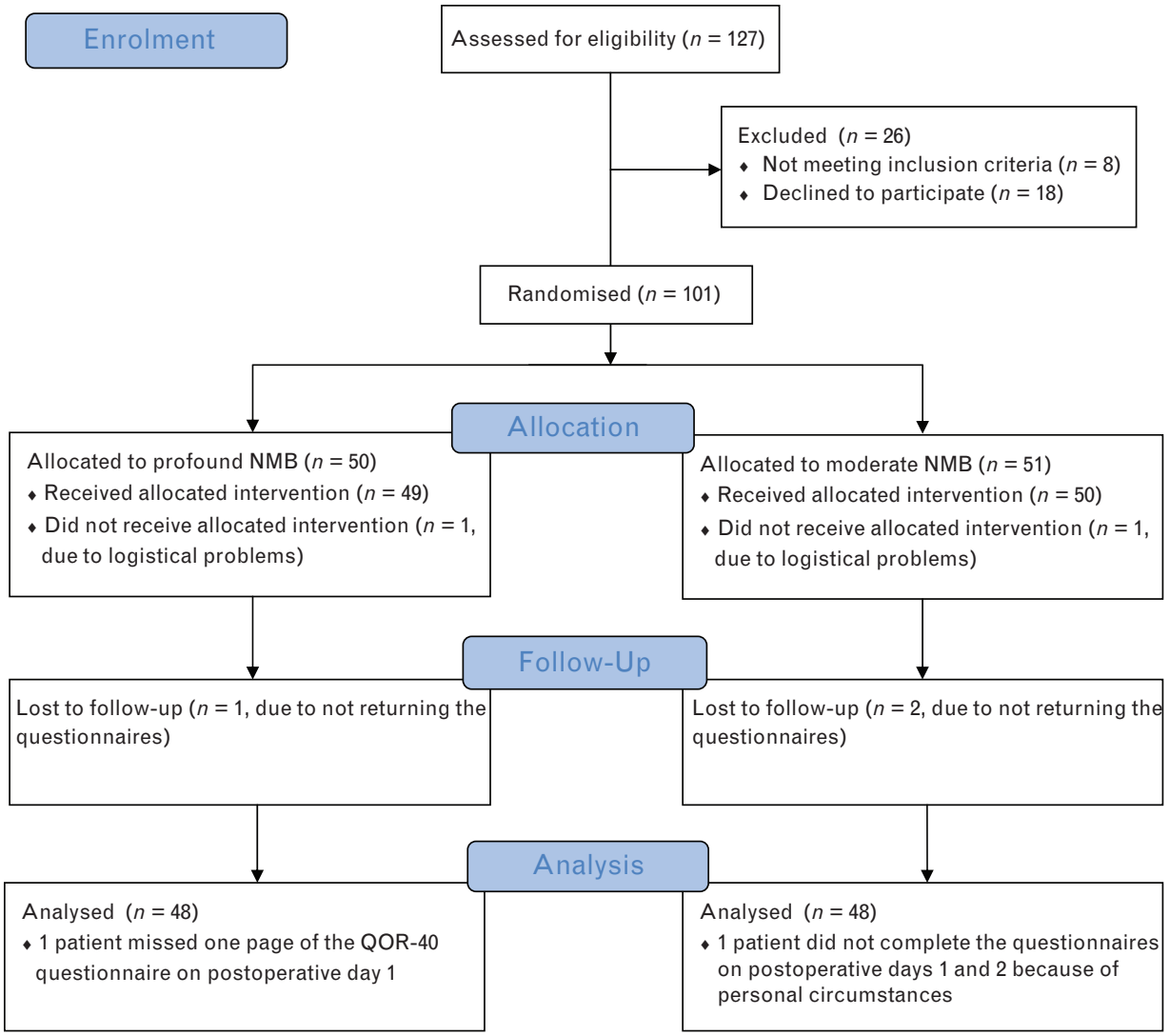
Primary outcome measure

The mean QoR-40 scores on postoperative day 1 in the profound NMB group and the moderate NMB group were 169 $\pm$ 18 and 169 $\pm$ 15, respectively (P = 0.95), as shown in Table 2. Correction for age, sex and side of nephrectomy did not affect the results. Also in the as-treated analysis, no differences were found in the mean QoR-scores on day 1 (P = 0.49).

