Clinical Trial Protocol

Title of Study

A double-blind, randomized, parallel design to compare the effectiveness of deep versus moderate neuromuscular blockade with standard-pressure pneumoperitoneum during laparoscopic gastrectomy on postoperative pain in surgical patients

Principle Investigator of Clinical Study

Byung-Moon Choi, Associate professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center

Name and location of the clinical trial institution

Name	Asan Medical Center
Location	88, Olympic-ro 43-gil, Songpa-gu, Seoul, Korea

NCT Number

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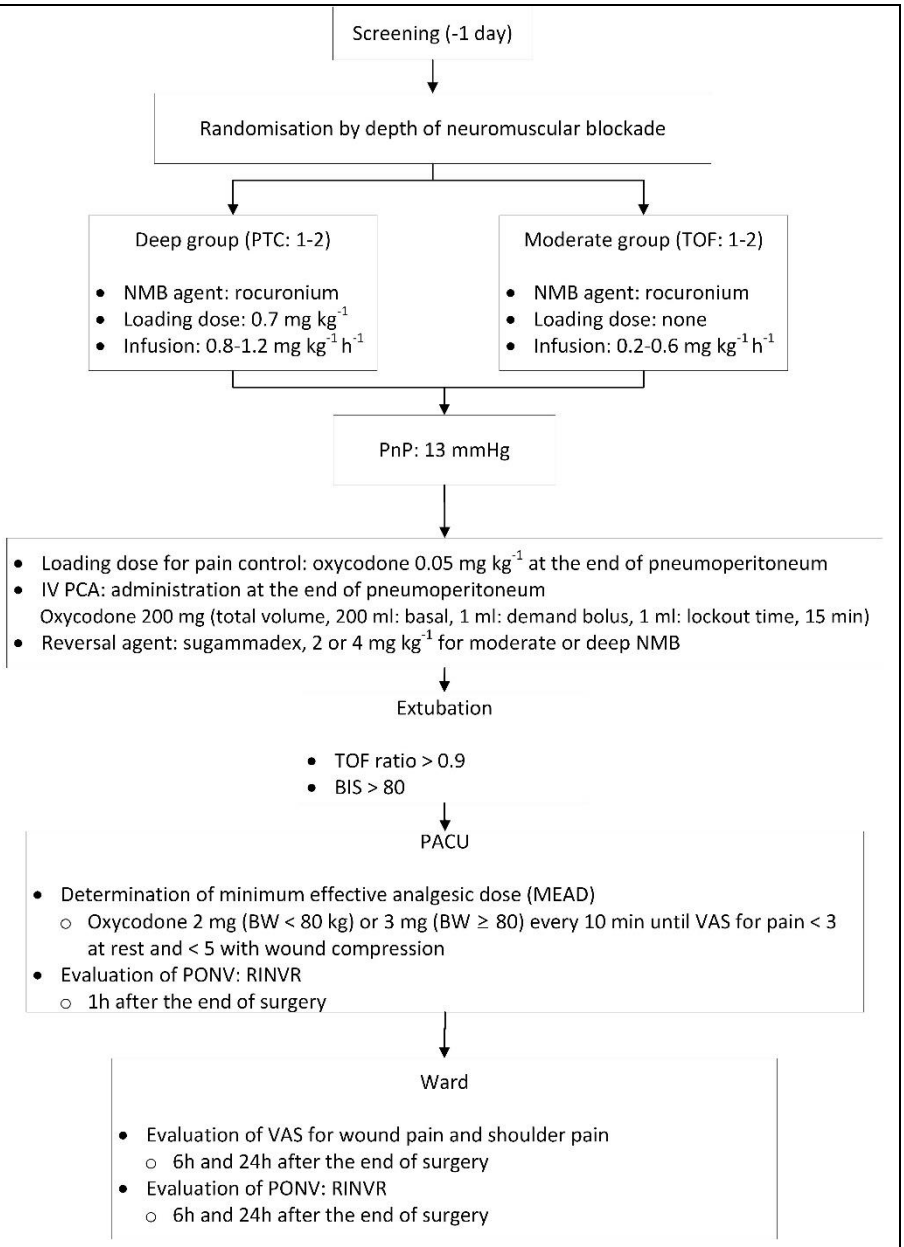
1. Synopsis

Title	A double-blind, randomized, parallel design to compare the effectiveness of deep versus moderate neuromuscular blockade with standard-pressure pneumoperitoneum during laparoscopic gastrectomy on postoperative pain in surgical patients
Investigational site	Asan medical center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea
Investigators	Byung-Moon Choi, M.D. & Ph.D.
Sponsor	Merck Sharp & Dohme (MSD)
Representatives	Byung-Moon Choi, M.D. & Ph.D.
Objectives	The aim of this study is to evaluate the influence of depth of neuromuscular blockade during laparoscopic gastrectomy on postoperative pain in surgical patients allocated randomly to either deep or moderate neuromuscular blockade group with standard-pressure pneumoperitoneum of 13 mmHg.
Study design	This study is investigator-initiated, randomized, double blinded clinical trial.



