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Original Article

A randomised controlled trial comparing deep neuromuscular blockade reversed with sugammadex with moderate neuromuscular block reversed with neostigmine

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Short title – *Recovery following deep versus moderate block*

Summary

Deep neuromuscular block aims to improve operative conditions during laparoscopic surgery with a lower intra-abdominal pressure. Studies are conflicting on whether meaningful improvements in quality of recovery occur beyond emergence, and whether lower intra-abdominal pressure is achieved. In this pragmatic randomised trial with 1:1 allocation, adults undergoing elective laparoscopic surgery were allocated to moderate neuromuscular block reversed with neostigmine, or deep neuromuscular block reversed with sugammadex. Allocation was revealed to the anaesthetist only. Primary outcome was cognitive recovery of the Postoperative Quality of Recovery Scale (PostopQRS), 7 days after surgery. Secondary outcomes included recovery in other domains of the PostopQRS at 15 and 40 minutes, days 1, 3, 7, 14, and 1 and 3 months after surgery. Chi-squared was used for the primary outcome, and generalised linear mixed model for recovery over time between groups. Of 350 participants randomised, 140 (deep) and 144 (moderate) were analysed for the primary outcome. There was no difference in the PostopQRS cognitive domain at day 7 (deep 92.9% vs. moderate 91.8%, OR 1.164; 95%CI 0.486–2.788, p=0.826), or at any other time-point. No significant difference was observed for physiological, emotive, activities of daily living, nociception, or overall recovery. Length-of-stay in the post anaesthesia care unit (mean (SD) deep 108 (58) vs. moderate 109 (57) min, p=0.78) and hospital (1.8 (1.9) vs. 2.6 (3.5) days, p=0.019) was not different. Intra-abdominal pressure and surgical operating conditions were not different between groups. Deep neuromuscular block did not improve quality of recovery compared with moderate neuromuscular block in operative laparoscopic surgery over a one hour duration.

The current standard of care for laparoscopic surgery is to use a moderate neuromuscular block and reversal with neostigmine (coupled with either atropine or glycopyrrolate) [1]. The rationale for deep neuromuscular blockade (NMB) in laparoscopic surgery is to improve surgical operating conditions by increasing the size of the operative field during pneumoperitoneum and reducing the risk of organ movement from either muscle tone or diaphragmatic activity [2]. A second aim is to provide adequate surgical conditions but at a lower intra-abdominal insufflation pressure [2,3], thereby reducing the haemodynamic and respiratory consequences of raised intra-abdominal pressure, and reducing venous congestion in abdominal organs and the brain, which may affect tissue oxygen utilisation [4]. The likely mechanism for any sustained recovery benefits associated with the use of deep NMB (such as reduced pain, less cognitive impairment, or less organ damage such as acute kidney injury) is most likely a result of reducing the intra-abdominal pressure during surgery.

The role of sugammadex is to facilitate rapid reversal of deep NMB, which is not possible with neostigmine [1]. However, neuromuscular blocking drugs and reversal agents are unlikely to be major contributors to quality of recovery beyond the immediate emergence and early post-operative acute care unit (PACU) stay, due to their short duration of action or from being highly ionised molecules unlikely to cross the blood–brain barrier. The evidence supporting deep NMB improving surgical operating conditions mostly arises from small investigational trials or observational series. A meta-analysis of 11 randomised controlled trials found that while deep NMB was associated with more “excellent or good” surgical ratings than moderate NMB in laparoscopic procedures, this association was not significant across subgroup analyses grouped by surgical rating scale assessment frequency and inflation pressure [3]. Several investigative trials have shown that a lower intra-abdominal pressure can be achieved with deep NMB, but whether this can be sustained in a pragmatic or “real-world” setting has not been tested.

The impact of deep NMB on quality of recovery outcomes is restricted to small investigative randomised controlled trials with conflicting results. The most common recovery outcomes assessed include postoperative pain and nausea, analgesia consumption, sedation and length of stay. Several studies showed no difference [5,6], where others primarily showed reduced abdominal or shoulder tip pain [7-9]. This literature is confounded by a wide range of intra-abdominal pressures and, therefore, difficult to associate the likely mechanism of benefit with the measured outcome. There is also an evidence gap around the multidimensional assessment of recovery, including cognition.

