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Original Article

Effects of depth of neuromuscular block on surgical conditions during laparoscopic colorectal surgery: a randomised controlled trial

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Summary

There have been few objective evaluations of the effects of deep neuromuscular blockade on intra-operative conditions. In this prospective randomised controlled study, we evaluated the effects of deep neuromuscular block on surgical conditions during laparoscopic colorectal surgery. Patients were randomly allocated using a computer-generated randomisation code to either moderate (train-of-four count 1–2 maintained and antagonised with neostigmine) or deep (post-tetanic count 1–2 maintained and reversed with sugammadex) levels of neuromuscular blockade. The primary outcome measure was the number of abrupt increases in intra-abdominal pressure intra-operatively. Secondary outcome variables were intra-operative restoration of spontaneous breathing, number of surgical requests for additional neuromuscular blockade, surgical rating of operating conditions and patient satisfaction. The surgeon who rated the surgical conditions score and investigator who checked the postoperative variables were blinded to patient allocation. In total, we recruited 70 patients of whom 64 (32 in each group) were analysed. Increases in intra-abdominal pressure (14/32 vs. 6/32; $p = 0.031$), intra-operative restoration of spontaneous breathing (16/32 vs. 2/32; $p < 0.001$) and request for additional neuromuscular blockade (21/32 vs. 8/32; $p = 0.001$) were more frequent in the moderate compared with the deep group. In patients undergoing elective laparoscopic colorectal surgery, deep neuromuscular blockade provided better surgical conditions than moderate neuromuscular blockade, as measured by a reduction in the incidence of intra-abdominal pressure alarms.

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Introduction

It has been historically recommended that moderate levels of neuromuscular block be maintained during surgery because cholinesterase inhibitors had a limited ability to antagonise deep levels of neuromuscular blockade. The introduction of sugammadex has made the immediate and complete reversal of deep neuromuscular block possible, thereby allowing a greater degree of intra-operative neuromuscular blockade to be maintained [1]. However, there have been few objective evaluations of the effects of deep neuromuscular blockade on intra-operative conditions.

Laparoscopic surgery is a procedure that might benefit from deep neuromuscular blockade. Slight patient movements can have significant effects on surgical conditions because surgeons work in enclosed spaces with a limited field of vision. Several studies have evaluated the effects of deep neuromuscular blockade on surgical conditions in different types of laparoscopic surgery [2–5]. However, these studies have utilised the surgical rating scale, which is wholly dependent on the surgeon's opinion and hence is a subjective outcome parameter. In this study, we hypothesised that intra-operative deep neuromuscular blockade would improve surgical conditions, as reflected by a decreased incidence of intra-abdominal pressure (IAP) alarms during pneumoperitoneum in patients undergoing laparoscopic colorectal surgery.

Methods

After ethical approval and trial registration, this prospective randomised controlled study was carried out at a single institution (Seoul National University Bundang Hospital) in compliance with the Declaration of Helsinki and good clinical practice research guidelines. Patients undergoing elective major laparoscopic colorectal surgery who provided written informed consent were included. We did not study patients meeting any of the following criteria: age < 18 years; ASA physical status ≥ 3; body mass index (BMI) < 18.5 or ≥ 35 $kg.m^{-2}$; history of neuromuscular, renal or hepatic disease; previous abdominal surgery; and treatment with drugs known to affect neuromuscular function. Patients were randomly allocated to either the moderate or deep group using a computer-generated randomisation code (Random Allocation Software, version 2.0). The surgeon who rated the surgical condition score and the investigator who checked the postoperative variables were blinded to the group allocation.

Patients were premedicated with intravenous (i.v.) midazolam 0.03 $mg.kg^{-1}$ in the reception area. In the operating room, routine monitoring was applied, including electrocardiography, non-invasive arterial pressure and pulse oximetry. Anaesthesia was then induced with propofol 1–2 $mg.kg^{-1}$ and a target-controlled infusion (TCI) of remifentanil starting at 3 $ng.ml^{-1}$. Anaesthesia was maintained with desflurane and remifentanil TCI titrated to maintain bispectral index 40–60 and mean arterial blood pressure within 20% of pre-operative values.

