Merck Investigator Studies Program (MISP)
IIS Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	A double-blind, randomized and controlled multicenter prospective trial to compare the oncological benefit of deep neuromuscular block in gastric cancer obesity patient
Request Date:	**3rd August 2016**
Last update date:	**8th May 2020**
Institution Name	**Korea University College of Medicine**
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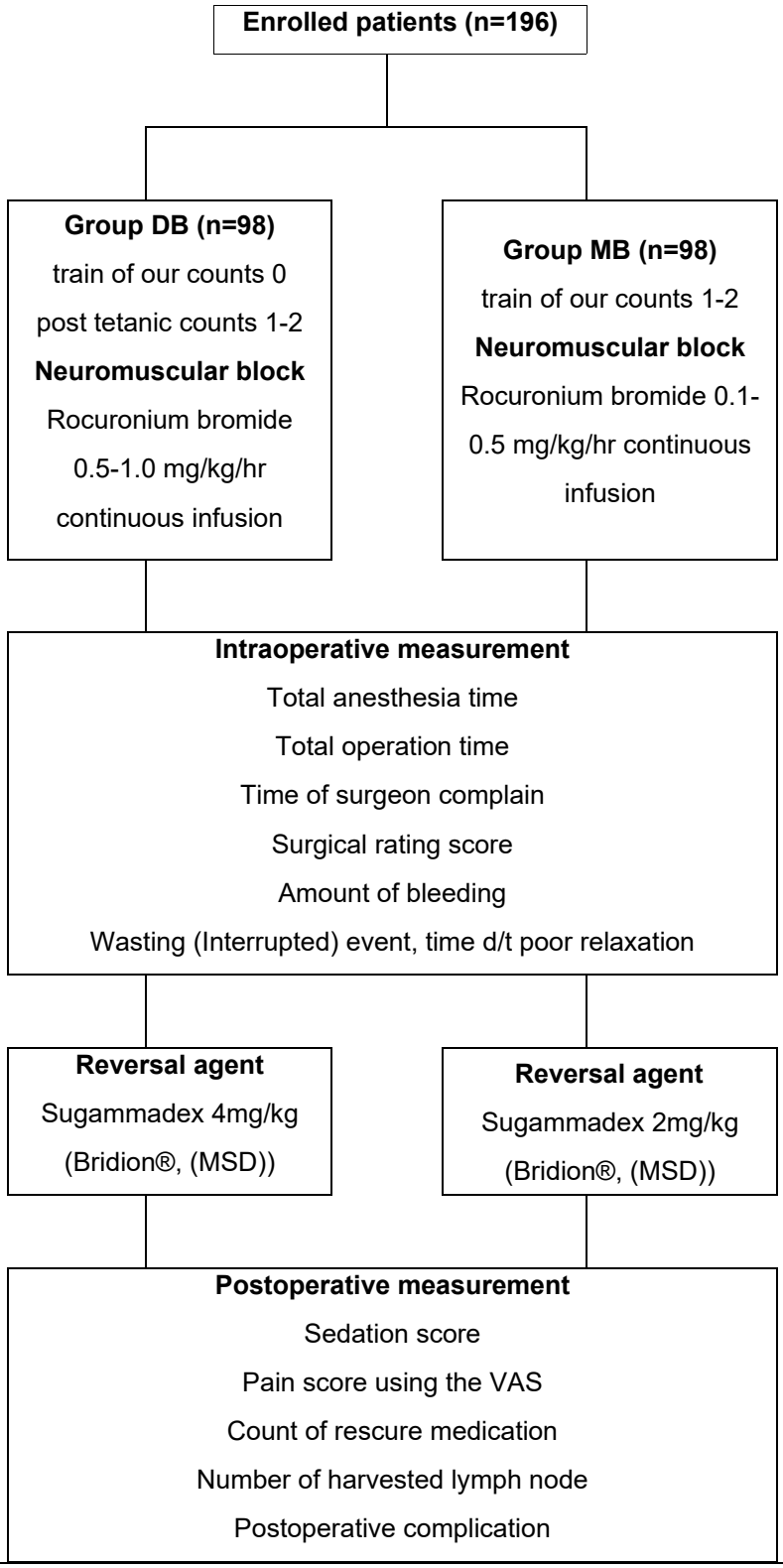
Registered in www.clinicaltrials.gov as NCT03196791