The haemodynamic and respiratory consequences of high intra-abdominal pressure are well-known and important management issues for anaesthetists. What is less appreciated is the effect of intra-abdominal pressure on tissue oxygenation for the brain and abdominal organs. Steep head up or head down positioning has potential (through the effects of gravity) to reduce oxygen delivery to the elevated regions and, conversely, increase venous congestion in the dependent regions [10]. This is further compounded by adding intra-abdominal pressure, and the higher the pressure, the more risk of inadequate oxygen delivery [11] or excessive venous congestion [10]. Tissue oxygenation is dependent on adequate delivery but also on the venous congestion pressure [12] . Either reduced oxygen delivery or increased venous pressure can adversely impair tissue oxygenation [12] which, in turn, may affect organ function [13]. Further the intra-abdominal pressure produces an external congesting pressure to intra-abdominal organs and, in animal studies, organ flow was reduced as intra-abdominal pressure increased [11]. Studies comparing low intra-abdominal pressure with standard pressure have reported less pain, a lower incidence of ileus or reduced length of stay [14,15]. There is an evidence gap, however, around whether increased venous congestion to the brain caused by high intra-abdominal pressure can lead to delayed or incomplete cognitive recovery. Further, the measurement of cognitive recovery can be confounded in early recovery due to the presence of inflammation or requirement for strong analgesics such as opioids. Unless cognitive testing occurs at a later time-point, where inflammation has resolved and strong analgesia requirement unlikely, then a small but clinically important difference in cognitive recovery could be masked.

Deep NMB is, therefore, a possible means to achieve lower intra-abdominal pressure during laparoscopic surgery, while still maintaining adequate operating conditions. Lower intra-abdominal pressure is the most likely mechanism for improved recovery outcomes due to haemodynamic, respiratory, or tissue oxygen utilisation, and potentially reduced inflammatory response. Deep NMB is, therefore, part of a bundle of interventions rather than an isolated technique. Whilst investigator trials have shown that a low pressure can be achieved with deep NMB, this has not been tested in a pragmatic trial.

The aim of this study was to compare deep with moderate NMB in a pragmatic trial to identify whether meaningful improvements in multidimensional quality of recovery outcomes exist after laparoscopic surgery beyond emergence and the PACU period, with particular focus on cognitive recovery.

Methods

This multicentre study was conducted over four hospitals and approved by the Human Research Ethics Committee at the Royal Melbourne Hospital. Local governance approvals were obtained from the Peter MacCallum Cancer Centre, the Royal Women's Hospital and Northpark Private Hospital. Written, informed consent was obtained from all participants.

This was a single-blind, multicentre, prospective, parallel randomised trial with 1:1 allocation ratio with recruitment between June 2017 and November 2018. Eligible participants were adults > 18 y, undergoing operative laparoscopic or robotic assisted laparoscopic procedures, duration of at least one hour, under general anaesthesia. This included gastrointestinal, gynaecology and urology surgical specialties. Exclusion criteria were: not fluent in English; diagnostic laparoscopic surgery only; currently pregnant; o any known allergies to rocuronium, desflurane, sugammadex or neostigmine.

Common management included: no pre-medication (other than oral analgesia); and induction with intravenous propofol and fentanyl (0.5–3 mcg.kg^{-1}), or equivalent dose of remifentanil. Multimodal analgesia was used as determined by the anaesthetist to treat peri-operative pain. Dual anti-emetic prophylaxis was used as per hospital guidelines. Desflurane was used for maintenance of anaesthesia in all participants and titrated to effect by the attending anaesthetist. Neuromuscular monitoring was applied and calibrated prior to induction of anaesthesia. Train-of-four (TOF) and post-tetanic count were used to assess the depth of neuromuscular block after induction of anaesthesia.

Participants were randomly allocated to receive either deep NMB reversed with sugammadex or moderate NMB reversed with neostigmine. For participants in the deep block group, the initial dose of rocuronium was 1.2 mg.kg^{-1}, followed by repeat doses of 0.15 mg.kg^{-1} until post-tetanic count ≤ 2. Reversal was with sugammadex, which was administered once post-tetanic count ≥ 1 (4 mg.kg^{-1} if TOF = 0 and post-tetanic count ≥ 1 and 2 mg.kg^{-1} if TOF ≥ 1). In the moderate block group, the initial dose of rocuronium was 0.6 mg.kg^{-1} followed by repeat doses of 0.15 mg.kg^{-1} if the TOF >2. Neostigmine was used as the reversal agent following a moderate block, and was co-administered with atropine (20 mcg.kg^{-1}) or glycopyrrolate (5 mcg.kg^{-1}) with a maximum neostigmine dosage of 5 mg. This was not administered until TOF ≥ 3 was observed. In both groups, the participants' tracheas were extubated when fully reversed (TOF = 4, and no fade, or TOF >0.9).

The Postoperative Quality of Recovery Scale (PostopQRS) tool was used to measure recovery. It is an externally validated assessment that is able to measure recovery over multiple domains including physiological, nociceptive, emotive, activities of daily living and cognition, as well as an additional domain with a focus on overall patient perspective including patient satisfaction [16]. For this study, the primary outcome was the differences in the incidence of recovery within the cognitive domain of the PostopQRS measured at postoperative day 7, which was chosen to reduce the potential of confounding from acute postoperative inflammation and the likely cessation of the need for opioid-based analgesia, which may impair cognitive function.