NMB: neuromuscular blockade, PTC: post-tetanic count, TOF: train of four, PnP: pneumoperitoneum, IV: intravenous, PCA: patient controlled analgesia, BIS: bispectral index, PACU: postanesthesia care unit, MEAD: minimum effective analgesic dose, BW: body weight, PONV: postoperative nausea and vomiting, RINVR: Rhodes index of nausea, vomiting and retching, VAS: visual analogue scale

Patients	Patients (n=114) scheduled for elective laparoscopic gastrectomy will

	be randomly assigned to deep or moderate NMB groups at a ratio of 1:1. **Inclusion criteria** – Patients 20 to 65 years old – American Society of Anesthesiologist Physical Status 1 or 2 or 3 – Patients undergoing laparoscopic gastrectomy – Patients who signed a written informed consent form **Exclusion criteria** – Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine pregnancy test – Patients with known hypersensitivity to rocuronium or sugammadex – Patient with VAS score of at least 1 before surgery – Patients with liver cirrhosis confirmed by abdominal CT – Patients with neuromuscular disease that may interfere with neuromuscular data (ex. Duchenne muscular dystrophy, myasthenia gravis) – Clinically significant impairment of cardiovascular function, defined by ejection fraction < 50% – Clinically significant impairment of renal function, defined by estimated GFR < 60 ml/min or need for hemodialysis – Clinically significant impairment of liver function, defined by alanine aminotransferase > 100 IU/L – Indication for rapid sequence induction – Use of opioids within the 7 days prior to surgery – History of abdominal surgery – History of chronic obstructive pulmonary disease – Body mass index (BMI) ≥ 35 kg/m^2 – Body weight < 50 kg – Conversion to laparotomy – Family history of malignant hyperthermia – Patients who are considered by the investigator to be unsuitable to participate in the study for any other reason not mentioned in the

	inclusion and exclusion criteria
Duration of study	From the IRB approval date to February 28, 2019
Study endpoints	**Primary endpoint** – MEAD of oxycodone at PACU **Secondary endpoints** – Mean VAS score for wound pain at PACU – Area under the curve of VAS score for wound pain over time at PACU – VAS score for wound pain at 6 h after the end of surgery – VAS score for wound pain at 24 h after the end of surgery – Frequency and amount of rescue analgesics at ward – Surgical rating score **Additional endpoints** – VAS score for should pain at 6 and 24 h after the end of surgery – Incidence and severity of PONV assessed by Rhodes index for nausea, vomiting and retching (Korean version of the RINVR, appendix 1) at 1, 6 and 24 h after the end of surgery – Incidence of other adverse events
Sample size	A preliminary study to determine the appropriate sample size was conducted by measuring the MEAD of oxycodone in 13 patients. The mean (SD) values were 9.00 (3.96) for deep NMB group and 13.33 (7.97) for moderate NMB group, respectively. The equality test was performed using these results. $n_t = \frac{(Z_{2/\alpha} + Z_\beta)^2 \sigma^2 (1+1/k)}{(\mu_t - \mu_c)} = \frac{(1.96+1.28)^2 \left(\frac{6 \times 3.96^2 + 5 \times 7.97^2}{11} \right) (1+1/1)}{4^2} = 49.1$ On the basis of this observation, a sample size of 50 patients per treatment arm was calculated to be sufficient to allow a detection of 4 mg difference in MEAD with 90% power at an alpha of 0.05.
Statistical analysis	All statistical analyses were conducted using R (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat 3.5 for Windows (Systat Software, Chicago, IL, USA). Normally distributed

	continuous variables are expressed as mean (SD), non-normally distributed variables as median (range), and categorical variables as counts and percentages. A P value less than 0.05 was considered statistically significant.

2. List of Abbreviation and Definition Structures

AE	Adverse event
ASA PS	American Society of Anesthesiologists Physical Status
AUC	Area under the curve
AUC_{VAS}	Area under the curve of visual analogue scale
BIS	Bispectral index
BMI	Body mass index
BW:	Body weight
CT	Computed tomography
eCRF	Electronic case report forms
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
HR	Heart rate
ICH	International conference on harmonization
IEC	Independent ethics committees
IRB	Institutional review board
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
L	Liter
MAP	Mean arterial blood pressure
MEAD:	Minimum effective analgesic dose
ml	Milliliter
NMB	Neuromuscular blockade
NIBP	Non-invasive blood pressure
PACU	Postanesthesia care unit

PCA	Patient controlled analgesia
PnP	Pneumoperitoneum
PONV	Postoperative nausea and vomiting
PTC	Post-tetanic count
RINVR	Rhodes index of nausea, vomiting and retching
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TOF	Train of four
VAS	Visual analogue scale

3. Introduction

Administration of neuromuscular blockade (NMB) is essential for laparoscopic surgeries because it causes an improvement of surgical conditions. Previous studies have suggested that deep NMB (post-tetanic count 1–2) results in an improved quality of surgical conditions compared with moderate NMB (train-of-four 1–2) during laparoscopic surgeries (Madsen, Staehr-Rye, Claudius, & Gatke, 2016; Martini, Boon, Bevers, Aarts, & Dahan, 2014; Staehr-Rye et al., 2014; Veelo et al., 2015). However, in review articles written by Kopman and Naguib, there are little objective data to support the proposition that deep NMB contributes to better patient outcome or improves surgical operating conditions, when compared with moderate block (Kopman & Naguib, 2015, 2016). The usefulness of deep NMB does not seem to be concluded yet.