After induction of anaesthesia, acceleromyography (TOF-Watch-SX; MSD BV, Oss, the Netherlands) was performed to monitor the baseline response of the corrugator supercilii muscle. Monitoring and management of neuromuscular function were performed following good clinical research practice guidelines for studies investigating neuromuscular blocking agents (NMBAs) [6]. The TOF-Watch-SX was attached to the patient's face using the eye adapter (Organon Ltd., Dublin, Ireland) to monitor contraction of the corrugator supercilii muscle (Fig. 1). Calibration and stabilisation of the TOF-Watch-SX was carried out before the administration of rocuronium: after 50 Hz tetanic stimulation for 5 s, the calibration button of the TOF-Watch-SX was activated, and a series of train-of-four (TOF) measurements was documented for > 2 min until a stable baseline was obtained (< 5% variation in TOF ratios). Rocuronium 0.6 $mg.kg^{-1}$ i.v. was then administered and the patient's trachea intubated after confirmation of full neuromuscular blockade. Neuromuscular blockade was maintained with a continuous i.v. rocuronium infusion: this was initially 20 $mg.h^{-1}$ in both groups and was then titrated to maintain a TOF count of 1–2 in the moderate group and a post-tetanic count (PTC) of 1–2 in the deep group. Train-of-four was measured every 15 s by using the repetitive mode of TOF-Watch-SX and the dose adjustment of rocuronium was by 10 $mg.hr^{-1}$ in both groups.

During the surgery, the number of alarms due to an abrupt increase in IAP or restoration of spontaneous

Figure 1 Monitoring of neuromuscular block using TOF-Watch-SX (MSD BV, Oss, the Netherlands). The electrodes were placed to stimulate temporal branch of facial nerve and the transducer was placed by using the eye adapter (Organon Ltd., Dublin, Ireland) to sense the contraction of the corrugator supercilii muscle.

ventilation was observed and recorded by the anaesthetist. The number of surgical requests for additional neuromuscular blockade was also recorded. Intra-abdominal pressure was maintained at 12 mmHg during pneumoperitoneum and the pressure alarm for IAP was set at > 15 mmHg. Alarms that occurred during trocar insertion, carbon dioxide insufflation or external pressure by the surgeon were excluded. At the end of surgery, neostigmine 50 $\mu g.kg^{-1}$ with glycopyrrolate 10 $\mu g.kg^{-1}$ i.v. was administered to the moderate group, and sugammadex 4 $mg.kg^{-1}$ i.v. was administered to the deep group to antagonise neuromuscular blockade. Patients were transferred to the recovery area after tracheal extubation, which was performed after confirmation of recovery to TOF ratio 0.9, spontaneous breathing and restoration of consciousness. The time taken to reach a TOF ratio 0.9 after the administration of neostigmine/sugammadex was recorded. Incidence of dry mouth and the time to first postoperative bowel movement after surgery were evaluated at 1 h, 24 h and 48 h postoperatively. Surgeons were asked to rate the surgical conditions before leaving the operating room on a 5-point scale (Table 1). A patient satisfaction score on a 5-point scale was also evaluated. Good to optimal ratings (scores of 4–5) in the surgical condition and patient satisfaction scores were regarded as acceptable. Duration of hospital stay was also recorded.

Table 1 The surgical rating scale [3].

1 Extremely poor	The surgeon is unable to work due to coughing or due to the inability to obtain a visible laparoscopic field due to inadequate muscle relaxation. Additional NMBAs must be given
2 Poor	There is a visible laparoscopic field, but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements, or both with the hazard of tissue damage. Additional NMBAs must be given
3 Acceptable	There is a wide visible laparoscopic field but muscle contractions, movements or both occur regularly causing some interference with the surgeon's work. There is the need for additional NMBAs to prevent deterioration
4 Good	There is a wide laparoscopic working field with sporadic muscle contractions, movements or both. There is no immediate need for additional NMBAs unless there is the fear of deterioration
5 Optimal	There is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional NMBAs

NMBA, neuromuscular blocking agent.