The cognitive domain of the PostopQRS includes five verbal cognitive tests. An example of the baseline PostopQRS survey time-point is shown in Supplementary Appendix S1. Generally, the PostopQRS assessment tool is administered pre-operatively to provide individual baseline measurements for each patient. Thereafter, recovery in various domains is defined by postoperative values equalling or exceeding individual baseline values, except for the cognitive domain where a tolerance level is added to adjust for normal performance variability [17]. That is, patients can perform a little worse than baseline in the cognitive domain, by the magnitude of the tolerance factor, and still be scored as recovered. Patients whose pre-surgery cognition values fall below the tolerance factor in 1 or more tests are categorised as 'low baseline cognition' and cognitive recovery is scored by the number of tests that score below the tolerance factor, and recovery is defined as the same or fewer tests scoring below the tolerance factor [18]. The PostopQRS was conducted face-to-face whilst in hospital and then via telephone after hospital discharge. The time-points for this study were: pre-surgery (baseline); 15 and 40 min in PACU; postoperative days 1, 3, 7 and 14; and again at 1 and 3 months following surgery.

Secondary outcomes included the incidence of recovery for all the other PostopQRS recovery domains and within the cognitive recovery domain at all other time-points of the study (15 min, 40 min, 1 day, 3 days, 14 days, 1 and 3 months following surgery). This includes each domain of the PostopQRS – physiological, nociceptive, emotive, activities of daily living and cognition as well as overall patient perspective (including satisfaction). Other outcomes included duration of anaesthesia, surgical procedure, operating room time, PACU stay and hospital length of stay; incidence of persistent neuromuscular block upon arrival at PACU (fade seen in patients, TOF ratio < 0.9 or TOF count < 4). Surgical operating conditions were rated by the treating surgeons. This assessment included maximal inflation pressure required for surgery and the number of times there was organ movement present in the participants during the procedure, as well as overall surgical satisfaction.

The randomisation sequence was generated using a web-based random sequence generator (https://www.sealedenvelope.com/simple-randomiser/v1/lists) with unequal block sizes of four, six and eight patients. Double-sealed opaque envelopes were produced by a non-participant of the study. Concealment of the randomisation was maintained until written informed consent was obtained and the participant was admitted to the operating theatre. The treating anaesthetists revealed the allocation only to themselves; it was not possible to blind the treating anaesthetists to the allocation due to the nature of the drugs. However, the randomisation was kept in a password protected file and it was not made available to the other research staff until the end of the study.

Missing data were not imputed, and incidence of recovery was analysed using available data. A Chi-squared test was used to analyse the primary outcome of cognitive recovery at 7 days after surgery. A generalised linear mixed model was used to analyse the incidence of recovery over time, with all outcome variables dichotomised as 'recovered' and 'not recovered' for the analysis [19]. Fixed effects included the allocated group, time as a categorical variable and the group by time interaction, and a random intercept for patients to account for within-patient correlation were included. Continuous data were analysed using Student's t test and all p values were two-sided. For the primary outcome, significance was defined as $p<0.05$, and to reduce the risk of a type-1 error for secondary outcomes, significance was defined as $p<0.01$. GENSTAT V18 (VSNi International Ltd, Hemel Hempstead, UK) was used to perform the generalised linear mixed model test, and SPSS V21 (SPSS Inc, Chicago, IL, USA) was used for other analyses.

The sample size estimate was based on the primary outcome of recovery in the cognitive domain of the PostopQRS at 7 days after surgery, and a clinically important difference in this outcome set at 15% between groups. Estimates of cognitive recovery were based on published PostopQRS research and using multiple ages and surgical cohorts [18,20-22]. If there is 'good recovery' it was estimated that, for this surgical cohort and duration of surgery, cognitive recovery would range from 70–85% at one week after surgery. Using a two-tailed estimate and Chi-squared analysis with good recovery defined as 85%, alpha value of 0.05 and power of 90% with 1:1 allocation ratio, the sample size required to detect an absolute difference of 15% was 161 participants per group. This was rounded to a total of 350 participants in the study cohort to compensate for potential participant non-completion. No interim analyses or stopping rules were planned.

Results

In the period from June 2017 to November 2018, 350 patients were enrolled across four hospital sites. As shown in Figure 1, 175 patients were equally enrolled into each group. Patient characteristics are shown in Table 1, with anaesthetic details in Table 2. There was no difference in anaesthesia, surgical and operating room duration, PACU times or hospital length of stay in both groups (p >0.01). No harm or unintended events occurred in any of the participants.

Recovery in the cognitive domain of the PostopQRS is shown in Figure 2. There was no significant difference at day 7 for recovery in the cognitive domain (deep block 92.9% and moderate block 91.8%, OR 1.164; 95%CI 0.486–2.788; p=0.826). There was also no difference in recovery across all time-points (p=0.954). Most patients had recovered in cognition at 3 months after surgery with only 3.6% not recovered in the deep and 1.4% not recovered in the moderate block group.