Section #2- Core Protocol	
2.1 Objectives & Hypotheses	2.1 List the objectives. The present randomized study is designed to evaluate the impact of muscle relaxation during laparoscopic gastrectomy on oncological benefit, especially with obese patients over BMI 25. Because surgeons still find that laparoscopic surgery for obese patients is challenging. The retrieval of lymph nodes (LNs) is difficult because they are embedded in thick fat tissue and are hard to distinguish with surrounding fat so that, the operative time should be prolonged. Studies have revealed that the association between obesity and longer operative outcomes than normal body weight patients. Therefore we assumed deep neuromuscular block was associated more adequate lymphadenectomy, smaller intraoperative bleeding, shorter operative time. 2.1.1 List the clinical hypotheses. The primary endpoint is number of harvested lymph node that is critical point regarding quality of surgery in gastric cancer treatment. The secondary endpoint is intraoperative bleeding, surgeons' satisfaction.
2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data	Administraion of muscle relaxation is essential in a variety of procedures as it causes an improvement of surgical conditions. Until recently, intraoperative deep neuromuscular block was eschewed because of concerns about recovery at the end of surgery. Since 2009, many studies have confirmed the rapid efficacy and better safety of sugammadex for reversing moderate and deep neuromuscular blockades induced by steroidal muscle relaxants than standard reversing agents,but most of studies have been focused only on surgical condition or concerns from the view points from anesthesiologists.
2.3 Study Design	Prospective, Randomized, double blind controlled trial Multicenter trial : 9 centers

2.4 Study Flowchart



2.5 Study Procedures	**Inclusion criteria** 1. Patient with obtaining written informed consent 2. American Society of Anesthesiologists Physical status I or III, Aged 19 to 75 yr 3. Underwent elective laparoscopic distal gastrectomy 4. Body mass index (BMI) > 25 kg/m^2 5. CStage I, II **Exclusion criteria** 1. End stage renal disease (ESRD) patient 2. A (family) history of malignant hyperthermia; significant renal or hepatic dysfunction; known or suspected neuromuscular disorders; allergies to narcotics or muscle relaxants; known previous abdominal surgeries **Anesthetic protocol** 1. The patients were randomly assigned to two groups using a computer-generated randomization table: 1) Deep neuromuscular block group the 'post-tetanic counts 1-2' (PTC1-2) 2) Moderate neuromuscular group the 'train-of-four counts 1-2' (TOF count1-2) 2. Premedication : None 3. Standard monitoring included electrocardiogram, noninvasive blood pressure and pulse oximetry at OR 4. Anesthesia is induced and maintained with propofol and remifentanil (BP within ± 20% of preinduction values) – TIVA TCI (target controlled infusion using effect-site concentration) 5. After loss of consciousness is confirmed, neuromuscular activity monitoring via acceleromyography is initiated. -Neuromuscular monitoring was performed using a TOF-Watch SX® (Organon; Roseland, NJ, USA) at the adductor pollicis muscle. -The ulnar nerve was supramaximally stimulated near the wrist with square pulses of 0.2 ms duration, delivered as TOF pulses of 2 Hz at 15-second intervals. The resulting contractions of the adductor pollicis muscle were quantified using an acceleromyographic monitor. -The acceleromyograph was calibrated with 50 Hz tetanic stimulation for 5 s and train-of-four (TOF) stimulation for 3 min 6. Muscle relaxation is induced rocuronium bromide (0.6 mg/kg) 7. Mechanical ventilation was initiated. (Tidal volume : Ideal body weitht (IBW) *8, Respiratory rate (RR) : EtCO2 35-45 유지) 8. Hypnotic depth was kept in the range of 45 to 60 using BIS VISTA® (Aspect Medical Systems, Inc., Norwood, MA, USA). 9. **Neuromuscular blocking agent protocol** **Neuromuscular assessment** Neuromuscular monitoring was performed using a TOF-Watch®. The ulnar nerve was supramaximally stimulated near the wrist with square pulses of 0.2 ms duration, delivered as TOF pulses of 2 Hz at 15-second intervals. The resulting contractions of the adductor pollicis muscle were quantified using an acceleromyographic monitor. TOF stimulation and PTCstimulation were repeated every 15 s and twomin, respectively. **In Moderate neuromuscular group**

If TOF count 1-2, rocuronium bromide 0.1-0.5 mg/kg/hr continusous infusion with TOF monitoring

