A Comparison of Lidocaine, Esmolol, and Placebo Without Use of a Tourniquet for Relieving Pain from Intravenous Administration of Propofol

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Study Title: A Comparison of Lidocaine, Esmolol, and Placebo Without Use of a Tourniquet for Relieving Pain from Intravenous Administration of Propofol

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Background

It has long been known that propofol causes pain on intravenous injection (1). This pain is multifactorial in origin, stemming from direct mucosal irritation as well as stimulation of nociceptive sensory nerve fibers in the venous adventitia (2). Lidocaine has frequently been administered either in advance or concomitantly with propofol to attenuate this response. Studies have noted varying degrees of success with this technique but have clearly demonstrated an improvement in propofol injection pain when lidocaine is administered in combination with venous occlusion by a tourniquet (3, 4, 5, 6, 7).

Adrenergic signaling pathways participate in the neurotransmission and modulation of pain. β_2 agonists have been shown to work synergistically with opioids to exert anti-nociceptive effects (8), and β_1 antagonists possess similar properties (9). Esmolol has been shown to decrease perioperative anesthetic and narcotic requirements (10, 11), and one study showed that perioperative esmolol administration decreased postoperative opioid requirements for up to three days after surgery (12). Another study demonstrated that an intraoperative esmolol infusion decreased emergence times, postoperative narcotic requirements, and the time to discharge after ambulatory surgery (13). Esmolol has also been found useful for decreasing pain upon injection of a venous irritant: it decreases the pain associated with rocuronium injection (14) and may be even more effective than lidocaine at attenuating propofol injection pain when used in combination with a tourniquet (15). Importantly, it has proven to be effective at blunting the cardiovascular response to a noxious stimulus without causing clinically significant bradycardia and hypotension (16).

Despite the results of the above cited studies, most clinicians seldom use a tourniquet when giving lidocaine to attenuate propofol injection pain. In addition, esmolol's utility in preventing this pain has not been studied in the absence of a tourniquet. The goal of the present study is to determine whether lidocaine or esmolol is effective at preventing propofol injection pain when a tourniquet is not used.

In clinical practice, we commonly administer IV lidocaine from premixed syringes containing 100 mg of the drug dissolved in 5 ml. Most providers administer 1 mg/kg body weight, and few if any will open a second syringe when patients weigh more than 100 kg. Since the goal of this trial is to observe the clinical efficacy of this drug when administered the way it is usually done

by practicing clinicians, we decided to administer 1 mg/kg lidocaine to a maximum of 100 mg. In order to maintain blinding and consistency in this trial, we decided esmolol should be administered to a maximum of 50 mg since it will be mixed to half the concentration of the lidocaine -- this ensures that an equal volume of study drug will be administered, thus helping us maintain double blinding.

The study will include three arms: lidocaine, esmolol, and placebo. Eligible patients will be 18-60 years old, ASA physical status 1-3, and scheduled for an elective surgical procedure. Patients will be randomized to receive lidocaine, esmolol, or placebo. Both the patients and the administering/observing providers will be blinded to the study drug or placebo being administered.

Objectives

Our primary hypothesis is that esmolol and lidocaine, when given without the use of a tourniquet, provide relief of propofol injection pain that is superior to placebo when assessed using our propofol pain scoring tool.

Setting

This study is taking place at Wake Forest Baptist Medical Center in the perioperative setting. Subjects will already be planning on having an elective surgical procedure and be anticipating having a general anesthetic receiving propofol as part of that procedure.

Subjects selection criteria

Inclusion criteria

- 18-60 years of age
- ASA 1-3
- Elective surgical procedure

Exclusion criteria

- BMI $\geq$ 45
- Pregnancy
- Requirement for RSI or awake intubation
- Suspected or known difficult airway
- Any use of opioids in the last week
- Significant cardiopulmonary or hepatic dysfunction
- Hypersensitivity to study medications

Study Procedures, Interactions and Interventions

- Obtain informed consent and randomize patient into one of three groups (lidocaine, esmolol, placebo)
- Dose medications based on actual body weight
- Start 20 gauge IV in either extremity and hang lactated ringers (LR)
- Administer no sedative or analgesic (i.e., no Versed or fentanyl) prior to induction
- Place standard monitors and preoxygenate patient

