Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: A randomized trial of Effects on postoperative gastrointestinal motility

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Running Title: Postoperative gastrointenstinal motility

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Abstract

Background: Acetylcholinesterase inhibitors (e.g., pyridostigmine bromide) are used for neuromuscular blockade (NMB) reversal in patients undergoing surgery under general anesthesia (GA). Concurrent use of anticholinergic agents (e.g., glycopyrrolate) decreases cholinergic side effects, but can impede bowel movements. Sugammadex has no cholinergic effects; its use modifies recovery of gastrointestinal (GI) motility following laparoscopic cholecystectomy compared to pyridostigmine/glycopyrrolate. This study evaluated the contribution of sugammadex to the recovery of GI motility compared with pyridostigmine and glycopyrrolate.

Methods: We conducted a prospective study of patients who underwent laparoscopic cholecystectomy. Patients were randomly allocated to the experimental group (sugammadex, Group S) or control group (pyridostigmine-glycopyrrolate, Group P). After anesthesia (propofol and rocuronium, 2% sevoflurane), recovery was induced by injection of sugammadex or a pyridostigmine-glycopyrrolate mixture. As a primary outcome, patients recorded the time of their first passage of flatus ("gas-out time") and defecation. The secondary outcome was stool types.

Results: 102 patients participated (Group S, 49 and Group P, 53). Mean time from injection of NMB reversal agents to gas-out time was 15.03 (6.36-20.25) hours in Group S and 20.85 (16.34-25.86) hours in Group P ($p = 0.001$). Inter-group differences were significant. The time until the first defecation or the types of stools were not significantly different.

Conclusions: Sugammadex after laparoscopic cholecystectomy under GA resulted in an earlier first postoperative passage of flatus compared with the use of a mixture of pyridostigmine and glycopyrrolate. These findings suggest that the use of sugammadex has positive effects on the recovery of postoperative GI motility.

Keywords: Pyridostigmine bromide; Glycopyrrolate; Sugammadex; Cholinergic antagonists; Defecation; Gastrointestinal motility; Flatulence.

Introduction

The use of acetylcholinesterases (e.g., rocuronium bromide) is essential in achieving neuromuscular blockade (NMB) for surgery under general anesthesia (GA), which requires a deep NMB [1]. For NMB reversal following the use of acetylcholinesterase, acetylcholinesterase inhibitors (e.g., neostigmine and pyridostigmine) are used as reversal agents. In addition, anticholinergic agents such as atropine and glycopyrrolate have been used to reduce the resulting cholinergic side effects, which include bradycardia and increased secretions [2, 3].

Regarding bowel movements, acetylcholinesterase inhibitors (AChEIs) increase motility, whereas anticholinergic agents decrease it. Recovery to normal bowel movements and prevention of postoperative ileus are important for early recovery after surgery. A study has reported that neostigmine, an AChEI, decreases postoperative ileus [4]. However, research comparing the effects of drugs with opposing effects on bowel movements has yet to be conducted.

Sugammadex, a recently introduced reversal agent, has no cholinergic side effects, and thus, it does not require the use of anticholinergic agents [3]. A number of studies have confirmed that the use of sugammadex for recovery from anesthesia leads to fewer respiratory complications and less residual NMB compared with the conventionally used AChEIs and anticholinergic agents, and that it contributes to enhanced recovery after surgery (ERAS®) [5, 6]. ERAS® addresses the prevention of postoperative ileus (a type of bowel obstruction) as an important issue, for which investigations have been conducted to evaluate various preventive mechanisms, including gum chewing, early enteral nutrition, and laparoscopic surgery. In this context, few studies have been conducted to investigate the effects of sugammadex on bowel movements [7, 8, 9, 10]. Moreover, only a small number of studies have compared the recovery of intestinal movements in groups administered AChEIs and

anticholinergic agents and those administered sugammadex, although the studies were conducted retrospectively[11]. This study, therefore, aimed to evaluate the contribution of sugammadex as a reversal agent to the recovery of gastrointestinal (GI) motility in patients undergoing laparoscopic cholecystectomy compared with the contribution of the combination of pyridostigmine and glycopyrrolate.