In laparoscopic surgery, low-pressure pneumoperitoneum is facilitated by the use of deep NMB. The most important benefit of low-pressure pneumoperitoneum is lower postoperative pain scores, which is supported by previous studies including meta analyses (Hua, Gong, Yao, Zhou, & Song, 2014; Ozdemir-van Brunschot et al., 2016). Recently, there is a randomized controlled trial to evaluate the effect of deep NMB and low-pressure pneumoperitoneum in laparoscopic hysterectomy (Madsen, Istre, et al., 2016). The authors concluded that deep NMB and low-pressure pneumoperitoneum (8 mmHg) reduced the incidence of postoperative shoulder pain as compared to standard-pressure pneumoperitoneum (12 mmHg) with standard NMB (Madsen, Istre, et al., 2016). However, we could not determine whether the deep NMB had an effect on postoperative shoulder pain due to the combination of the two interventions in this study. Theoretically, there is a possibility that the deep NMB may have an analgesic effect because deep NMB facilitates maximum stretching of abdominal wall muscle fibers during laparoscopic surgery. This leads to an increased abdominal wall compliance that may reduce pressure-related postoperative pain. However, the question of whether the use of deep NMB influences postoperative pain scores after laparoscopic surgery remains unanswered.

The aim of this study is to evaluate the influence of depth of neuromuscular blockade during laparoscopic gastrectomy on postoperative pain in surgical patients allocated randomly to either deep or moderate neuromuscular blockade group with standard-pressure pneumoperitoneum of 12 mmHg

4. A pilot study for pivotal study

A preliminary study to determine the appropriate sample size was conducted by measuring the minimum effective analgesic dose (MEAD) of oxycodone in 13 patients undergoing laparoscopic

gastrectomy. Patients allocated to deep or moderate NMB groups received a bolus dose of rocuronium of 1.0 mg/kg or 0.5 mg/kg, followed by a continuous infusion of rocuronium of 1.0 mg/kg/h or 0.3 mg/kg/h for maintaining deep NMB (post tetanic count 1–2) or moderate NMB (train of four 1–2) during operation, respectively (Martini et al., 2014). For both groups, an abdominal pressure of 13 mmHg was maintained during the laparoscopic surgery. The patients were administered a bolus dose of oxycodone of 0.05 mg/kg at the end of pneumoperitoneum. After the end of surgery, patients were taken to the postoperative anesthesia care unit (PACU), and assessed for pain every 10 min using a visual analogue scale (VAS) (0=no pain; 10=the most severe pain). Pain was measured at rest and when the wound areas were compressed with a force of 20 N (i.e., 2 kg of pressure imposed by three fingers on a 10 cm^2 area). The wound compression was performed by a blinded researcher who were trained with an algometer (Commander Algometer, J Tech Medical Industries, Midvale, UT, USA) to apply this force consistently. The patient was administered intravenous oxycodone 2 mg (body weight <80 kg) or 3 mg (>80 kg) every 10 min until the VAS assessments showed that the pain intensity had decreased to <3 at rest and <5 on wound compression. At this point, MEAD of oxycodone was determined (Choi et al., 2016). Demographics of these patients are summarized in Table 1.

Table 1. Demographics of patients enrolled in a preliminary study.

	Deep NMB group (n=7)	Moderate NMB group (n=6)
Age, yr	51.1 ± 8.0	50.3 ± 10.8
Weight, kg	69.0 ± 11.0	68.4 ± 11.5
Height, cm	168.5 ± 3.5	166.7 ± 8.8
Male / Female	6/1	4/2
ASA PS I/II	3/4	3/3

Data are expressed as mean ± SD or count as appropriate. Patient characteristics were compared using the two-sample *t*-test. No significant differences between deep NMB and moderate NMB groups were found between any of the observations., NMB: neuromuscular blockade, ASA PS: American Society of Anesthesiologists Physical Status.

The distribution of MEAD of oxycodone is shown in Figure 1.

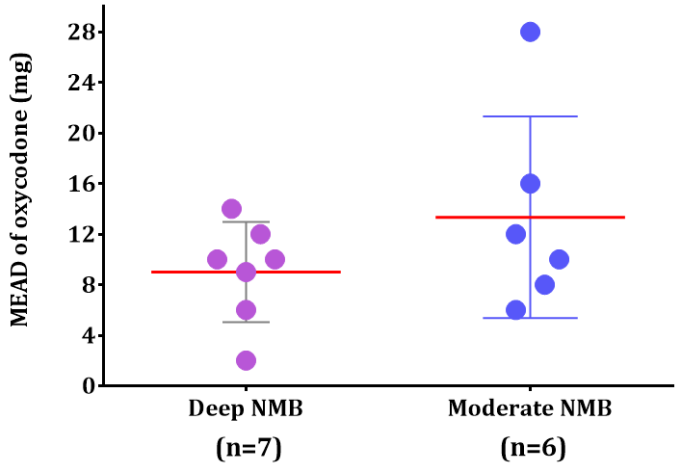


Fig. 1. The distribution of minimum effective analgesic dose (MEAD) of oxycodone in patients undergoing laparoscopic gastrectomy. The mean (SD) values of MEAD were 9.00 (3.96) for deep neuromuscular blockade group and 13.33 (7.97) for moderate neuromuscular blockade group, respectively. The red solid horizontal lines and whiskers represent mean and standard deviation of MEAD.

The VAS for pain over time at PACU is shown in Figure 2.