All domain recovery (recovery across all of the individual recovery domains) as well as recovery within each of the individual domains of the PostopQRS are shown in Figure 3. All domain recovery was similar in both groups (p=0.371, for time by group interaction) and increased over time, with the incidence of recovery at 3 months being 73% for deep and 75.7% for moderate block. With regard to specific domains of the PostopQRS, there was no difference in the physiological domain (p=0.982). Recovery in the nociceptive domain of the PostopQRS showed a similar trend to all domain recovery with a gradual increase in the incidence of recovery within both groups but without any significant difference between the groups (p=0.362), with the subdomain of postoperative pain contributing most to the nociceptive domain of the PostopQRS. There was no difference in the recovery in the emotive domain of the PostopQRS (p=0.619), nor in recovery in the functional domain of the PostopQRS (p=0.28).

Patient perspective on the impact of surgery on their ability to work, activities of daily living, and clarity of thought, and satisfaction is shown in Figure 4. There were no differences between groups and satisfaction with care was universally high at all time-points.

The cognitive subdomains of the PostopQRS can be found in Supplementary Figure S1. There was an increase from 15 min initially to Day 1 across all the items of the cognitive domain, which is consistent with the cognitive recovery as shown in Figure 2. Supplementary Figure S1E shows a higher rate of recovery in the word generation subdomain of the deep block group (p=0.013), with a difference seen at 3 days (moderate block 87.1% and deep block 97.2%, OR, 5.095; 95%CI, 1.678–

15.47, p=0.002) and 1 month after surgery (moderate 88.3% and deep 96.9%, OR, 4.215; 95%CI, 1.359–13.069, p=0.008).

The incidence of persistent neuromuscular block arrival in PACU was low in both groups (<5%) and not different across both groups (Table 3).

Surgical satisfaction with operating conditions was high and not different between groups (p=0.73; Table 4). Organ movement was infrequent and not different between groups. When asked to guess which block the patient was randomised to, surgeons were unable to differentiate between deep and moderate block groups. The maximal inflation pressure was not different between groups (moderate block group mean (SD) 15.0 (3.6) vs. deep block 15.2 (3.5) mmHg, p=0.59)

Discussion

Given the almost identical overlap of recovery curves between the two groups, it is unlikely that small differences would be identified even with a larger sample size. As such, we are confident that the sample size was large enough to detect clinically important differences. Statistical differences observed within the cognitive domain, though statistically different were not particularly large clinical differences and may represent a type-1 error. Kim et. al. [23] found earlier recovery of the digits backwards neurocognitive test using sugammadex to reverse neuromuscular block after eye surgery. However, unless this finding is verified in future studies, these results should not be overemphasised at present. There was a shorter hospital length of stay within the deep block group, though this was not significant as a secondary endpoint (p>0.01), the relative effect size was considerable at 0.8 days and 31%. However, this may warrant further investigation to identify if this is a reproducible finding.

The literature is contradictory on whether deep NMB reduces pain, especially shoulder tip pain, with some studies finding a reduction in pain and/or opioid requirement [7,24,25] and others finding no difference [26-28]. However, if postoperative pain is related to the intra-abdominal inflation pressure, then it is unlikely to show any difference due to both groups having similar insufflation pressure. Interestingly, we did not find a difference in the surgical rating of operative conditions, which is contrary to other studies [7,25,26].

A lower intra-abdominal pressure is the most likely mechanism for improved recovery associated with the deep NMB approach. Our study did not find any difference in intra-abdominal pressure

which is consistent with other literature [5,29]. Our study is the largest randomised trial investigating the deep NMB technique and, importantly, was conducted in a pragmatic manner where we did not control insufflation pressure. The reason that lower intra-abdominal pressure was not achieved may relate to the limitations of the conventional insufflator device, which uses a low flow carbon dioxide delivery system (e.g. 5 $l.min^{-1}$ through a Varies needle to 10 $l.min^{-1}$ through a 5 mm trocar) [30]. When the surgeon uses suction to evacuate smoke or fluids from the abdominal cavity, the pneumoperitoneum will collapse if the suction volume exceeds the pneumoperitoneum volume and the capacity of the insufflator to introduce fresh gas. As the typical suction rate of surgical suction devices is 40 $l.min^{-1}$ (ISO standard 10079-3), it greatly exceeds the capacity of the insufflator and would lead to collapse of the pneumoperitoneum unless the surgeon "over-pressures" the abdomen. Whilst small investigational randomised controlled trials have shown that a low-pressure pneumoperitoneum can be achieved [7,25], this did not occur in our trial. It is important, therefore, to consider the deep NMB technique as a part of a bundle of care rather than an isolated technique. Studies using a high-flow, low-pressure port system using recirculating carbon dioxide has shown that a low-pressure pneumoperitoneum can be maintained with good operating conditions, and with improvements in recovery outcomes [14,15]. However, the combination of this type of insufflator technology with the deep NMB technique has not been tested in a pragmatic, randomised trial, nor measuring multi-dimensional quality of recovery outcomes beyond the early recovery phase.