In Deep neuromuscular group
followed by a continuous infusion of 0.5–1.0 mg/kg/hr (IBW) with TOF monitoring

10. Additionally, if the surgeon asked the anesthesiologist for deeper NMB to achieve an adequate surgical field, rocuronium bolus 0.15 mg/kg was administered.
11. rocuronium infusion stop at end of Laparoscope

12. **Reversal agent & Dose protocol**
-In Moderate neuromuscular group (second twitch appeared at TOF)
Sugammadex 2mg/kg (Bridion®, (MSD))
-In Deep neuromuscular group (end of surgery)
Sugammadex (Bridion®, Merck Sharp and Dohme (MSD), Oss, The Netherlands) 4 mg/kg
13. When the TOF ratio recovered to 0.9 and spontaneous breath, opening of the eyes to verbal commands, extubation will be done.
14. Insufflation pressure: 12mmHg

Evaluation method
At OR : Anesthesiologists
Total anesthesia time
Total surgical time (Incision – dressing)
The time from the end of the operation to the administration of the reversal agent
Total fluid
Total rocuronium dose
Hemodynamic parameter
systolic,diastolic,mean BP
-HR
-EtCO2
-Temperature
-Peak inspiration pressure

Sedation score(MOAA/S)

0	does not respond to pain
1	does not respond to mild prodding or shaking
2	responds only after mild prodding or shaking
3	responds only after name is called loudly and/or repeatedly
4	lethargic response to name spoken in normal tone
5	responds readily to name spoken in normal tone

Surgeon
Report of surgeon's specific complains
The wasting operative time due to poor neuromuscular relaxation
Patient motion
Surgical rating score : consists of individual 4 parts of critical lymph node dissection areas -
during lymph node dissection at 4sb, 6, supraduodenal area and suprapancreatic area

	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 **Ward** Pain score using the VAS until postoperative 48 hours PONV Count of rescue medication First flatus time Postoperative complication until POD 30
2.6 Study Duration	2 years after IRB approval
2.7 Statistical Analysis and Sample Size Justification	Statistical analyses were performed with IBM SPSS 20 software. Quantitative variables were expressed as means (standard deviation) and were compared by Mann-Whitney and Wilcoxon nonparametric tests. Qualitative variables were described by numbers and percentages and 95% confidence intervals. The various parameters were compared by Pearson's and Fisher's Chi-squared tests. For all statistical tests, a P value < 0.05 was considered significant The major objective of this study is to estimate the number dissected lymph nodes. Based upon a sample size of n=89 patients per group, this study has 80% power to detect a 6.3 difference between groups in harvested lymph nodes; this calculation is based on a between subject standard deviation of change of 15 for harvested lymph node (reference for where this variability statement originated). The calculations are the customary ones based on normal distributions –estimation of sample size and power for comparing two means in Bernard Rosner's fundamentals of biostatistics. After considering 10% of follow—up loss, a total of 196 patients will be needed. Regarding increasing effect of BMI on surgery, we will process it as continuous variable when we analyze data and if there is significance, we could decide a cut off value of BMI for specific anesthetic indication. In addition, to control the surgeons' factors impacting results, we will perform surgeon stratified randomization. And if there is a serious surgeon's technical problems being able to distort objective data when interim analysis, we would drop the surgeon out of this study.

2.8 Specific Drug Supply Requirements	N/A
2.9 Adverse Experience Reporting	Reporting Procedures for Exchange of Adverse Event Information. (i) For purposes of this Agreement the below terms shall be defined as follows: "Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug. "Device Deficiency" shall mean inadequacy of a Study Drug device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. "Incident" shall mean any malfunction or deterioration in the characteristics and/or performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user, or of other persons or to a serious deterioration in the state of health. "Medical Device Event" shall mean any malfunction or deterioration in the characteristics and/or the performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which led to or could have led to an untoward event for the user or any other person. "Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious". "Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