Materials and Methods

This study was conducted with the approval of the Institutional Review Board (IRB) of Daegu Fatima Hospital (IRB approval number ; DFH18MRIO366). We explained to the patients the purpose of this prospective study and obtained their written consent before commencing the study.

We explained the method of anesthesia to the patients scheduled for laparoscopic cholecystectomy under GA as well as to their guardians. They were also informed about the use of NMB agents and the need for NMB reversal agents. We then explained to them the merits and demerits of the two types of reversal agents and obtained their consent to the randomized allocation of a drug.

1.1. Patient Characteristics

We selected patients aged between 20 and 70 years, who were scheduled for GA-induced laparoscopic cholecystectomy and had American Society of Anesthesiologists (ASA) physical status I or II.

1.2. Exclusion Criteria

We excluded patients requiring emergency care due to their inability to control nothing by mouth (NPO) fasting time, and those diagnosed with diabetes, ulcerative colitis, or Crohn's disease, all of which can affect patients' GI motility. Patients with renal dysfunction were also excluded [12, 13].

1.3. Intervention

Figure 1 shows the flow diagram of this study.

The study participants were allocated randomly to the experimental group, Group S (sugammadex), and the control group, Group P (pyridostigmine). Preoperatively, both groups fasted from midnight on the day of surgery and then consumed two cans of oral carbohydrate solutions (NONPO® 400 ml) 4 hours prior to surgery [8, 9, 14]. As premedication, midazolam 2 mg (IM) and famotidine 20 mg (IV) were administered 30 minutes before surgery. Upon arrival at the OR, the patients were subjected to

the induction of GA using propofol 2 mg/kg and rocuronium 0.6 mg/kg, both intravenously, while train-of-four (TOF) monitoring was in progress. Intubation proceeded with the confirmation of a TOF ratio of 0. To maintain GA, we used FiO2 0.5 and 2% sevoflurane (inhalational anesthetic) and injected a mixture of remifentanil 2 mg and normal saline 50 ml via infusion pump. For intraoperative fluid management, we avoided calcium ions, which can induce constipation. Instead, we used crystalloids (plasma solution A) intravenously at rates of 4 cc/kg/hour for the first 10 kg, 2 cc/kg/hour for the second 10 kg, and 1 cc/kg/hour for every kg above 20 kg according to the 4-2-1 rule, and additional 1 cc/kg/hour according to perioperative fluid management guidelines [15, 16].

Following completion of surgery, administration of sevoflurane was stopped for recovery from GA. For NMB reversal, when a TOF of 2 or above was observed, we intravenously injected the patients with one of the two NMB reversal agents, i.e., sugammadex 2 mg/kg (Group S) or pyridostigmine 0.2 mg/kg and glycopyrrolate 0.008 mg/kg (Group P), and recorded the time of injections. When the patients' TOF ratio was confirmed to have reached a minimum of 90%, we proceeded with extubation and transported the patients to the post-anesthesia care unit (PACU). On arrival in the PACU, palonosetron 0.075 mg was administered intravenously to prevent postoperative nausea and vomiting (PONV).

For pain control, we intravenously administered a mixture of propacetamol 2 g and normal saline 100 ml; in addition, as patient-controlled analgesia, instructions were provided for administration of normal saline 100 ml mixed with ketorolac tromethamine 240 mg. When the patients complained of continued postoperative pain, with an NRS of 6 or above, we provided additional pain control with intravenous administration of fentanyl 1 mcg/kg (max. 2 injections). The amount of intraoperative remifentanil use was computed based on the amount of mixed fluid use recorded immediately after surgery.

After the patients were moved to their rooms, we intravenously administered tramadol PRN up to 3 times when pain intensity of 5 or above was indicated on the visual analogue scale (VAS). The patients maintained their NPO fasting throughout the day of the surgery.

1.4. Outcome

The patients were instructed to consume carbohydrate drink (NONPO® 400 ml) on the morning of POD (postoperative day) 1 and to start with soft foods in the afternoon. To evaluate the patients' bowel movement recovery, following intake of food, they were instructed to record the time of their first passage of flatus ("gas out") in their rooms and the time of the first defecation to the minute. As a primary outcome, the data on the time elapsed between the injection of NMB reversal agents and the first gas out and defecation were collected and compared. As the secondary outcome, the presence of any adverse effects (such as nausea, vomiting, and dry mouth), as well as the types of stools additionally based on the Bristol stool scale (Fig. 2), were recorded for comparison.