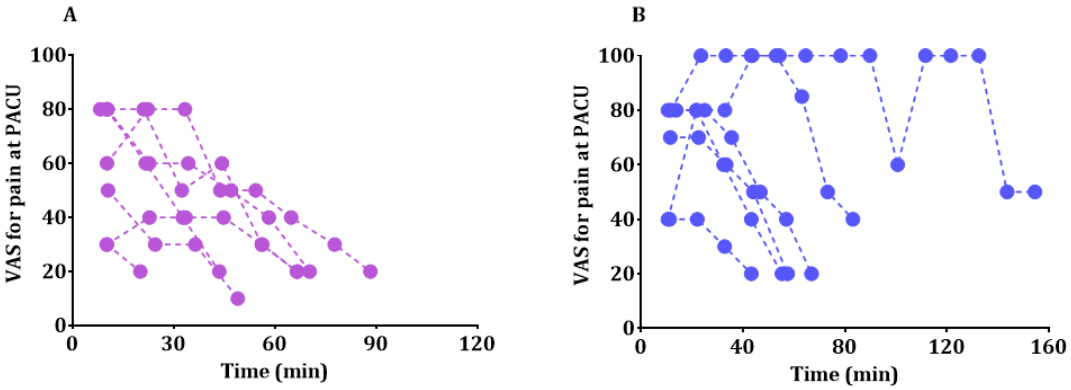


Fig. 2. Visual analogue scale for over time at postanesthesia care unit in patients assigned to

deep neuromuscular blockade group (A) or moderate neuromuscular blockade group (B).

The area under the VAS-time curve (AUC_{VAS}) at PACU was calculated using WinNonlin 6.3 (Pharsight, a Certara Company, St. Louis, MO, USA). The distribution of AUC_{VAS} is shown in Figure 3.

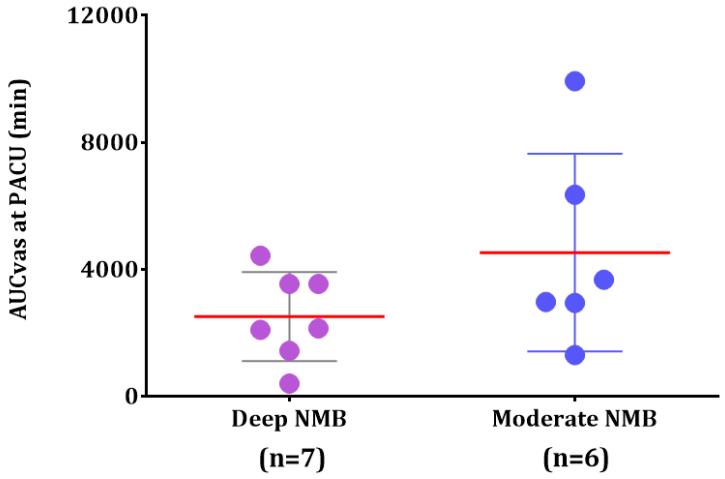


Fig. 3. The distribution of the area under the curve of visual analogue scale (AUC_{vas}) in patients assigned to deep or moderate neuromuscular blockade (NMB) group. The mean (SD) values of AUC_{vas} were 2509.3 (1398.4) for deep NMB group and 4524.1 (3116.3) for moderate NMB group, respectively. The red solid horizontal lines and whiskers represent mean and standard deviation of AUC_{vas}.

4.1. Sample size calculation

A preliminary study to determine the appropriate sample size was conducted by measuring the MEAD of oxycodone in 13 patients. The mean (SD) values were 9.00 (3.96) for deep NMB group and 13.33 (7.97) for moderate NMB group, respectively. The equality test was performed using these results.

$$n_t = \frac{(Z_{2/\alpha} + Z_\beta)^2 \sigma^2 (1+1/k)}{(\mu_t - \mu_c)} = \frac{(1.96+1.28)^2 \left(\frac{6\times 3.96^2 + 5\times 7.97^2}{11} \right)(1+1/1)}{4^2} = 49.1$$

On the basis of this observation, a sample size of 50 patients per treatment arm was calculated to be sufficient to allow a detection of 4 mg difference in MEAD with 90% power at an alpha of 0.05.

5. Study aims

The aim of this study is to evaluate the influence of depth of neuromuscular blockade during laparoscopic gastrectomy on postoperative pain in surgical patients allocated randomly to either deep or moderate neuromuscular blockade group with standard-pressure pneumoperitoneum of 12 mmHg.

6. Study design

The study flow diagram is shown in Figure 4.