The primary outcome measure was the incidence of IAP alarms. The sample size was calculated based on our pilot study which indicated that the incidence of IAP alarms was around 40% with moderate neuromuscular blockade. On the basis that deep neuromuscular blockade would result in a 30% decrease in the incidence of IAP alarms, 32 patients per group were required ($\alpha = 0.05$ and $\beta = 0.2$). We decided to recruit 35 patients per group, anticipating a 10% dropout rate. Minitab v.17 (Minitab Inc., State College, PA, USA) was used for statistical analysis. Chi-square and Mann–Whitney U-test were used to analyse the incidence of IAP alarms and spontaneous ventilation, requests for addition neuromuscular blockade, surgical rating scales and patient satisfaction scores. Patient characteristics and other intra- and postoperative variables were analysed using Student's t-test and Mann–Whitney U-test. P values < 0.05 were considered statistically significant.

Results

In total, 76 patients were assessed for eligibility, of whom 64 were analysed (Fig. 2). Baseline patient characteristics did not differ significantly between the groups (Table 2). The incidence of IAP alarms, intra-operative restoration of spontaneous ventilation and surgical requests for additional neuromuscular blockade were significantly higher in the moderate compared with the deep group (Table 3). The moderate group received less rocuronium intra-operatively, but despite this, recovery to TOF 0.9 was significantly slower than that seen in the deep group (Table 3). Anaesthetic and surgical times were similar in both groups (Table 3).

Fewer patients in the moderate group achieved acceptable surgical rating and patient satisfaction scores compared with the deep group (Tables 3 and 4). The time to first bowel movement after surgery did not differ significantly between the groups, although more patients in the moderate group complained of a dry mouth 24 h postoperatively (Table 4).

Discussion

To our knowledge, this is the first study to use IAP alarms during pneumoperitoneum as an indicator of surgical conditions. Maintaining intra-operative deep neuromuscular blockade decreased the incidence of