1.5. Randomization

We employed simple randomization with a closed envelope technique for the allocation of the reversal agents. Two sealed envelopes were prepared, each containing a mark for Group S or Group P. Regarding patient assignments, neither we nor the patients were allowed to select or check the envelopes. Third parties with no involvement in the study selected the envelopes and then delivered them to other individuals ("fourth parties") who did not partake in the observation of the test results. The fourth parties were the ones who opened and checked the contents of the envelopes. According to the allocations revealed, each drug (sugammadex vs. pyridostigmine and glycopyrrolate) was prepared to be administered as a reversal agent using 5 cc syringes and normal saline. Prepared in

equal amounts, both agents were delivered back to the third parties and then administered randomly to the patients. The drug allocation chart was maintained by the fourth parties until the completion of data collection. It was not until the delivery of the analyzed and compared results from the data from the fourth parties that we gained access to the details of the randomization. The patients and the third parties were also denied access to the information up to that point.

1.6. Sample size

Power analysis was conducted using G*Power 3.1.9.4. Sample size of previous study was based on gas-out time in the general surgery ward [18]. Likewise estimated of effective sizes were made using our previous record of cholecystectomy patients in general surgery ward. An effect size of 0.527 was calculated using mean gas-out time of 17 hours with a standard deviation (SD) of 7.4 hours in the sugammadex group and 20.6 hours with a SD of 6.2 hours in pyridostigmine group. A sample size of 48 patients per group was found to provide 80% power to detect the effect size with a set α of 0.05 for a two sided design. Taking into account a potential drop-out rate of 10%. Finally, the study included total 106 patients who underwent laparoscopic cholecystectomy.

1.7. Statistical Analysis

We used Student's *t*-test to analyze the height, weight, and age of the patients, the amount of remifentanil administered intraoperatively, and the amount of fentanyl administered in the PACU. Sex and ASA scores of the patients were examined with Fisher's exact test. The Mann-Whitney U test was used for the analysis of gas-out and defecation times and Fisher's exact test for stool type and analysis of data on adverse effects.

Results

A total of 106 patients were initially enrolled for the study. Of these, three patients were excluded owing to insufficient NMB reversal following administration of the reversal agent (experimental drug). In case of insufficient reversal, additional administration of sugammadex 2 mg/kg was performed. Another patient was excluded as his surgery was changed intraoperatively from laparoscopic cholecystectomy to open surgery. As a result, 102 patients participated in the study (53 in Group P and 49 in Group S). The baseline characteristics of the patients were homogeneous (Table 1). Although the female participants in Group S outnumbered their male counterparts, the difference was not statistically significant. The two groups did not exhibit any significant differences in the operation time, anesthesia time, amount of remifentanil administered intraoperatively, or amount of fentanyl administered in the PACU (Table 1).

As a primary outcome, the time that elapsed between the injection of the NMB reversal agent and the first gas-out was compared between the groups. Group P took 20.85 (16.34-25.86) hours and Group S 15.03 (6.36-20.25) hours ($p = 0.001$) (Table 2). The sugammadex group took less time, and the difference was statistically significant.

Since cholecystectomy patients are usually discharged between POD 2 and POD 5, some of the study participants left the hospital without their first defecation time was recorded. We were able to check the defecation records of 28 out of 49 patients in Group S and of 28 among 53 patients in Group P. We found no significant difference between the groups ($p = 0.694$) (Table 2).

Group P took 47.26 (38.72-68.54) hours and Group S took 38 (25.07-64.74) hours to achieve their first defecation ($p = 0.087$). Despite the shorter duration associated with Group S, the difference was not statistically significant (Table 2). Our analysis of stool types showed no significant differences

between the groups (Table 2). Differences in the incidence of adverse effects, namely nausea and vomiting, were also not significant. Dry mouth, on the contrary, was experienced by 5 patients in Group S, whereas 17 in Group P reported having experienced the same. This difference was found to be significant (Table 3).