Peroperative outcome measures

Peroperative data are shown in Table 3. There were no differences in operation time, warm ischaemia time or

Fig. 1



Consort flow diagram of patient enrolment.

estimated blood loss between groups. The mean L-SRS scores in the profound NMB group and the moderate NMB group were 4.8 ± 0.3 and 4.7 ± 0.5, respectively ($P = 0.23$), Only the as-treated analysis showed less contractions in the deep NMB group when compared with the moderate NMB group ($P = 0.03$). In four patients in the profound NMB group, the surgeon requested an extra bolus of rocuronium, versus 13 patients in the moderate NMB group ($P = 0.02$). Two patients were converted to hand-assisted LDN, both in the moderate NMB group: the first to provide better sight during dissection of the renal arteries, the second because the large kidney did not fit in the extraction bag. Intra-operative adverse events were observed in one patient in the profound NMB group (i.e. venous bleeding), versus six patients in the moderate NMB group [i.e. venous bleeding ($n = 2$), arterial bleeding ($n = 2$), ureteral laceration ($n = 1$) and adrenal laceration ($n = 1$)].

Secondary outcome measures

There was no difference in the mean total QoR-40 score 48 h after extubation between groups in the intention-to-treat analysis. However, a larger proportion of the patients with profound NMB could be discharged on day 2 when compared with the moderate NMB group (50.0 versus 29.8%, $P = 0.04$). In the additional as-treated analysis, a difference of 7.2 was found in the mean QoR-40 score on day 2, with a mean score of 179 ± 13 in the profound NMB group versus 172 ± 19 in the moderate NMB group, $P = 0.05$.

Table 1 Baseline characteristics

	Profound NMB, $n = 48$	Moderate NMB, $n = 48$	*P* value
Age (year)	55.7 ± 10.2	56.6 ± 9.7	0.66
Gender (male)	21 (43.8%)	24 (50%)	0.54
BMI (kg m^{-2})	26.7 ± 2.9	26.5 ± 3.0	0.74
Centre (Radboud: LUMC)	35 : 13	38 : 10	0.47
Previous abdominal surgery	13 (27.1%)	10 (20.8%)	0.47
Previous pregnancies	21 (43.8%)	21 (43.8%)	1.00
Side of nephrectomy (left)	42 (87.5%)	42 (87.5%)	1.00
Vascular anatomy (multiple vessels)	13 (27.1%)	17 (35.4%)	0.38

Values are presented as mean ± SD, or the number of patients (%). NMB, neuromuscular blockade.

Table 2 Quality of Recovery-40 Questionnaire

	Intention-to-treat			As-treated		
	Prof. NMB	Mod. NMB	*P* value	Prof. NMB[a]	Mod. NMB[b]	*P* value
Pre-operative	$n = 48$	$n = 48$		$n = 41$	$n = 53$	
Overall score	194.9 ± 6.6	196.9 ± 3.8	0.07	195.1 ± 6.0	196.5 ± 5.1	0.24
Physical comfort	57.9 ± 2.5	58.8 ± 1.8	**0.05**	58.0 ± 2.3	58.6 ± 2.1	0.17
Emotional status	43.2 ± 2.5	43.8 ± 1.7	0.19	43.2 ± 2.6	43.7 ± 1.8	0.32
Physical independence	24.8 ± 0.9	25.0 ± 0.2	0.14	24.9 ± 0.5	24.9 ± 0.7	0.91
Support	34.6 ± 1.3	34.9 ± 0.6	0.15	34.7 ± 0.9	34.8 ± 1.0	0.71
Pain	34.4 ± 1.3	34.5 ± 1.3	0.58	34.3 ± 1.3	34.5 ± 1.2	0.48
POD 1	$n = 47$	$n = 47$		$n = 40$	$n = 52$	
Overall score	169.3 ± 18.3	169.5 ± 15.5	0.95	171.1 ± 18.3	168.7 ± 15.9	0.49
Physical comfort	47.6 ± 8.4	47.1 ± 9.0	0.76	48.1 ± 8.7	47.0 ± 8.9	0.55
Emotional status	40.3 ± 4.6	41.7 ± 3.0	0.09	40.7 ± 4.4	41.3 ± 3.6	0.45
Physical independence	18.9 ± 3.6	18.7 ± 3.9	0.81	19.3 ± 3.6	18.7 ± 3.8	0.41
Support	33.4 ± 4.6	34.4 ± 1.4	0.19	33.5 ± 4.8	34.2 ± 1.7	0.37
Pain	27.6 ± 5.4	27.7 ± 4.1	0.92	27.8 ± 5.6	27.6 ± 4.2	0.81
Discharge on POD 1	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00
POD 2	$n = 48$	$n = 47$		$n = 41$	$n = 52$	
Overall score	175.6 ± 17.8	175.3 ± 16.5	0.93	179.5 ± 13.6	172.3 ± 19.2	**0.05**
Physical comfort	51.5 ± 7.3	50.7 ± 8.3	0.61	52.5 ± 6.6	49.9 ± 8.6	0.12
Emotional status	40.3 ± 4.8	41.2 ± 4.0	0.34	41.3 ± 3.7	40.2 ± 5.0	0.24
Physical independence	33.9 ± 2.6	34.5 ± 1.0	0.11	34.6 ± 0.8	33.9 ± 2.6	0.12
Support	33.9 ± 2.6	34.5 ± 1.0	0.11	34.6 ± 0.8	33.9 ± 2.6	0.12
Pain	28.9 ± 4.1	28.0 ± 4.5	0.32	29.5 ± 3.9	27.7 ± 4.5	**0.05**
Discharge on POD 2	24 (50.0%)	14 (29.8%)	**0.04**	21 (51.2%)	16 (30.8%)	**0.04**
Duration of hospital stay (days)	3.65 ± 0.76	3.79 ± 0.62	0.32	3.59 ± 0.71	3.81 ± 0.66	0.12