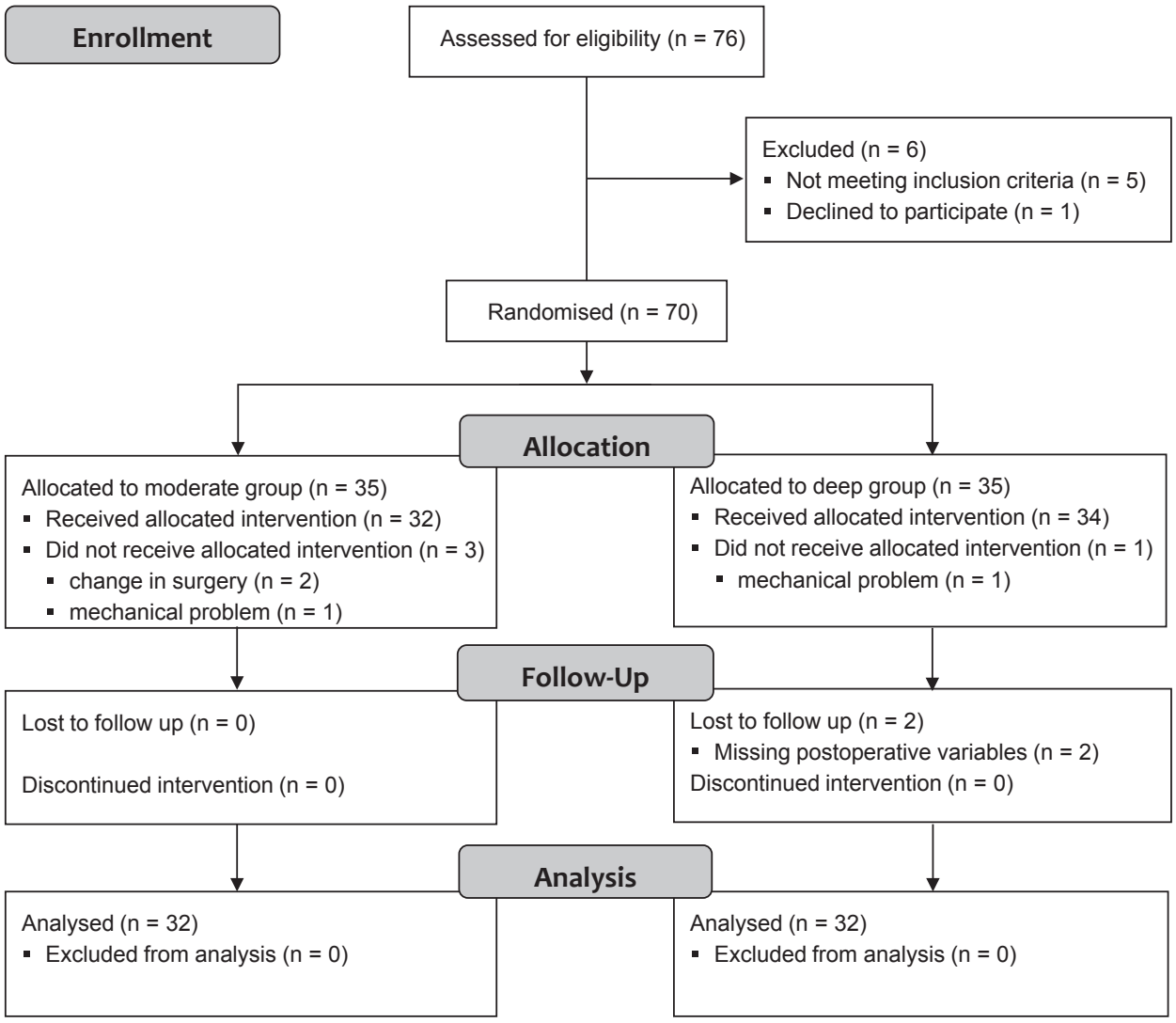

Figure 2 CONSORT flow chart.

IAP alarms during laparoscopic colorectal surgery, which is thought to reflect an improvement in surgical conditions.

Since the introduction of sugammadex, studies evaluating the utility of intra-operative deep neuromuscular blockade have been ongoing, and controversy still exists over its clinical usefulness [7–9]. The main focus of the studies are laparoscopic surgeries, for which deep neuromuscular blockade appears to improve surgical conditions [2–5, 10]. The improved surgical conditions and effectiveness have also been shown in laryngeal microsurgery and in surgery involving morbidly obese patients [11, 12]. However, controversy persists, with conflicting results seen in gynaecological laparoscopic surgery [4, 13–15]. Pelvic organs are contained in more rigid bony structures (i.e. the pelvic cavity) and, therefore, surgical procedures seem less likely to be affected by the degree of neuromuscular blockade compared with those performed on abdominal organs.

We could find only one study evaluating deep neuromuscular block in colorectal laparoscopic surgery, which is thought to represent a different surgical environment from upper abdominal or pelvic organ surgeries [16]. Mean IAP during pneumoperitoneum, which was titrated by the operating surgeon, was lower with deep (PTC 1-2) compared with moderate neuromuscular blockade (TOF 1-2) during laparoscopic colorectal surgery. Our results provide further evidence of the beneficial effects of deep neuromuscular blockade on surgical conditions during laparoscopic colorectal surgery.

Table 2 Baseline patient characteristics. Values are number or mean (SD).

	Moderate group n = 32	Deep group n = 32
Sex; male	20	19
Age; year	60 (12)	58 (12)
Weight; kg	64 (11)	65 (12)
Height; cm	164 (8)	164 (9)
BMI; $mg.kg^{-2}$	24 (3)	24 (4)
ASA physical status 1/2	18/14	16/16
History of cigarette smoking	16	17
Operator 1/2	16/16	23/9
Diagnosis		
Colon cancer	13	15
Rectal cancer	16	13
Colon polyp	3	4

Table 3 Intra-operative variables. Values are number or mean (SD).

	Moderate group n = 32	Deep group n = 32	p value
IAP alarm	14	6	0.031
Spontaneous ventilation	16	2	< 0.001
Surgical requests for additional NMBA	21	8	0.001
Total rocuronium dose; $mg.kg^{-1}$	1.5 (0.5)	2.4 (0.7)	< 0.001
Time to TOF 0.9; min	7.2 (3.7)	3.7 (1.6)	< 0.001
Operation time; min	174 (53)	167 (49)	0.585
Anaesthesia time; min	224 (57)	212 (57)	0.421
Acceptable surgical rating score	21	28	0.040

IAP, intra-abdominal pressure; TOF, train-of-four ratio; NMBA, neuromuscular blocking agent.

Table 4 Postoperative variables. Values are number or mean (SD).