	(ii) 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) within two (2) business days 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. (iii) MSD may define certain Non-Serious Events of Interest. If any Non-Serious Events of Interest are defined, Merck will provide such information in writing to Principal Investigator at the time of Protocol approval, execution of this Agreement or anytime thereafter. Reporting of any defined Non-Serious Events of Interest will be handled in the same manner as SAEs unless mutually agreed otherwise in writing by the parties. (iv) All reports of Study Drug exposure during pregnancy or lactation (including a female partner of a male Study subject using the Study Drug), whether associated with an AE or not, must be reported to MSD GS in accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to MSD GS. (v) Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the Study. (vi) SAE reports and any other relevant safety information are to be forwarded to MSD GS facsimile number: 215-993-1220
2.10 Itemized Study Budget	Annexed sheet
2.11 References	MH Kim, KY Lee, KY Lee et al., Maintaining Optimal Surgical Conditions With Low Insufflation Pressures is Possible With Deep Neuromuscular Blockade During Laparoscopic Colorectal Surgery. Medicine, 95 : 9: March 2016 M. V. Mads en , A. K. Staehr-Rye , C. Claudius et al. Is deep neurom uscular block ade beneficial in laparoscopic surgery? Yes , probably. Acta Anaesthesiologica Scandinavica. 60 (2016) 710‑716

	Aaron F. Kopman, Mohamed Naguib et al. Is deep neurom uscular block beneficial in laparoscopic surgery ? No , probably not., Acta Anaesthesiologica Scandinavica. 60 (2016) 717‐722 Anne K. Staehr-Rye, Lars S. Rasmussen, Jacob Rosenberg etal., Surgical Space Conditions During Low-Pressure Laparoscopic Cholecystectomy with Deep Versus Moderate Neuromuscular Blockade: A Randomized Clinical Study.Anesthesia & Analgesia November 2014 · Volume 119 · Number 5 Rachid Badaoui, Aure ´ lie Cabaret, Youssef Alami et al. Reversal of neuromuscular blockade by sugammadex in laparoscopic bariatric surgery: In support of dose reduction. Anaesth Crit Care Pain Med 35 (2016) 25‐29 Y. Caesar, I. Sidlovskaja, A. Lindqvist et al. Intraabdominal Pressure and Postoperative Discomfort in Laparoscopic Roux-en-Y Gastric Bypass (RYGB) Surgery: a Randomized Study OBES SURG DOI 10.1007/s11695-016-2091-6 Hemanga K., Bhattac harjee, Azarudeen Jalaludeen et al. Impact of standard-pressure and low-pressure pneumoperitoneum on shoulder pain following laparoscopic cholecystectomy: a randomised controlled tria. Surg Endosc (2016) DOI 10.1007/s00464-016-5108-2 Bon-Wook Koo, Ah-Young Oh, Kwang-Suk Seo et al., Randomized Clinical Trial of Moderate Versus Deep Neuromuscular Block for Low-Pressure Pneumoperitoneum During Laparoscopic Cholecystectomy World J Surg DOI 10.1007/s00268-016-3633-8 Martini CH, Boon M., Bevers R.F., et al. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block Br J Anaesth 2013 1-8 Boon M, Martini CH, Aarts LP, Effect of variations in depth of neuromuscular blockade on rating of surgical conditions by surgeon and anesthesiologist in patients undergoing laparoscopic renal or prostatic surgery (BLISS trial): study protocol for a randomized controlled trial Trials 2013, 14:63 Lee JH, Paik YH, Lee JS, Ryu KW, Kim CG, Park SR, et al. Abdominal shape of gastric cancer patients influences short-term surgical outcomes. Ann Surg Oncol 2007;14:1288–1294. Shim JH, Song KY, Kim SN, Park CH. Laparoscopy-assisted distal gastrectomy for overweight patients in the Asian population. Surg Today 2009;39:481–486. Kim KH, Kim MC, Jung GJ, Kim HH. The impact of obesity on LADG for early gastric cancer. Gastric Cancer 2006;9:303–307. Seo HS, Lee HH. Short-Term Outcomes of Three-Port Totally Laparoscopic Distal Gastrectomy in the Treatment of Gastric Cancer: Comparison with a Four-Port Approach Using a Propensity Score Matching Analysis. J Laparoendoscopic & Advanced Surgical Techniques 2016;26:531-535. Lee HJ, Kim YS, Park I. Calculation of sample size in clinical trials. CISE 2013;16:53-57.
2.12 Publication Plan	Expected number of papers published with this trial: 1 paper –to make a high impact result, we are going to incorporate all surgical and anesthetic variables altogether. But if we could make collateral data, there would be more. Target journal: Annals of Surgery Abtracts: 2 to 3

	Scientific meetings considered with this study results: SAGES and ACS, and Korean International Surgical Meetings including KINGCA and KSELS.
2.13 Curriculum Vitae	Annexed sheet
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.