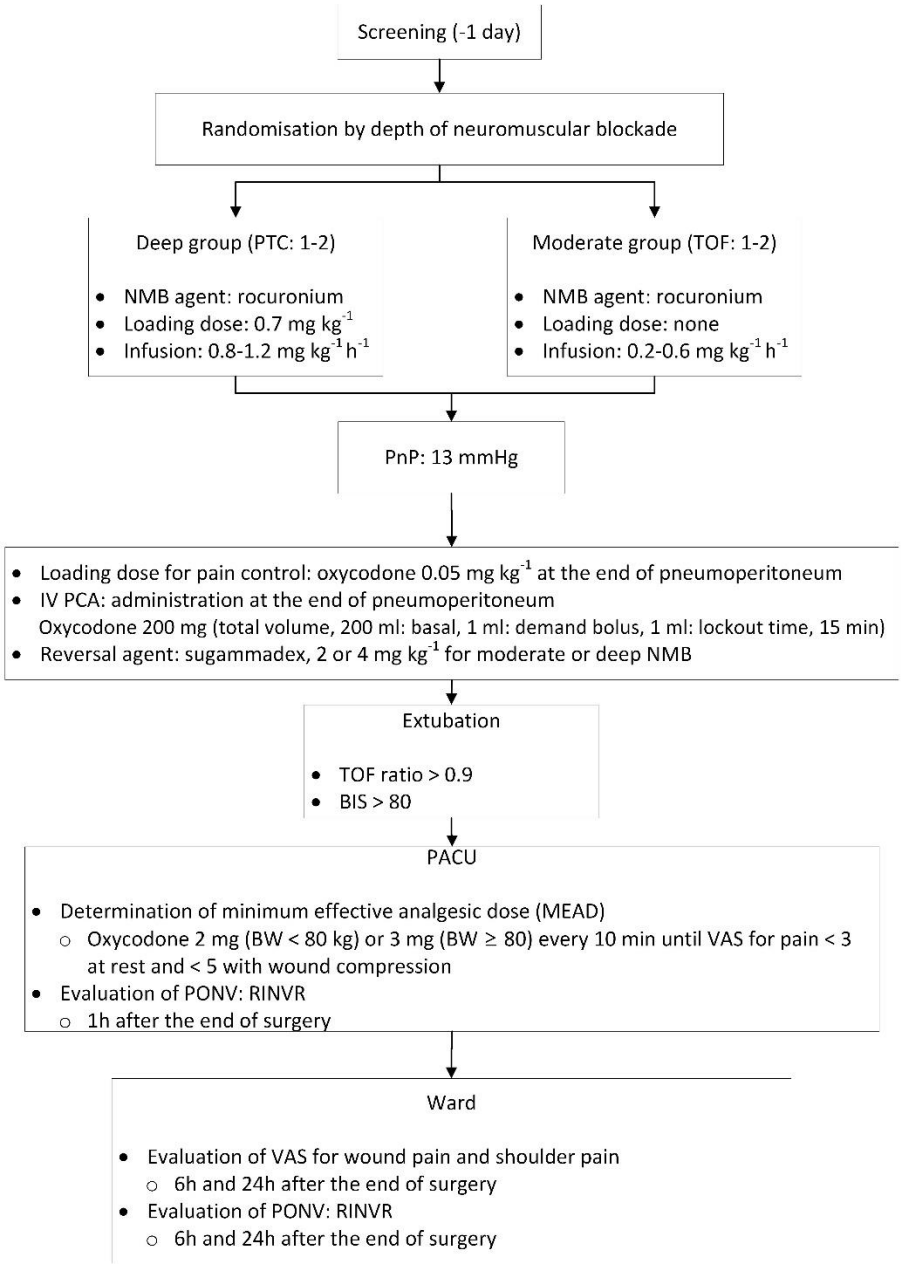


Fig 4. Study flow diagram. NMB: neuromuscular blockade, PTC: post-tetanic count, TOF: train of four, PnP: pneumoperitoneum, IV: intravenous, PCA: patient controlled analgesia, BIS: bispectral index, PACU: postanesthesia care unit, MEAD: minimum effective analgesic dose, BW: body weight, PONV: postoperative nausea and vomiting, RINVR: Rhodes index of nausea, vomiting and retching, VAS: visual analogue scale.

7. Study population

Patients (n=100) scheduled for elective laparoscopic gastrectomy will be randomly assigned to deep or moderate NMB group at a ratio of 1:1.

- Deep NMB group (n=50): The abdomen is insufflated to 13 mmHg pneumoperitoneum with deep NMB (post tetanic count 1–2) during operation
- Moderate NMB group (n=50): The abdomen is insufflated to 13 mmHg pneumoperitoneum with moderate NMB (train of four 1–2) during operation

8. Eligibility

8.1. Inclusion criteria

- Patients 20 to 65 years old
- American Society of Anesthesiologist Physical Status 1, 2 or 3
- Patients undergoing laparoscopic gastrectomy
- Patients who signed a written informed consent form

8.2. Exclusion criteria

- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine pregnancy test
- Patients with known hypersensitivity to rocuronium or sugammadex
- Patient with VAS score (0=no pain; 114=the most severe pain) of at least 10 before surgery
- Patients with liver cirrhosis confirmed by abdominal CT
- Patients with neuromuscular disease that may interfere with neuromuscular data (ex. Duchenne muscular dystrophy, myasthenia gravis)
- Clinically significant impairment of cardiovascular function, defined by ejection fraction < 50%
- Clinically significant impairment of renal function, defined by estimated GFR < 60 ml/min or need for hemodialysis
- Clinically significant impairment of liver function, defined by alanine aminotransferase > 100 IU/L
- Indication for rapid sequence induction
- Use of opioids within the 7 days prior to surgery
- History of abdominal surgery

- History of chronic obstructive pulmonary disease
- Body mass index (BMI) ≥ 35 kg/m^2
- Body weight < 50 kg
- Conversion to laparotomy
- Family history of malignant hyperthermia
- Patients who are considered by the investigator to be unsuitable to participate in the study for any other reason not mentioned in the inclusion and exclusion criteria