The study included a relatively wide range of surgical types and conditions, ranging from prolonged robotic surgery for cancer, to upper gastro-intestinal or gynaecological operative procedures. However, the groups were well balanced and we did not find a difference in the number of patients who were inadequately reversed either at extubation or in PACU. In part, this may be due to the nature of the trial where extubation was permitted after achieving adequate neuromuscular reversal (TOF 4/4 and no fade). The incidence of inadequate reversal was very low compared to other published audits, though there were two participants in the moderate NMB group given sugammadex as a safety measure to avoid prolonged residual paralysis after neostigmine reversal.

Our study has several limitations. It was designed as a pragmatic trial and, therefore, we did not mandate a protocol to produce the lowest insufflation pressure. The potential advantage of deep NMB could be related to allowing adequate surgical conditions at a lower inflation pressure which, in turn, could reduce the congestion pressure and improve organ tissue oxygenation. It is possible that the absence of a protocol to maintain the lowest inflation pressure may have diminished any

potential difference between groups. The primary outcome was designed to measure cognitive recovery at 7 days after surgery to avoid confounding from analgesics and inflammation. We did measure recovery at earlier and later time-points and the recovery curves overlapped very closely, suggesting that a clinically meaningful difference is unlikely. We deliberately excluded diagnostic laparoscopy as those procedures tend to be brief with potentially less inflammatory response, which should lead to faster recovery.

We conclude that using conventional insufflation techniques in patients undergoing operative laparoscopy > 1 h in duration, deep neuromuscular block did not improve cognitive recovery, nor other recovery domains and did not facilitate a reduction in intra-abdominal pressure.

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Table 1. Patient demographics. Values are mean (SD) or number (proportion).

	Deep block n = 175	**Moderate block n = 175**
Age; y	54.4 (15.5)	54.6 (16.3)
Male	96 (54.9%)	73 (41.7%)
ASA physical status		
1	30 (17.1%)	24 (13.7%)
2	104 (59.4%)	99 (56.6%)
3	38 (21.7%)	45 (25.7%)
BMI; $kg.m^2$	28.8 (6.1)	29.5 (6.0)
Education; y	13.3 (3.4)	13.5 (4.0)
Alcohol consumption; [standard drinks]	3.9 (6.3)	4.8 (8.1)
Smoking status		
Previous smoker	86 (49.1%)	85 (48.6%)
Current smoker	15 (8.6%)	24 (13.7%)
Employment	114 (65.1%)	93 (53.1%)
Surgical access		
Laparoscopic	131 (74.9%)	125 (71.4%)
Robotic assisted	44 (21.1%)	50 (28.6%)
Surgical specialty		
Abdominal	87 (49.7%)	75 (42.9%)
Urology	41 (23.4%)	45 (25.7%)
Gynaecology	47 (26.9%)	55 (31.4%)
Outpatient	13 (7.4%)	12 (6.9%)
Anaesthetic technique		
General anaesthesia	164 (93.7%)	164 (93.7%)
General, with spinal analgesia	9 (5.1%)	11 (6.3%)
General, with regional block	2 (1.1%)	0

Table 2. Anaesthetic details. Values are mean (SD).

	Deep block n = 175	**Moderate block n = 175**	**p value**
Anaesthetic duration; min	164 (96)	165.4 (88.8)	0.89
Time to eye-opening; min	9.8 (6.2)	10.5 (6.5)	0.32
Time to arrival in PACU; min	14.6 (7.3)	15.4 (7.4)	0.3
Surgery duration; min	133.1 (78.2)	135.2 (82.4)	0.81
Operating room duration; min	179.8 (94.1)	182.8 (92.8)	0.77
Time spent in PACU; min	107.5 (58)	109.4 (57.0)	0.78
Discharge from hospital; days	1.8 (1.9)	2.6 (3.5)	0.019

Time is measured from the cessation of desflurane anaesthesia. PACU, post-anaesthesia care unit

Table 3. Incidence of residual neuromuscular block. Values are number (proportion)

	Deep block n = 175	**Moderate block n = 175**	**p value**
Full reversal before extubation, 4 twitches and ratio >0.9	161 (92%)	158 (90.3%)	0.68
No fade on TOF	162 (97%)	166 (96.5%)	1
No evidence of clinically inadequate reversal	170 (99.4%)	169 (98.8%)	1
NMB tested and positioned prior to surgery	135 (77.1%)	130 (74.3%)	0.68
How often was NMB checked during surgery?			0.15
None at all	0	4 (2.3%)	
Every min or less	19 (10.9%)	27 (15.4%)	
1-5 min	67 (38.3%)	52 (29.7%)	
6-10 min	35 (20%)	28 (16%)	
11-15 min	32 (18.3%)	37 (21.1%)	
16-30 min	16 (9.1%)	20 (11.4%)	
Only prior to extubation	2 (1.1%)	5 (2.9%)	

TOF, train-of-four; NMB, neuromuscular block

Table 4. Surgical operating conditions. Values are mean (SD) or number (proportion).

