Study Protocol

Official title: Effects of deep neuromuscular block on surgical pleth index-guided remifentanil administration in laparoscopic herniorrhaphy: A prospective randomized trial

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1.1 Objectives & Hypotheses

The purpose of this study is to compare the remifentanil requirements in deep versus moderate neuromuscular blocks during the surgical pleth index (SPI)-guided anesthesia in patients undergoing laparoscopic herniorrhaphy.

We hypothesis that deep neuromuscular block using sugammadex will reduce the total remifentanil dose during SPI - guided anesthesia for laparoscopic herniorrhaphy, because the deep neuromuscular block is associated with less intra-operative nociception.

1.2 Background & Rationale, Significance of Selected Topic & Preliminary Data

General anesthesia results from a combination of hypnosis, antinociception, and immobility. Referring a goal-directed approach to each component, the measurement of neuromuscular paralysis or depth of anesthesia has been established as using neuromuscular monitoring or BIS (or PSI). Traditionally, clinicians utilize symptoms of the physiological stress response to nociceptive stimuli (i.e. increase of heart rate, blood pressure or lacrimation) to guide analgesic administration. However, administration of intraoperative analgesics guided by clinical symptoms alone appears to be of very limited value.

The SPI first introduced in 2007, uses pulse plethysmography and photoplethysmography, both obtained from pulse oximetry monitoring, to provide an index of the nociception–anti-nociception balance. It correlates with surgical stimuli and dosage of analgesic and predicts the effect of pain stimuli and analgesic therapy with greater certainty than common clinical parameters.

SPI = 100 - (normalised heart beat interval X 0.33 + normalised plethysmographic pulse wave amplitude X 0.67)

SPI had moderate correlation to the stress hormones during general anesthesia. And adjusting the remifentanil dosage according to the SPI reduced the consumption of both remifentanil and propofol and resulted in faster recovery compared with that according to clinical parameters. During equi-MAC anesthesia of 1.0 MAC, sevoflurane and desflurane did not show similar intraoperative remifentanil consumption under SPI-guided opioid administration.

Excessive intraoperative administration of remifentanil leads to opioid induced and acute opioid tolerance and opioid-induced hyperalgesia, including non-analgesic side-effects such as immunosuppression.

During laparoscopic surgery, deep neuromuscular block with sugammadex as reversal agent has been reported to reduce the postoperative pain than moderate neuromuscular block with neostigmine as reversal agent, although being controversial. The cause is postulated that at deep relaxation the tension

on the abdominal wall exerted by the intra-abdominal pressure is less harmful in comparison to the tension created during moderate relaxation.

1.3 Study Design

- This study is single center, prospective, double blinded, and randomized controlled study.

- Total **134 patients** undergoing laparoscopic herniorrhaphy included in the study.

- Inclusion criteria: American Society of Anesthesiologists (ASA) class 1, 2, and 3, laparoscopic hernia repair needing general anesthesia, and age between 19 and 85 years

Exclusion criteria: patients refusal, hyperbilirubinemia, chronic pain, opioid abuse, infection, and peripheral disease

- Using a computer-generated randomization (http://www.random.org), the patients were assigned into one of the 2 groups; Moderate neuromuscular block (NMB) group and Deep NMB group. Group assignment was concealed with sealed and opaque envelope. Immediately before anesthesia induction, the envelope was opened by independent investigator, who performed all interventions (control of NM block using rocuronium and reversal of NM block using study drug) but was not involved in outcome assessment. The anesthetic provider, patients, and preoperative and postoperative outcome assessors were blinded to the type of intervention (group assignment) throughout the study period.

- Patients monitoring include the noninvasive blood pressure, electrocardiogram, oximetry, and bispectral index. Anesthesia is induced with propofol of 2 mg/kg, rocuronium of 0.6 mg/kg and remifentanil infusion using TCI (target-controlled infusion). Anesthesia was maintained with continuous infusion of remifentanil and sevoflurane 1 MAC. After tracheal intubation, remifentanil infusion is stopped. One minute before skin incision, the remifentanil infusion was started in the flash mode, the target effect-site concentration of remifentanil was initially set at 3.0 ng/ml.

Subsequently, remifentanil infusion was continuously adjusted throughout the study period to achieve an SPI range between 20 and 50 with maintaining sevoflurane 1 MAC by an independent researcher who was blinded to the group allocation. Neuromuscular function is measured at the wrist. The TOF-SCAN generate the stimulus the ulnar nerve and measure contraction of the adductor pollicis muscle. At 15 min intervals, the TOF is measured and in the case of TOF=0, this is followed by the PTC. A bolus dose of intravenous rocuronium (5-10 mg) was used to maintain moderate (TOF count of 1-2) or deep (posttetanic count [PTC] of 1 or 2) neuromuscular blockade.

- **Moderate NMB group**: moderate NMB (T1-2), reversal using neostigmine 50 ug/kg + glycopyrrolate 10 ug/kg

- **Deep NMB group**: deep NMB (1-2 PTC), reversal using sugammadex 4 mg/kg based on actual body weight

- Primary Outcome

    Remifentanil infusion rate from pneumoperitoneum to removal of laparoscope (primary outcome)