Discussion

The findings of this study showed that sugammadex, used as a reversal agent in postoperative patients who had undergone surgery under GA, resulted in a quicker recovery of patients' GI motility compared with a pyridostigmine-glycopyrrolate mixture.

This result differs from previous study. Sen et al. were expected to improve bowel movement in patients undergoing thyroidectomy due to neostigmine without consideration of the action of atropine, There was no difference in gas-out time between the sugammadex and neostigmine groups because of increase gastric emptying due to the affinity of steroid hormones for sugammadex[18]. However our study was on the base of hypothesis of that glycopyrrolate would predominate on the bowel movement effect when glycopyrrolate and pyridostigmine is injected simultaneously. The opposite action of pyridostigmine and glycopyrrolate may not be completely offset due to the difference in onset time and duration. Therefore the use of sugammadex, which does not affect bowel movements, may have a positive effect on postoperative bowel movements compared to pyridostigmin/ glycopyrrolate.

This finding is based on the patients' report of their first postoperative passage of flatus. The finding can also be interpreted to represent a more natural postoperative recovery of GI motility, since the use of sugammadex does not affect patients' bowel movements or peristalsis. However, we need to consider the conflicting intestinal motility effects of the pyridostigmine-glycopyrrolate combination. In this regard, we may assume that the anticholinergic effects of glycopyrrolate on bowel movements can overcome the cholinergic side effects of pyridostigmine. One study has reported that neostigmine can promote GI motility in cases of postoperative ileus [19].

Another study found that AChEIs such as neostigmine and pyridostigmine are effective for acute colonic pseudo-obstruction and not ileus induced by mechanical bowel obstruction [20]. Both these

studies indicate that AChEIs can increase bowel motility. And we found a previous study reporting that the concurrent use of neostigmine and atropine increased GI motility, the study design did not compare the drug mixture with any other agents. Further, that study only investigated the impact on bowel movements depending on the timing of atropine administration before neostigmine injection [21].

We acknowledge the slight differences between the published studies that we examined for our study. The duration of action associated with glycopyrrolate is 2-4 hours and that associated with pyridostigmine is longer than 2 hours, which may lead to anticholinergic effects on bowel movements [22]. A number of previous studies have confirmed that the use of sugammadex for the reversal of NMB agents can lead to fewer incidents of respiratory complications, residual MNB, and PONV compared with the use of AChEIs [5,6]. The relevant literature also lists the advantages of the drug in terms of recovery of the cardiovascular system, urinary system, and other systems [23, 24].

Based on the aforementioned findings, we may expect that sugammadex will have positive effects on the recovery of GI motility when used as an NMB reversal agent for patients who underwent surgery under GA and can help to decrease postoperative ileus. For prevention of postoperative ileus, a variety of approaches have been explored: gum chewing to induce a stimulatory effect; early mobilization that can reduce insulin resistance and have stimulatory effects; laparoscopic surgery that minimizes tissue trauma and bowel handling to reduce inflammatory reactions; use of non-steroidal anti-inflammatory drugs (NSAIDs) to reduce inflammatory reactions and opioid sparing; and early enteral nutrition and other similar regimens. Still, further benefits may be obtained with the use of comprehensive, multi-faceted approaches [10]. The use of sugammadex can be one such approach. Sugammadex is believed to enable faster postoperative nutrition and decrease GI complications such as constipation and postoperative ileus. These effects lead to reduced length of stay (LOS), which in turn contributes to ERAS® [25].

Notably, we did not find any significant inter-group differences in terms of time elapsed until the first defecation reported by the patients. This is considered to be the limitation of our study due to the small number of samples. We attribute this lack of significant differences to the data loss caused by a relatively shorter LOS associated with laparoscopic cholecystectomy; a large number of patients left the hospital without reporting the first postoperative defecation within the LOS. The lost data resulted in a smaller sample size (N=56) (Table 2). With a longer LOS and/or post-discharge phone interviews, we might have secured sufficient data on defecation times, which may have yielded statistically significant results. Inclusion of larger sample of patients who remain committed to study participation until the time of their first postoperative defecation might have led to a significant difference in the types of stools.