	Deep block (n = 175)	**Moderate block (n = 175)**	**p value**
Maximum inflation pressure; mmHg	15.2 (3.5)	15.0 (3.6)	0.59
Number of organ movements	0.3 (1.0)	0.6 (2.6)	0.18
Operating conditions			0.73
Excellent	99 (56.6%)	104 (59.4%)	
Good	48 (27.4%)	38 (21.7%)	
Acceptable	16 (9.1%)	20 (11.4%)	
Unacceptable	1 (0.6%)	3 (1.7%)	
Very unacceptable	1 (0.6%)	1 (0.6%)	
Surgeon guess which block the patient was in			0.81
Deep block	111 (68.9%)	112 (67.5%)	
Moderate block	50 (31.1%)	54 (32.5%)	

Figures

Figure 1. CONSORT participant flow diagram

Figure 2. Cognitive recovery at postoperative day seven as well as recovery across all time-points in patients receiving a deep block (-■-) or moderate Block (-o-). No significant differences between groups in the primary outcome of cognitive recovery at postoperative day seven, there was also no significant difference between groups in cognitive recovery across all postoperative time-points.

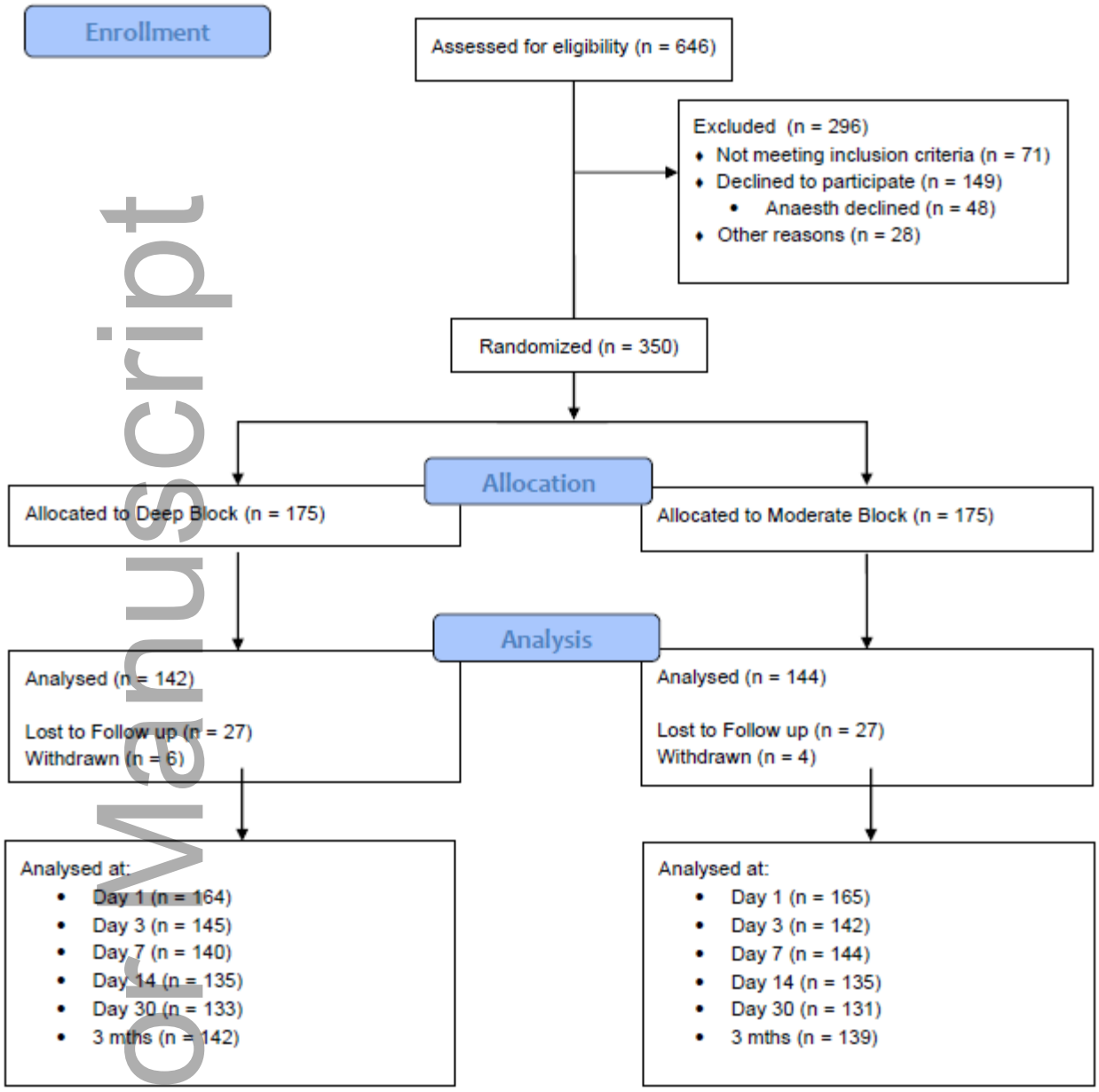
Figure 3. Incidences of domain level recovery in patients receiving a deep block (-■-) or moderate block (-o-). Panel A shows recovery in all the domains of the PostopQRS, Panel B is recovery in the physiological domain of the PostopQRS (vital signs and physical observations), Panel C is recovery in the nociceptive domain of the PostopQRS (pain and nausea), Panel D is recovery in the emotive domain of the PostopQRS (sadness/depression and anxiety/nervousness) and Panel E is recovery in the functional domain of the PostopQRS (activities of daily living). No significant differences between groups in any of the domains of the PostopQRS across all time-points.