	Moderate group n = 32	Deep group n = 32	p value
Dry mouth			
1 h	19	19	1.000
24 h	30	23	0.043
48 h	22	18	0.439
First bowel movement			
1 h	0	1	1.000
24 h	2	6	0.257
48 h	14	13	1.000
Hospital stay; days	9.9 (3.6)	9.1 (2.7)	0.219
Acceptable patient satisfaction score	20	28	0.021

Most previous studies investigating deep neuromuscular blockade have focused on surgical conditions as scored by surgeons; no study has used the frequency of IAP alarms during pneumoperitoneum as an outcome variable. We sought to use a more objective indicator of surgical conditions and suggest that IAP alarms may capture subtle movements that could be missed by a person; gross patient movements were very rare in both groups. We excluded IAP alarms caused by external factors, such as trocar insertion, gas insufflation or pressure by the surgeon, and believe the abrupt increase in IAP can reflect subtle muscle contractions of the patients. The restoration of spontaneous ventilation showed a similar pattern to the IAP alarms, that is, it was more frequently observed in the moderate compared with the deep group. This may be explained by differences in the sensitivity of muscles to NMBAs, with diaphragmatic muscles recovering faster from neuromuscular blockade than abdominal or peripheral muscles [17]. The sensitivity of the corrugator supercilii muscles to NMBAs is situated between that of the most resistant (diaphragm muscle) and most sensitive (orbicularis oculi muscle, abdominal muscles and peripheral muscles of the limbs) muscles [18, 19]. That is, onset and recovery are faster in the corrugator supercilii muscle compared with the adductor pollicis muscle. Monitoring neuromuscular block using the corrugator supercilii muscle better predicts the conditions for tracheal intubation [20] and better reflects abdominal muscle relaxation during the recovery period [18]. Consequently, the depth of neuromuscular blockade in both groups may have been deeper in the present study than in studies using the adductor pollicis muscle as a monitoring site. Care must, therefore, be taken when comparing our results with those of previous studies. This may also have contributed to the relatively high surgical ratings in the moderate group compared with other studies.

Based on our clinical experience and previous studies, maintaining deep intra-operative neuromuscular blockade that is reversed by sugammadex at the end of surgery, makes practitioners more comfortable and satisfied, which itself could be related to patient outcome [10, 21]. However, empirically demonstrating these intuitively beneficial effects is a separate matter. We were unable to demonstrate a reduction in the duration of surgery. This

is in contrast to our previous study, which showed a significant decrease in the duration of operations with deep compared with moderate neuromuscular block during laparoscopic cholecystectomy [22].

Our study has several limitations. First, two patients in the deep group recommenced spontaneous ventilation. By definition, deep neuromuscular blockade included a spectrum of conditions from a PTC of 1 to multiple tetanic stimuli before the appearance of a twitch response to TOF stimulation. The PTC was measured every 10 min in the deep group and the possibility of the degree of neuromuscular blockade temporarily reaching a moderate degree of neuromuscular blockade cannot be ruled out. Second, we did not record data on the amount of remifentanil used, which might have influenced intra-operative variables, especially spontaneous ventilation. However, we presume that the amount of remifentanil used was comparable in both groups. A previous study that employed a similar anaesthetic technique to that used in our work did not show differences in intra-operative propofol and sufentanil doses between patients allocated to moderate or deep neuromuscular blockade [3]. Third, surgeons could also hear the IAP alarms and this might have affected their surgical rating of operative conditions score or requesting of additional neuromuscular blockade. However, they were blinded to patient allocation and this effect appears to have been minimal. Finally, we used different reversal agents, that is, neostigmine for the moderate group and sugammadex for the deep group, which might have affected postoperative variables. In particular, time to TOF 0.9, patient satisfaction score and incidence of dry mouth seems to be related more to the effect of reversal agents than depth of neuromuscular blockade. However, other intra-operative variables including our primary outcome measure, that is, the IAP alarms, surgical satisfaction and requests for additional neuromuscular blockade, are related to deep neuromuscular blockade and not the reversal agents used.

In conclusion, in patients undergoing elective laparoscopic colorectal surgery, deep neuromuscular blockade was associated with better surgical conditions than moderate neuromuscular blockade, as measured by a reduction in the incidence of IAP alarms.

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