Neostigmine (AChEIs) is known to increase the incidence of nausea and vomiting. However, its concurrent use with atropine or glycopyrrolate does not increase this incidence [26]. Controversial findings have been reported indicating that AChEIs can increase the risks of nausea and vomiting [27]. As indicated in the aforementioned research findings, differences in the incidence of nausea and vomiting were not statistically significant. Considering that the primary outcome of the study was not postoperative nausea and vomiting, other risk factors (e.g., sex, smoking, and history of PONV) that could have been induced were not controlled by the study design. Hence, we see some difficulty in acknowledging the accuracy of the findings. Glycopyrrolate is associated with potent inhibition of salivary gland and respiratory secretions [28]. A significant difference in terms of dry mouth incidence was found in the pyridostigmine group.

The type of surgery targeted may also be a limitation of this study. Laparoscopic cholecystectomy, the focus of our study, involves less handling of the bowel and has fewer effects on bowel movements. Future studies should investigate other types of procedures such as gastrointestinal surgery and

colorectal surgery, which directly influence bowel movements due to the bowel handling and anastomosis involved. Using these surgical procedures, more clear outcomes may emerge in the recovery of GI motility in patients who receive surgery under GA and are administered with the two reversal agents [29, 30].

Furthermore, measuring gastrointestinal transit time by using a scintigraphic method with radioisotopes attached to drugs will likely enable a more accurate comparison of sugammadex against conventional reversal agents.

In conclusion, for patients undergoing laparoscopic cholecystectomy surgery under GA, the use of sugammadex as an NMB reversal agent resulted in an earlier first postoperative passage of flatus compared with the use of a mixture of pyridostigmine and glycopyrrolate. These findings suggest that the use of sugammadex has positive effects on the recovery of postoperative GI motility.

References

[1] Blobner M, Frick CG, Stäuble RB, Feussner H, Schaller SJ, Unterbuchner C, et al. Neuromuscular blockade improves surgical conditions (NISCO). Surg Endosc 2015 ;29(3):627-36.

[2] Mirakhur RK, Briggs LP, Clarke RSJ, Dundee JW, Johnston HML. Comparison of atropine and glycopyrrolate in a mixture with pyridostigmine for the antagonism of neuromuscular block. Br J Anaesth 1981 ;53(12):1315-1320.

[3] Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine–glycopyrrolate and edrophonium–atropine. Anesth Analg 2007 Mar 1;104(3):569-74.

[4] Althausen PL, Gupta MC, Benson DR, Jones DA. The use of neostigmine to treat postoperative ileus in orthopedic spinal patients. J Spinal Disord 2001;14(6):541-5.

[5] Olesnicky BL, Traill C, Marroquin-Harris FB. The effect of routine availability of sugammadex on postoperative respiratory complications: a historical cohort study. Minerva Anestesiol 2017;83(3):248-54.

[6] Brueckmann B, Sasaki N, Grobara P, Li MK, Woo T, De Bie J, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth 2015 ;115(5):743-51.

[7] Sustic A, Dijana D. Early postoperative gastric emptying in patients undergoing laparoscopic cholecystectomy: Sugammadex vs. neostigmine/atropine neuromuscular blockade reversal agents: 9AP4-1. Eur J Anaesthesiol 2012;29:140.

[8] Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group

recommendations. Arch Surg 2009;144(10):961-9.

[9] Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. World J Surg 2013;37(2):259-84.

[10] Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand 2015;59(10):1212-31.

[11] Chae, Y. J., Joe, H. B., Oh, J., Lee, E., & Yi, I. K. Thirty-day postoperative outcomes following sugammadex use in colorectal surgery patients; retrospective study. Journal of clinical medicine 2019; 8(1):97.[12] Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. Ann Intern Med 1983;98(3):378-84.

[13] Annese V, Bassotti G, Napolitano G, Usai P, Andriulli A, Vantrappen G. Gastrointestinal motility disorders in patients with inactive Crohn's disease. Scand J Gastroenterol 1997;32(11):1107-17.

[14] Jones C, Badger SA, Hannon R. The role of carbohydrate drinks in preoperative nutrition for elective colorectal surgery. Ann R Coll Surg Engl 2011;93(7):504-7.