Figure 4. Overall patient perspective in patients receiving a deep block (-■-) or moderate block (-o-). Panel A shows the impact on ability to work, Panel B Is the impact on daily living activities, Panel C is the impact on clarity of thought and Panel D is patient satisfaction. No significant differences between groups in overall patient perspective.

Appendices

Appendix S1: The Postoperative Quality of Recovery Scale Baseline assessments

Figure S1: Incidence of recovery within the cognitive domain in patients receiving a Deep Block (■) or Moderate Block (○). Panel A shows recovery in the cognitive subdomain, orientation. Panel B is recovery in the patients ability to repeat digits forwards, Panel C is recovery in the patients ability to repeat digits backwards, Panel D is recovery in the patients ability to recall words and Panel E is recovery in the patients ability to generate words where there was a significant difference with a greater incidence of recovery in the deep block group at day 3 and 1 month following surgery.



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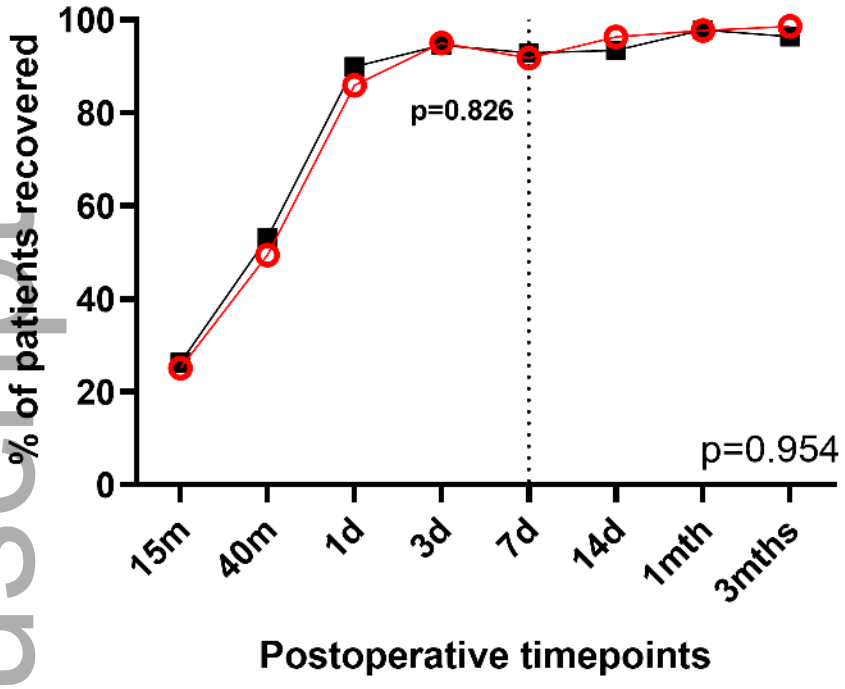