9. Study procedures

- All patients were fasted from midnight without premedication
- Once in the operating room, the patients were monitored using electrocardiography, pulse oximetry, end-tidal carbon dioxide partial pressure, non-invasive blood pressure, and bispectral index (Aspect 2000; Aspect Medical Systems, Inc., Newton, MA, USA) measurements.
- Neuromuscular transmission was monitored using the M-NMT® module at the adductor pollicis muscle (Carescape® B850, GE Healthcare, Milwaukee, WI, USA).
- Throughout the surgery, these data were continuously downloaded to personal computers by using RS232C cables.
- Following pre-oxygenation with 100% O_2, anesthesia was induced with propofol and remifentanil, which were administered using a target effect-site concentration-controlled infusion pump (Perfusor® Space, B. Braun Melsungen, Germany) by using the models suggested by Schnider et al. and Minto et al (Minto et al., 1997; Schnider et al., 1998).
- Tracheal intubation was facilitated with rocuronium 0.6 mg/kg.
- After tracheal intubation, the lungs of the patients were then ventilated with oxygen in air (1:1) and the ventilation rate was adjusted to maintain the end-tidal carbon dioxide partial pressure between 35 and 45 mmHg.
- For deep NMB group, an intravenous bolus of rocuronium (0.7 mg/kg) was given 2 minutes after intubation, followed by a continuous infusion of rocuronium of 0.8–1.2 mg/kg/h for maintaining deep NMB (post tetanic count 1–2) during operation. PTC was measured every 5 minutes. In the case of deviations from the target PTC, the pump speed could be increased or decreased or a bolus dose (10 mg) could be given.
- For moderate NMB group, no further loading dose of rocuronium was given. An intravenous infusion with rocuronium (0.4–0.6 mg/kg/h) was started at a TOF count of 1 for maintaining

moderate NMB (train of four 1–2) during operation. TOF was measured every 5 minutes. In the case of deviations from the target TOF, the pump speed could be increased or decreased or a bolus dose (10 mg) could be given.

- The target effect-site concentrations of propofol were adjusted within a range of 2.5–3 μg/ml to maintain the bispectral index values at less than 60 during the induction and maintenance of anesthesia.
- The target effect-site concentrations of remifentanil were titrated to prevent signs of inadequate anesthesia and to maintain stable hemodynamics (SBP > 80 mmHg and HR > 45 beats/min).
    - Signs of inadequate anesthesia: systemic arterial blood pressure increased to greater than 15 mm Hg higher than the patient's normal value; heart rate exceeding 90 beats/min in the absence of hypovolemia; somatic responses, such as body movements (minimal muscle paralysis allowed physical movement), swallowing, coughing, grimacing, or opening of the eyes; and autonomic signs of inadequate anesthesia (Ausems, Vuyk, Hug, & Stanski, 1988)
- If necessary, ephedrine or atropine is administered to maintain systolic blood pressure above 80 mmHg and heart rate above 45 beats/min during anesthesia.
- An abdominal pressure of 13 mmHg was maintained during the laparoscopic surgery.
- When the surgeon asks for muscle relaxation due to the inability to obtain a visible laparoscopic field, additional bolus dose of rocuronium (10 mg) should be given.
- All patients were administered a bolus dose of oxycodone of 0.05 mg/kg at the end of pneumoperitoneum.
- IV PCA with oxycodone is started after the administration of loading dose. A semi-electronic pump (Automed 3200; Ace Medical, Seoul, South Korea) is used for PCA with demand bolus of 1 ml, background infusion of 1 ml/h and lock-out time of 15 min. The concentration of oxycodone in IV PCA bag is 1 mg/ml, and the volume of oxycodone-normal saline mixture delivered to patients for approximately 4 days is 200 ml.
- Rocuronium infusions are discontinued after deflation of CO_2.
- After the end of surgery, a single intravenous bolus dose of sugammadex 2 or 4 mg/kg was administered for reversal of moderate and deep NMB, respectively.
- After the end of surgery, patients were taken to the PACU, and assessed for pain every 10 min using a VAS (0=no pain; 10=the most severe pain).

- Researchers who evaluate postoperative pain will be blinded to the patient's allocation
- Pain was measured at rest and when the wound areas were compressed with a force of 20 N (i.e., 2 kg of pressure imposed by three fingers on a 10 cm^2 area). The wound compression was performed by a blinded researcher who was trained with an algometer (Commander Algometer, J Tech Medical Industries, Midvale, UT, USA) to apply this force consistently.
- The patient was administered intravenous oxycodone 2 mg (body weight <80 kg) or 3 mg (>80 kg) every 10 min until the VAS assessments showed that the pain intensity had decreased to <3 at rest and <5 on wound compression. At this point, MEAD of oxycodone was determined.
- VAS for wound and shoulder pain were also assessed at 6 and 24 h after the end of surgery.
- Postoperative nausea and vomiting were evaluated using the Rhodes index of nausea vomiting retching (RINVR) at 6 and 24 h after the end of surgery (Lee et al., 2016).
- After the end of surgery, the surgeon scored the surgical working conditions according to a five-point ordinal scale ranging from 1 (extremely poor conditions) to 5 (optimal conditions) (Table 2) (Martini et al., 2014).
- If the surgeon requests blind cessation for patient safety reasons, blindness is lifted.

Table 2. The surgical rating scale.

1	Extremely poor conditions	The surgeon is unable to work because of coughing or because of the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional neuromuscular blocking agents must be given.
2	Poor conditions	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 neuromuscular blocking agents must be given.
3	Acceptable conditions	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 neuromuscular blocking agents to prevent

		deterioration.
4	Good conditions	There is a wide laparoscopic working field with sporadic muscle contractions, movements, or both. There is no immediate need for additional neuromuscular blocking agents unless there is the fear of deterioration.
5	Optimal conditions	There is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional neuromuscular blocking agents.