Mod. NMB, moderate neuromuscular blockade; Prof. NMB, profound neuromuscular blockade; PTC, posttetanic count; TOF, train-of-four. [a] Including patients with TOF count 0, PTC at least 4. [b] Including patients with shallow NMB; POD, postoperative day. Values are presented as mean ± SD or the number of patients (%).

Table 3 Peroperative parameters

	Intention-to-treat			As-treated		
	Prof. NMB, $n = 48$	Mod. NMB, $n = 48$	*P* value	Prof. NMB[a], $n = 41$	Mod. NMB[b], $n = 53$	*P* value
Total dose rocuronium (mg)	184.6 ± 83.1	67.0 ± 41.2	**0.00**	197.9 ± 82.0	70.8 ± 42.2	**0.00**
Total rocuronium dose related to body weight and ORT (mg kg^{-1} h^{-1})	0.9 ± 0.3	0.4 ± 0.2	**0.00**	1.0 ± 0.3	0.4 ± 0.2	**0.00**
% Profound NMB (0 to 90 min)	50.1 ± 32.8	NA		55.6 ± 30.2	NA	
% TOF count 0, PTC ≥ 0 (profound or deep NMB) (0 to 90 min)	85.2 ± 29.1	14.2 ± 22.5	**0.00**	93.2 ± 17.9	14.9 ± 22.2	**0.00**
Request for extra bolus rocuronium	4 (8.3%)	13 (27.1%)	**0.02**	4 (9.8%)	13 (24.5%)	0.07
ORT (min)	148.4 ± 40.7	143.0 ± 36.4	0.49	151.4 ± 42.3	141.8 ± 35.4	0.24
PNP time (min)	122.8 ± 44.5	113.8 ± 39.2	0.30	126.1 ± 46.6	112.8 ± 37.8	0.13
WIT1 (min)	3.6 ± 1.3	3.9 ± 1.6	0.30	3.6 ± 1.3	3.9 ± 1.6	0.39
EBL (ml)	60.2 ± 68.5	69.1 ± 72.3	0.54	62.3 ± 72.4	68.2 ± 69.7	0.69
Conversion to higher IAP	7 (14.6%)	4 (8.3%)	0.34	7 (17.1%)	4 (7.5%)	0.15
Conversion to HALDN	0 (0%)	2 (4.2%)	0.15	0 (0.0%)	2 (3.8%)	0.21
AEs	1 (2.1%)	6 (12.5%)	**0.05**	1 (2.4%)	6 (11.3%)	0.10
SRS total (mean 0 to 90 min)	4.8 ± 0.3	4.7 ± 0.5	0.23	4.8 ± 0.3	4.7 ± 0.5	0.16
SRS sight (mean 0 to 90 min)	4.7 ± 0.4	4.7 ± 0.5	0.46	4.8 ± 0.4	4.7 ± 0.5	0.39
SRS contractions (mean 0 to 90 min)	4.8 ± 0.3	4.7 ± 0.5	0.08	4.9 ± 0.3	4.7 ± 0.5	**0.03**

Mod. NMB, moderate neuromuscular blockade; Prof. NMB, profound neuromuscular blockade; PTC, posttetanic count; TOF, train-of-four. [a] Including patients with TOF count 0, PTC at least 4. [b] Including patients with shallow NMB; AEs, adverse events; EBL, estimated blood loss; HALDN, hand-assisted laparoscopic donor nephrectomy; IAP, intra-abdominal pressure; ORT, operation time; PNP, pneumoperitoneum; SRS, surgical rating scale; WIT1, first warm ischaemia time. Values are presented as mean ± SD, or the number of patients (%).