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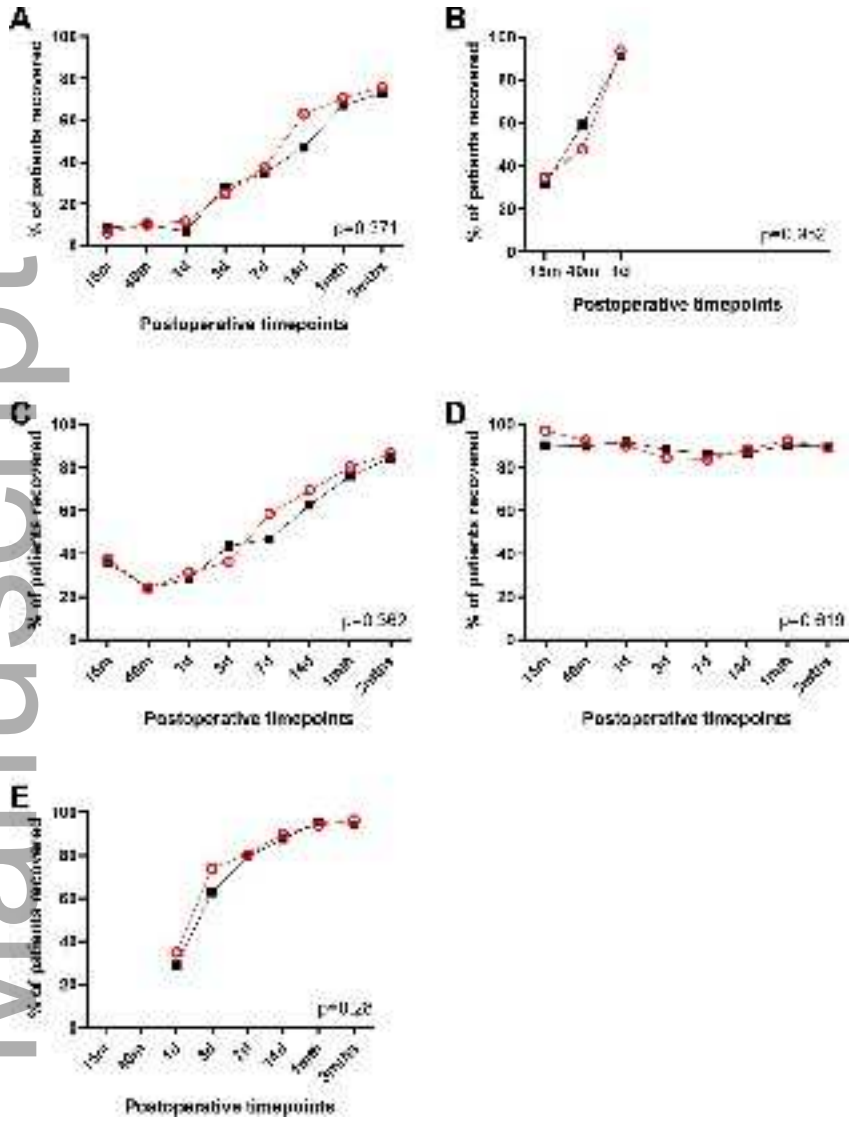

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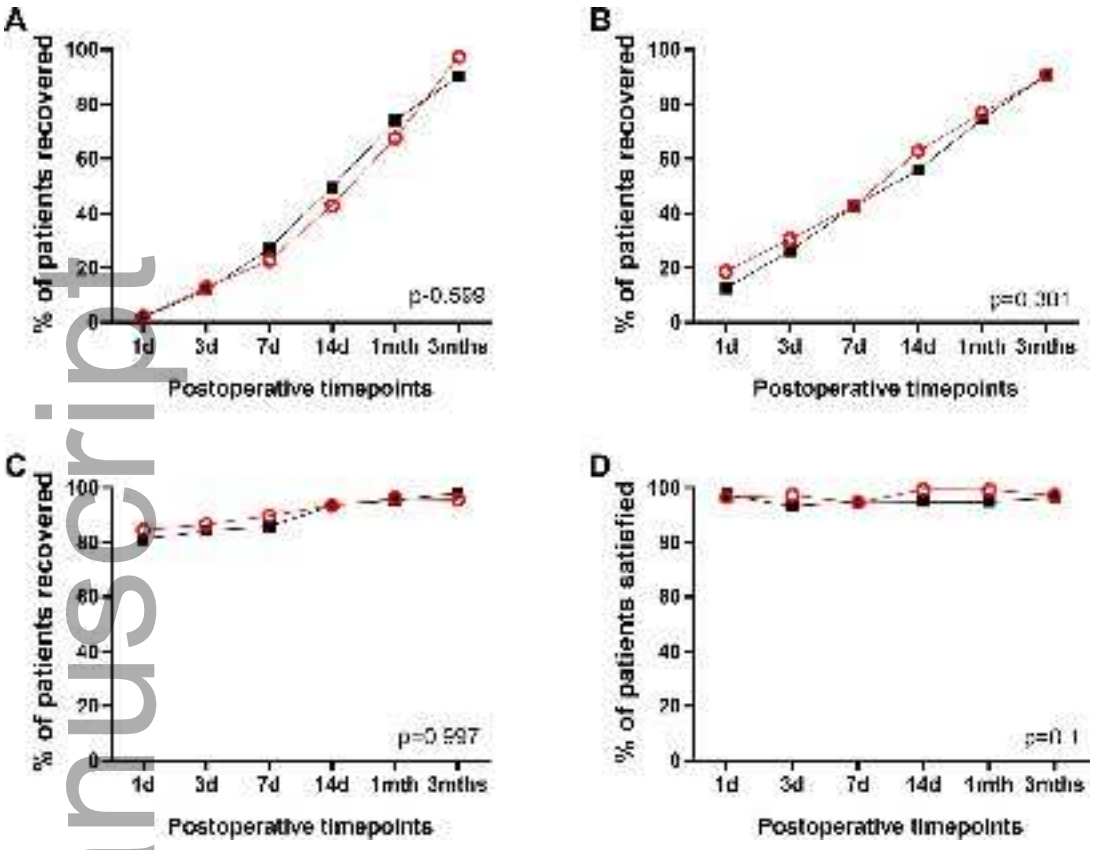

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