10. Study endpoints

10.1. Primary endpoint

- MEAD of oxycodone at PACU

10.2. Secondary endpoints

- Mean VAS score for wound pain at PACU
- Area under the curve of VAS score for wound pain over time at PACU
- VAS score for wound pain at 6 h after the end of surgery
- VAS score for wound pain at 24 h after the end of surgery
- Frequency and amount of rescue analgesics at ward
- Surgical rating score

10.3. Additional endpoints

- VAS score for should pain at 6 and 24 h after the end of surgery
- Incidence and severity of PONV assessed by Rhodes index for nausea, vomiting and retching (Korean version of the RINVR, appendix 1) at 1, 6 and 24 h after the end of surgery
- Incidence of other adverse events

11. Statistical analysis

All statistical analyses were conducted using R (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat 3.5 for Windows (Systat Software, Chicago, IL, USA). Normally distributed continuous variables are expressed as mean (SD), non-normally distributed variables as median (range), and categorical variables as counts and percentages. A P value less than 0.05 was considered statistically significant. The area under the curve of visual analogue scale for wound pain was calculated by non-compartmental methods (WinNonlin Professional 6.3; Pharsight, St. Louis, MO).

12. Study Management

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Guidelines

This study is to be performed in full compliance with International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived by the investigator as required by regulatory authorities.

12.1.2. Institutional Review Board or Independent Ethics Committees

The protocol, informed consent, and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committees (IEC) constituted and functioning in accordance with ICH E6, Section 3.

A signed letter of study approval from the IRB/IEC Chairman must be sent to the PI prior to study start. Study progress is to be reported to IRB/IECs annually (or as required) by the Investigator, depending on local regulatory obligations. Serious Adverse Events (SAEs) should be reported to the IRB/IEC in accord with local regulatory requirements. In the case of early Termination/temporary halt of the study, the Investigator should notify the IEC within 15 days and a detailed written explanation of the reasons for the Termination/halt should be given.

12.1.3. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain signed and dated informed consent from each subject prior to participating in this study. As part of administering the informed consent document, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any compensation or potential discomfort. Each subject must be informed that participation in the study is voluntary and that subject may withdraw from the study at any time and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician. This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document after adequate explanation of the aims, methods, objectives and potential hazards of the study.

12.1.4. Data Collection and Study Documentation

OpenClinica, a secure web-based application, will be used for electronic data acquisition and storage. OpenClinica will provide electronic case report forms (eCRFs) for transfer of all research data from data source documentation to a computer data base. Each responsible person will have user access to OpenClinica through his/her unique username and password, with permissions providing each person his/her needed access. Two data monitoring persons will verify all data against its source. Monitoring will be enhanced by computer assisted data management identifying missing or possibly erroneous data. This approach will allow initial monitoring, and communication between data monitoring persons and study personnel before and between data monitoring, and will expedite data review and cleaning. Missing data and identified data errors (or possible errors) will be communicated by the data monitoring persons to study investigators

using OpenClinica for correction or acknowledgement that data is correct as entered. OpenClinica and all study data are housed in a secure computing environment. OpenClinica further provides a real-time data entry validation (e.g. for data types and range checks), and audit trail of all data entry.

For accurate, complete, and legible source documentation, the following criteria are to be maintained:

- All entries are to be completed using a black ink ballpoint pen.
- There are to be no erasers, write-overs, use of correction fluid or tape, and the original entry must remain legible.
- Errors are to be corrected by placing one line through the error: The correct entry should appear next to the error, dated, and initialed by the responsible person making the change; the name of anyone making corrections must appear on the Signature Log collected at the beginning of the study and as study assignments change throughout the conduct of the study; each error is to be corrected separately.
- The Investigator must sign and date the source documents where noted; a signature stamp may not be used.
- Changes that have been previously signed by the Investigator must be initialed and dated by the Investigator after the change is made; changes made to electronic CRFs via data clarification forms issued by the Sponsor must likewise be signed by the Investigator.
- Subject's name is not to appear on documents in order to maintain confidentiality.

12.2. Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the Investigators, the Investigator's staff, and IRB, and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the consent of the Principal Investigator. No data collected as part of this study will be utilized in any written work, including publications, without the consent of the Principal Investigator. Collected data should be kept for up to 5 years after the end of the study and discarded thereafter.

13. Procedures for Reporting Adverse Events and Unanticipated Problems

13.1. Clinical Adverse Events

A human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research"

(modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). All clinical AEs encountered during the clinical study will be reported on the AE page of the CRF. Relationship of the AE to the treatment should also be assessed. Pre-existing conditions that worsen during a study are to be reported as AEs.

13.2. Unanticipated problems

In general, unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IEC or IRB. It is the responsibility of the Investigator or Sub investigator(s) to perform periodic and special assessments for unanticipated problems and submit reports to their respective IRBs. Any distributed reports shall include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

13.3. Serious Adverse Events (SAE)

The following definition of SAE will be used for this study: A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE must fulfill at least one of the following criteria:

- is fatal (results in the outcome death*)
- is life-threatening
- required in-patient hospitalization or
- prolongation of existing hospitalization

- results in persistent or significant disability/incapacity is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

An AE that is serious or potentially serious requires detailed reports and follow-up and should be recorded in the CRF. The content of these detailed reports should address the Investigator's estimate of causality, and outcome of the AE.