Table 4 Postoperative pain and analgesics

	Intention-to-treat			As-treated		
	Prof. NMB	Mod. NMB	*P* value	Prof. NMB[a]	Mod. NMB[b]	*P* value
Postoperative 1 h (PACU)	*n* = 48	*n* = 48		*n* = 41	*n* = 53	
Overall maximum pain score	4.0 ± 2.3	4.31 ± 2.4	0.49	4.1 ± 2.3	4.2 ± 2.4	0.78
Referred shoulder component	0.0 ± 0.2	0.3 ± 1.1	0.21	0.1 ± 0.2	0.2 ± 1.1	0.30
Postoperative 6 h	*n* = 48	*n* = 48		*n* = 41	*n* = 53	
Overall maximum pain score	3.7 ± 2.7	4.5 ± 2.2	0.13	3.5 ± 2.4	4.6 ± 2.4	**0.04**
Referred shoulder component	0.7 ± 1.6	1.0 ± 1.8	0.44	0.5 ± 1.3	1.0 ± 1.8	0.19
POD 1	*n* = 48	*n* = 47		*n* = 41	*n* = 52	
Overall maximum pain score	5.0 ± 2.3	5.6 ± 2.1	0.18	4.7 ± 2.3	5.7 ± 2.1	**0.03**
Referred shoulder component	2.5 ± 2.7	3.2 ± 2.8	0.22	2.1 ± 2.5	3.3 ± 2.9	**0.04**
POD 2	*n* = 48	*n* = 47		*n* = 41	*n* = 52	
Overall maximum pain score	4.6 ± 1.9	4.9 ± 2.2	0.47	4.2 ± 1.6	5.2 ± 1.6	**0.02**
Referred shoulder component	2.4 ± 2.7	3.3 ± 2.9	0.15	2.1 ± 2.4	3.5 ± 3.0	**0.02**
Cumulative morphine equivalent use	*n* = 48	*n* = 48		*n* = 41	*n* = 53	
Morphine equivalent dose, 1 h (mg)	5.8 ± 4.8	6.1 ± 4.9	0.80	6.0 ± 4.6	5.8 ± 5.0	0.85
Morphine equivalent dose, 6 h (mg)	11.2 ± 7.6	12.1 ± 7.9	0.61	11.7 ± 8.0	11.7 ± 7.7	0.99
Morphine equivalent dose, day 1 (mg)	18.3 ± 10.7	21.5 ± 13.1	0.19	18.9 ± 11.4	21.0 ± 12.6	0.40
Morphine equivalent dose, day 2 (mg)	4.9 ± 6.9	4.9 ± 6.9	0.98	4.2 ± 6.7	5.3 ± 7.0	0.47
Morphine equivalent dose, 48 h (mg)	23.2 ± 14.7	26.7 ± 16.9	0.29	23.1 ± 15.6	26.5 ± 16.3	0.31

Mod. NMB, moderate neuromuscular blockade; Prof. NMB, profound neuromuscular blockade; PTC, posttetanic count; TOF, train-of-four. [a]Including patients with TOF count 0, PTC at least 4. [b]Including patients with shallow NMB; PACU, post anaesthesia care unit; POD, postoperative day. Values are presented as mean ± SD.

Postoperative components of pain scores (NRS) are presented in Table 4. The profound NMB group experienced less intra-abdominal pain on the first postoperative day [2.9 ± 2.8 (profound), versus 4.1 ± 2.7 (moderate), $P = 0.04$] with a comparable amount of opiate consumption. In the as-treated analysis, we found the same results on day 1, but also reduced pain scores in the profound NMB group 6 h after surgery, and a reduction of overall pain scores and referred shoulder pain on days 1 and 2.