[15] Khosla S. Hypercalcemia and hypocalcemia. In: Harrison's principles of internal medicine, 17th ed. Edited by Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL: New York, USA: McGraw-Hill. 2009, p 959

[16] Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's clinical anesthesiology. 5th ed. New York, McGraw-Hill. 2013, pp 1166-9

[17] Bristol Stool Chart http://www.cabothealth.com.au/articles/bristolstool-chart-2/

[18] Sen A, Erdivanli B, Tomak Y, Pergel A. Reversal of neuromuscular blockade with sugammadex or neostigmine/atropine: Effect on postoperative gastrointestinal motility. J Clin Anesth 2016;32:208-

13.

[19] Kreis ME, Kasparek M, Zittel TT, Becker HD, Jehle EC. Neostigmine increases postoperative colonic motility in patients undergoing colorectal surgery. Surgery 2001 Sep 1;130(3):449-56.

[20] De Giorgio R, Barbara G, Stanghellini V, Tonini M, Vasina V, Cola B, et al. The pharmacological treatment of acute colonic pseudo-obstruction. Aliment Pharmacol Ther 2001;15(11):1717-27.

[21] Wilkins JL, Hardcastle JD, Mann CV, Kaufman L. Effects of neostigmine and atropine on motor activity of ileum, colon, and rectum of anaesthetized subjects. Br Med J 1970 Mar 28;1(5699):793-4.

[22] Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's clinical anesthesiology. New York: McGraw-Hill. 2013, pp 235-236

[23] Fuchs-Buder T, Meistelman C, Raft J. Sugammadex: clinical development and practical use. Korean J Anesthesiol 2013 Dec;65(6):495.

[24] Cha JE, Park SW, Choi YI, Oh ID, Kang HY, Lee SH, et al. Sugammadex use can decrease the incidence of post-operative urinary retention by avoiding anticholinergics: a retrospective study. Anesth Pain Med 2018;13(1):40-6.

[25] Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols: Time to change practice?. Can Urol Assoc J 2011;5(5):342

[26] Cheng CR, Sessler DI, Apfel CC. Does neostigmine administration produce a clinically important increase in postoperative nausea and vomiting?. Anesth Analg 2005;101(5):1349.

[27] Miller RD, Eriksson LI, Fleisher L, Wiener-Kronish JP, Cohen NH. Miller's Anesthesia. 8th ed. Elsevier Health Sciences. 2014, pp 995-1025

[28] Mirakhur RK, Dundee JW. Glycopyrrolate: pharmacology and clinical use. Anaesthesia 1983 ;38(12):1195-204.

[29] Hearing SD, Thomas LA, Heaton KW, Hunt L. Effect of cholecystectomy on bowel function: a

prospective, controlled study. Gut 1999;45(6):889-94.

[30] Livingston EH, Passaro EP. Postoperative ileus. Dig Dis Sci 1990;35(1):121-32.

Table 1. Patient characteristics and perioperative data

Variable		Sugammadex group (n=49)	Pyridostigmine group (n=53)	p-value
Sex	Male	16 (33%)	25 (47%)	0.160
	Female	33 (67%)	29 (53%)	
Age		51.29 ± 12.93	46.81 ± 13.86	0.095
ASA	I	4 (8%)	4 (7%)	1.000
	II	45 (92%)	49 (93%)	
Height (cm)		162.47 ± 8.57	164.32 ± 9.22	0.318
Weight (kg)		66.98 ± 15.28	68.19 ± 11.93	0.659
Diagnosis	Acute cholecystitis	22 (45%)	20 (38%)	0.467
	Chronic cholecystitis	20 (41%)	19 (36%)	
	Gall bladder polyp	3 (6%)	8 (15%)	
	Gall bladder empyema	4 (8%)	6 (11%)	
Operation time (min)		35.86 ± 14.37	36.34 ± 14.67	0.867
Anesthesia time (min)		57.06 ± 15.58	58.75 ± 15.14	0.579
Intraoperative remifentanil (ml)		7.55 ± 3.41	7.49 ± 3.18	0.937
PACU fentanyl (μg)		93.47 ± 28.91	84.72 ± 30.23	0.138

Values are presented as number (%) or mean ± SD. Student's *t*-tests were performed, with values presented as mean ± SD. Chi-squared and Fisher's exact tests were performed for sex and diagnosis, with values presented as number (%).