13.4. Time Frame for Reporting Unanticipated Problems

The investigator must comply with the applicable local requirements related to the reporting of SAEs or unanticipated events involving his/her subjects to the IEC that approved the study. In particular, all deaths must be promptly reported to the IEC that approved the study. Unless clearly defined otherwise by national or site-specific regulations and duly documented, the Investigator must promptly notify the concerned IEC of safety reports.

The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, the following guidelines are recommended in order to satisfy the requirement for prompt reporting:

- Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Medical Device Event, Potential Incident, Device Deficiency or Incident Reporting: Principal Investigator shall forward to MSD's Global Safety ("MSD GS") group, any SAE and SUSAR, Medical Device Event, Device Deficiency or Incident information, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) immediately but no later than 1 business day of learning of the information. If learned during a weekend or holiday, report within one business day or no later than three (3) calendar days (whichever is

shorter)from the day of learning of the information. This information shall be transmitted to MSD GS using the contact information provided below or such other modified contact information as provided by MSD in writing. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to MSD GS at end of Study if the Study Drug has been blinded in the Study.

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Appnedix.1 Rhodes index of nausea, vomiting and retching (RINVR): Korean version

1. 수술이 끝난 후 **X**시간 동안 ( )번 토했다.	7번 이상	5 – 6번	3 – 4번	1 – 2번	토하지 않았다.
2. 수술이 끝난 후 **X**시간 동안 헛구역질 때문에 ( ) 고생하였다.	전혀 고생하지 않았다.	경미하게	중간 정도로	많이	못 견딜 정도로
3. 수술이 끝난 후 **X**시간 동안 토하는 것 때문에 ( ) 고생하였다.	못 견딜 정도로	많이	중간 정도로	경미하게	전혀 고생하지 않았다
4. 수술이 끝난 후 **X**시간 동안 ( )시간 동안 메스꺼웠다.	전혀 메스껍지 않았다.	1시간 이하.	2 – 3시간	4 – 6시간	6시간 이상
5. 수술이 끝난 후 **X**시간 동안 메스꺼움 때문에 ( ) 고생하였다.	전혀 고생하지 않았다.	경미하게	중간 정도로	많이	못 견딜 정도로
6. 수술이 끝난 후 **X**시간 동안 한번 토할 때 마다 ( ) 토했다.	매우 많이 (3 컵 이상)	많이 (2 컵 이상 3컵 미만)	중간 정도로 (반 컵에서 2 컵 미만)	적게 (반 컵까지)	토하지 않았다.
7. 수술이 끝난 후 **X**시간 동안 ( )번 메스꺼웠다.	7번 이상	5 – 6번	3 – 4번	1 – 2번	0번
8. 수술이 끝난 후 **X**시간 동안 토하지는 않았으나 ( )번 헛구역질은 하였다.	0번	1 – 2번	3 – 4번	5 – 6번	7번 이상

X: 1, 6 혹은 24.

Scoring system for RINVR

Directions for Use

Complete Rhodes INVR Scale at 6 and 24 h after the end of surgery.

Directions for Use

To score the Rhodes INVR, reverse items 1, 3, 6 and 7. Assign a numeric value to each response from 0, the least amount of distress, to 4, the most distress. Total symptom experience from nausea and vomiting is calculated by summing the patient's responses to each of the eight items on the Rhodes INV. The potential range of scores is from a low of 0 to a maximum of 32. Subscale scores also can be obtained from the Rhodes INVR for the following.

Calculation of Subscale Scores		
Subscales for Symptom Experience	Items on Scale	Potential Range of Scores
Nausea experience	4, 5, 7	0-12
Vomiting experience	1, 3, 6	0-12
Retching experience	2, 8	0-8
Total experience score	All items	0-32
Subscales for Symptom Occurrence	Items on Scale	Potential Range of Scores
Nausea occurrence	4, 7	0-8
Vomiting occurrence	1, 6	0-8
Retching occurrence	8	0-4
Total occurrence score	All items	0-20
Subscales for Symptom Distress	Items on Scale	Potential Range of Scores
Nausea distress	5	0-4
Vomiting distress	3	0-4
Retching distress	2	0-4
Total distress score	All items	0-12

Rhodes index of nausea, vomiting and retching (RINVR): English version

1. In the last **X** hours, I threw up ( ) times.	7 or more	5-6 times	3-4 times	1-2 times	I did not throw up
2. In the last **X** hours, from reteching or dry heaves have felt ( ) distress.	no	mild	moderate	great	severe

3. In the last **X** hours, from vomiting or throwing up, I have felt ( ) distress.	severe	great	moderate	mild	no
4. In the last **X** hours, I have felt nauseated or sick at my stomach ( ).	not at all	1 hour or less	2-3 hours	4-6 hours	more than 6 hours
5. In the last **X** hours, from nausea/sickness at my stomch, I have felt ( ) distress.	no	mild	moderate	great	severe
6. In the last **X** hours, each time I threw up I produced a ( ) amount.	very large (3 cups or more)	large (2-3 cups)	moderate (1/2-2 cups)	small (up to 1/2 cup)	I did not throw up
7. In the last **X** hours, I have felt nauseated or sick at my stomach ( ) times.	7 or more	5-6 times	3-4 times	1-2 times	no
8. In the last **X** hours, I have had periods of reteching or dry heaves without bringing anything up ( ) times.	no	1-2 times	3-4 times	5-6 times	7 or more

X: 1, 6 or 24.