No influence of neuromuscular blockade was found on postoperative nausea, discharge criteria or the mean length of hospital stay. Follow-up after 30 days showed no differences between groups in postoperative pain scores, and return to daily activities and work (data not shown). Postoperative complications during hospital stay and after 30 and 60 days are shown in Table 5. One patient (from the moderate NMB group) was readmitted to the hospital, because

Table 5 Postoperative complications

	Intention-to-treat			As-treated		
	Prof. NMB	Mod. NMB	*P* value	Prof. NMB[a]	Mod. NMB[b]	*P* value
During hospital stay	*n* = 48	*n* = 48		*n* = 41	*n* = 52	
Number of complications	2 (4.2%)	4 (8.5%)	0.38	2 (4.9%)	4 (7.7%)	0.58
Type of complications						
Infection (ClavienDindo grade 2)	1 (2.1%)	3 (6.4%)	0.30	1 (2.4%)	3 (5.8%)	0.42
UTI	0 (0%)	2 (4.3%)		0 (0%)	2 (3.8%)	
Epididymitis	0 (0%)	1 (2.1%)		0 (0%)	1 (1.9%)	
Other	1 (2.1%)	0 (0%)		1 (2.4%)	0 (0%)	
Hypertension (ClavienDindo grade 2)	1 (2.1%)	1 (2.1%)	1.00	1 (2.4%)	1 (1.9%)	0.87
30 days after surgery	*n* = 48	*n* = 48		*n* = 41	*n* = 52	
Total number of complications	7 (14.6%)	5 (10.6%)	0.56	5 (12.2%)	7 (13.5%)	0.86
Type of complications						
Infection (ClavienDindo grade 2)	6 (12.5%)	4 (8.5%)	0.53	4 (9.8%)	6 (11.5%)	0.79
UTI	3 (6.2%)	2 (4.3%)		2 (4.9%)	3 (5.8%)	
Epididymitis	1 (2.1%)	1 (2.1%)		0 (0%)	2 (3.8%)	
Wound infection	1 (2.1%)	0 (0%)		1 (2.4%)	0 (0%)	
Other	1 (2.1%)	1 (2.1%)	1.00	1 (2.4%)	1 (1.9%)	0.87
Hypertension (ClavienDindo grade 2)	1 (2.1%)	1 (2.1%)		1 (2.4%)	1 (1.9%)	
60 days after surgery	*n* = 48	*n* = 48		*n* = 41	*n* = 52	
Total number of complications	9 (18.8%)	5 (10.6%)	0.27	7 (17.1%)	7 (13.5%)	0.63
Type of complications						
Infection (ClavienDindo grade 2)	8 (16.7%)	4 (8.5%)	0.23	6 (14.6%)	6 (11.5%)	0.66
UTI	4 (8.3%)	2 (4.3%)		3 (7.3%)	3 (5.8%)	
Epididymitis	1 (2.1%)	1 (2.1%)		0 (0%)	2 (3.8%)	
Wound infection	2 (4.2%)	0 (0%)		2 (4.9%)	0 (0%)	
Other	1 (2.1%)	1 (2.1%)	1.00	1 (2.4%)	1 (1.9%)	0.87
Hypertension (ClavienDindo grade 2)	1 (2.1%)	1 (2.1%)		1 (2.4%)	1 (1.9%)	
Number of unplanned readmissions	0 (0.0%)	1 (2.1%)	0.31	0 (0.0%)	1 (1.9%)	0.37

Mod. NMB, moderate neuromuscular blockade; Prof. NMB, profound neuromuscular blockade; PTC, posttetanic count; TOF, train-of-four. [a]Including patients with TOF count 0, PTC at least 4. [b]Including patients with shallow NMB; UTI, urinary tract infection. Values are presented as number of patients (%).

of a postoperative infection treated with intravenous antibiotics.

Discussion

The study did not show a significant effect of profound NMB during LDN on the quality of recovery at the first day after surgery, which was the primary outcome measure. Despite a clear protocol regarding neuromuscular monitoring and rocuronium dosing, in 14 patients allocated to a profound NMB more than 50% of the measurements reflected a deep NMB, instead of a profound NMB. In five patients within the profound NMB group, only a moderate NMB was achieved. Therefore, we performed an as-treated analysis, in which we compared profound NMB (including patients with TOF count 0, PTC ≥ 4) with moderate NMB (including patients with shallow NMB).

The as-treated analysis revealed that the quality of recovery was better at postoperative day 2 for those patients who received a profound NMB that was adequately maintained during surgery as compared with those receiving a moderate NMB. This improvement in quality of recovery in patients with a profound NMB may be attributed to significantly lower overall and referred shoulder pain scores. Furthermore, a larger proportion of the patients in the profound NMB group could be discharged at day 2 after surgery, when compared with the group with moderate NMB, although this did not lead to a significant reduction in the mean length of hospital stay. Finally, we observed less intra-operative adverse events within the profound NMB group when compared with the moderate NMB group, therefore we hypothesise that the use of profound NMB improves patient safety during the procedure.