Table 2. Comparison of outcomes

		Sugammadex group (n=49)		Pyridostigmine group (n=53)		p-value
Gas-out time (hours)		15.03(16.34-25.86)		20.85(6.36-20.25)		0.001
Defecation (o/x)		28 (57%)	21 (43%)	28 (53%)	25 (47%)	0.694
Defecation time (hours)		38(25.07-64.74)		47.26(38.72-68.54)		0.087
Stool type according to Bristol stool chart	Type 1	1		2		0.746
	Type 2	3		1		
	Type 3	2		6		
	Type 4	9		7		
	Type 5	4		4		
	Type 6	7		6		
	Type 7	2		2		

Gas-out time and Defecation time are presented as median measurement (interquartile range). Values are presented as number (%). Statistical analyses were performed using the chi-squared and Fisher's exact tests

Table 3. Incidence of adverse effects

Adverse effect	Sugammadex group (n=49)	Pyridostigmine group (n=53)	p-value
Nausea	8 (16%)	8 (15%)	1.000
Vomiting	4 (8%)	3 (6%)	0.708
Dry mouth	5 (8%)	17 (32%)	0.008

Values are presented as number (%). Statistical analyses were performed using the chi-squared and Fisher's exact tests

Figure Legends

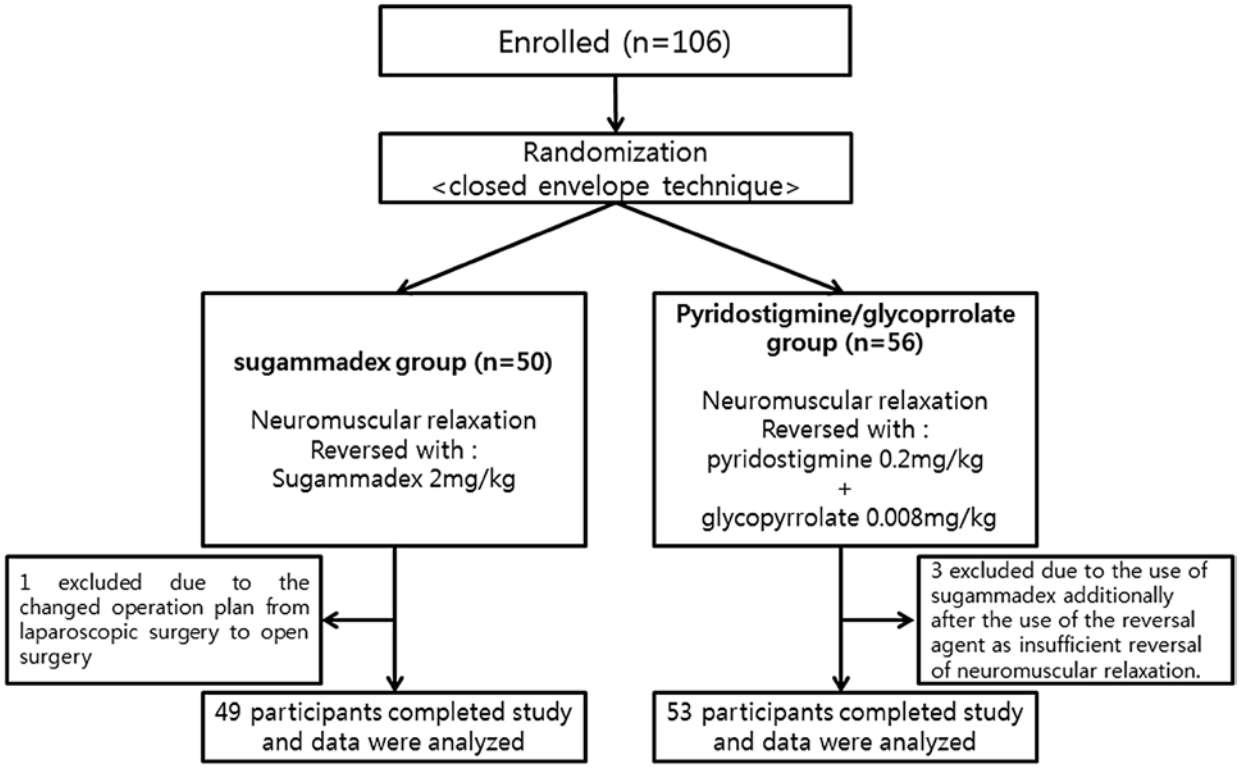

Fig. 1 Study flow diagram

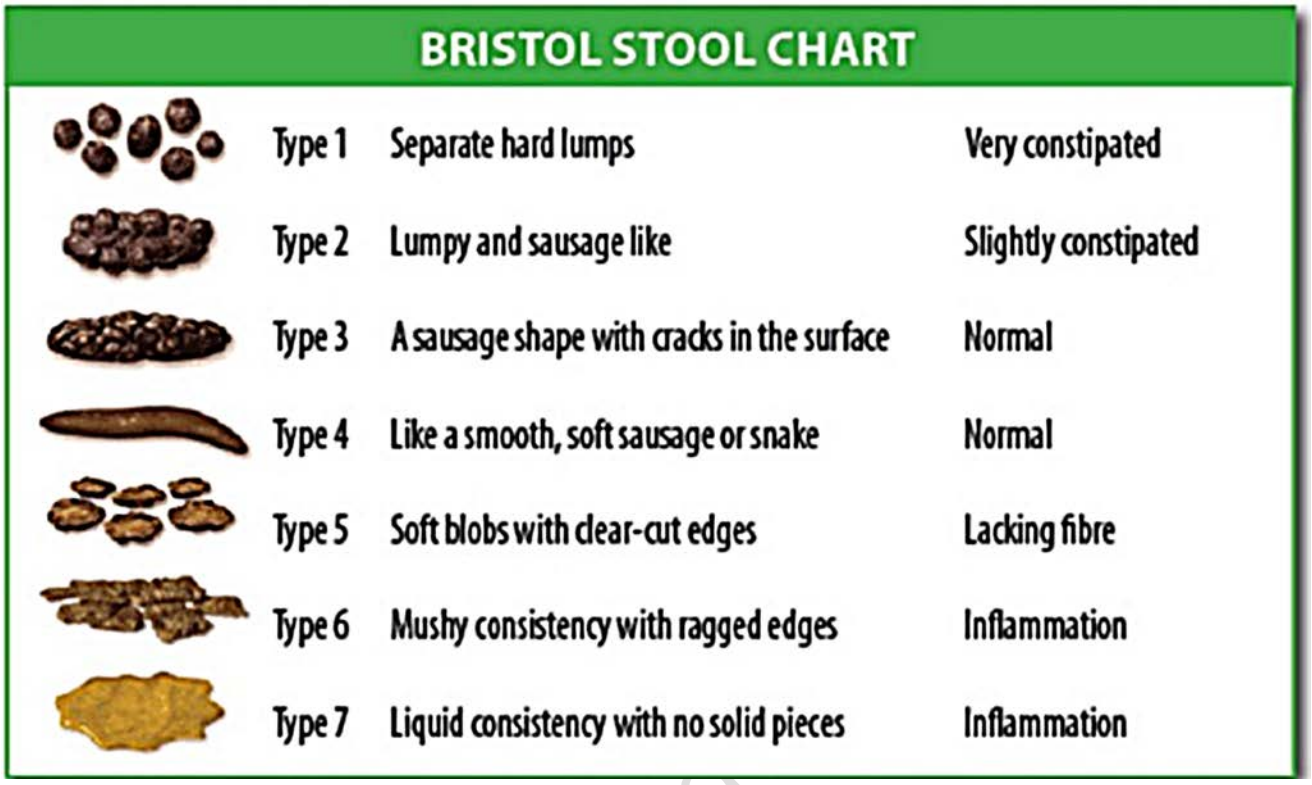

Fig. 2 Bristol stool chart. Adapted from Cabot Health, Bristol Stool Chart http://www.cabothealth.com.au/articles/bristolstool-chart-2/ (accessed 30 november 2013)[17]