- Administer study medication as a bolus
    - 1 mg/kg lidocaine to a max of 100 mg, 0.5 mg/kg esmolol to a max of 50 mg, or placebo
    - Lidocaine will be 20 mg/ml and esmolol will be 10 mg/ml
        - These concentrations allow us to simply administer 0.05 ml solution per kg regardless of which group the patient has been randomized into – 100 kg patient would receive 5 ml solution that would contain 100 mg lidocaine (= 1 mg/kg), 50 mg esmolol (= 0.5 mg/kg), or saline
    - Allow patient's IV to run freely
- 20-30 seconds after administration of study medication, bolus 0.5 mg/kg propofol to a max of 50 mg
- Record patient's pain over the next thirty seconds
    - Use the pain scale previously published by McCrirrick and Hunter (Anaesthesia 1990;45(6):443-4).
        - 0 = no pain
        - 1 = mild pain
            - Pain reported in response to questioning AND NOT accompanied by a physical sign (grimacing, withdrawal, tears, etc.)
        - 2 = moderate pain
            - Pain reported in response to questioning AND accompanied by a physical sign
            - Pain reported spontaneously AND NOT accompanied by a physical sign
        - 3 = severe pain
            - Pain eliciting a strong vocal response
            - Pain reported spontaneously AND accompanied by a physical sign
- Proceed with induction at the discretion of the attending anesthesiologist
    - If patient requires a NDMB, use vecuronium instead of rocuronium (due to venous irritation caused by rocuronium)
- Record vital signs every minute after induction for ten minutes
    - Also record administration of any medications given to treat hemodynamic derangements during this time frame (phenylephrine, ephedrine, propofol, etc.)
    - Do not administer esmolol for tachycardia during this time frame unless the patient shows evidence of myocardial ischemia or other significant derangements

Sample Size

150 patients (50 in each arm) is anticipated to be needed in this study.

Outcome Measure

Our primary outcome measure will be the proportion of patients with pain using a pain scoring system previously used by studies looking at various remedies to decrease propofol injection pain (15, 17). In this scoring system, patients are observed and their responses and behaviors are rated according a specific rubric (Table 1) (17). This assessment will be performed by a blinded

member of the study team following administration of a sub-induction dose of propofol, 0.5 mg/kg up to 50 mg, just prior to full induction.

Our secondary outcome measure will be heart rate, blood pressure, and SpO_2 every minute following induction. We will record vital signs each minute for the first 10 minutes following induction.

Analytical Plan

In preparation for this study, we obtained pilot data using five patients in each of the three proposed study arms. As shown in Table 2, lidocaine and esmolol both decreased the incidence of propofol injection pain in relation to placebo. Given that 40% (95% CI 0-83%) and 60% (95% CI 17-100%) patients given lidocaine and esmolol respectively reported little to no pain defined as a pain score of 0 on our propofol pain injection while 0% of patients who received placebo reported no pain, we used a sample size calculator for proportions with a 25% difference considered clinically significant, 90% power, and a 95% confidence level to determine a sample size of 32. In order improve our certainty we will increase this to 50 patients per group.

We will perform descriptive statistics on all demographic data. We will perform an individual comparison of all three groups using Pearson's chi-square test with Bonferroni correction for multiple comparisons. Other inferential statistics will be performed as necessary.

Human Subjects Protection

Subject Recruitment Methods

Subjects will be identified through the daily review of the preanesthesia assessment clinic as well as the daily surgical schedule for those meeting inclusion criteria. They will then be approached by a member of the research staff regarding their participation.

Informed Consent

Written informed consent will be obtained by a member of the research staff discussing this study in depth with them. Adequate time will be given for the subject to consider their participation. The risk of harm or discomfort that may occur as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. The rights and welfare of study will be protected through the use of measures to maintain the confidentiality of study information. Study results will be presented or published in lieu of providing individual subjects additional information regarding the study.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data

collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed per institutional guidelines (investigator initiated research data maintained for 6 years) consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. Wes Templeton will serve as a project mentor and will be involved in planning the study, navigating the IRB process, collecting and analyzing data, and preparing and submitting the manuscript.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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Appendix

Table 1.

Pain score	Degree of pain	Response
0	None	Negative response to questioning.
1	Mild	Pain reported in response to questioning only, without any behavioral signs (withdrawal of extremity, grimacing, etc.)
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign OR pain reported spontaneously without questioning
3	Severe	Strong vocal response OR spontaneous response accompanied by a behavioral sign

Table 2.

	Esmolol	Lidocaine	Placebo
Patients reporting pain	2	3	5
Total patients	5	5	5
Incidence of pain	40%	60%	100%