The L-SRS is a Likert scale to score the intra-operative surgical conditions, ranging from 1 (extremely poor conditions) to 5 (optimal conditions).[9] In contrast to our earlier published systematic review and meta-analysis,[11] this study revealed no improvement in the overall surgical space conditions for the group allocated to profound NMB, when compared with moderate NMB. This can possibly be explained by the fact that the mean SRS was already very high (4.7/5) in patients receiving a moderate NMB. Possibly the use of standard IAP (12 mmHg) during transperitoneal laparoscopic procedures in nonobese patients, provides optimal surgical conditions in a majority of cases with moderate muscle relaxation. Moreover, the five-point L-SRS may not be able to detect subtle improvements in surgical conditions when profound NMB is applied. Nevertheless, we observed a small but significant improvement in the subscore for muscle contractions in patients allocated to a profound NMB.

The secondary analysis suggests that an adequately maintained profound NMB reduces postoperative pain scores after LDN, when compared with moderate NMB. A possible explanation is that profound NMB more effectively relaxes the abdominal wall as compared with moderate NMB, which leads to less pressure-induced tissue-injury, and hence less deep intra-abdominal pain and shoulder tip pain. Combining profound NMB with low-pressure PNP might lead to even further reduction of postoperative pain scores. Further research is required to study the beneficial impact of lower IAP combined with profound NMB on the quality of recovery after laparoscopic surgery.

The main strengths of this study are related to its double-blinded randomised controlled design, with computer-generated randomisation with allocation concealment and blinding for the assessment of the primary outcomes. Second, the multicentre design with different surgical teams and many different anaesthesiologists provides a good basis for the subsequent generalisation of our findings. And third, we published a study protocol beforehand. All the reported outcomes and analyses were described *a priori* in this protocol, which reduces the risk of reporting bias.

The main limitation of this study is related to the difficulty to achieve and maintain the intended depth of neuromuscular blockade. Patients allocated to the profound NMB group were titrated towards a PTC of 1 to 3. Despite high dosages of rocuronium with continuous infusion (on average a total of $1.2 \pm 0.4\,\text{mg}\,\text{kg}\,\text{IBW}^{-1}\,\text{h}^{-1}$ including the intubation dose and up to >300 mg total dose), achieving and/or maintaining the intended profound NMB was not successful in 21/48 patients who were allocated to the profound NMB group. Criteria for re-allocation of patients were defined in our study protocol that was published beforehand. The differences between the intention-to-treat and the as-treated analyses indicate that to achieve the maximum effect in pain reduction, quality of recovery and intra-operative safety, the profound NMB must be consistently maintained and continuously monitored to guide the necessary frequent additional dosing of neuromuscular blocking agent.

Possible explanations for our failure to reach or maintain an adequate depth of NMB in some patients could be that the initial intubation dose of rocuronium in the profound NMB group was too low to ensure an adequately profound block at the start of surgery. Because of differences between patients in sensitivity for and elimination of rocuronium, some patients need higher dosages to reach the same level of neuromuscular blockade.[20]

In our view, future studies should focus on the use of profound NMB to improve the safety during laparoscopic surgery. As pointed out by Biro *et al.*[14] in certain operations, a PTC of 1 to 3 is required to prevent minor patient movements or diaphragm contractions, therefore it would be favourable to distinguish between deep (TOF count 0, PTC ≥ 4) and profound NMB (PTC 1 to 3). For translation into routine clinical practice, it is very important that anaesthesia staff are well trained in how to achieve and

maintain an adequate profound NMB, guided by neuromuscular monitoring. When using an inhalational anaesthetic such as sevoflurane, instead of an infusion of propofol, lower (maintenance) doses of rocuronium might be sufficient for the maintenance of profound NMB during anaesthesia.[21]

In conclusion, our results did not show a beneficial effect of profound NMB on the quality of recovery after LDN at the first day after surgery, when compared with moderate NMB. Nevertheless, the secondary analysis indicates that an adequately maintained profound NMB during LDN improves postoperative pain scores and quality of recovery. To achieve the maximum effect in pain reduction, postoperative recovery and intra-operative safety during LDN, profound NMB must be consistently maintained with high dosages of neuromuscular blocking agent guided by vigilant neuromuscular monitoring.

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