## University of Arkansas for Medical Sciences (UAMS) Clinical Protocol

**Study Title** Narcotic Free TIVA (Total Intravenous Anesthesia) and the incidence of unacceptable movements under general Anesthesia during ACDF (Anterior Cervical Discectomy and Fusion) surgery: A Randomized Controlled Trial

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## Background and Rationale

Anterior Cervical Discectomy and fusion (ACDF) is one of the most common spine surgeries, with patients typically presenting with neck pain and possibly some neurological deficits in their upper or lower limbs. Given the critical location of the surgery on the neck and being very close to the cervical spinal cord, neurophysiological monitoring is routinely used to insure safety and help guide the surgeon. The use of remifentanil-based total intravenous anesthesia (TIVA) to facilitate neurophysiological monitoring for neurosurgery has become a common/standard of care.

Neurophysiological monitoring such as transcranial motor-evoked potentials (TC-MEPs) and somatosensory evoked potentials (SSEPs) are routinely done under an anesthetic regimen that includes propofol infusion, 0.5 minimum Alveolar Concentration (MAC)I or less of sevoflurane and remifentanil infusion without muscle relaxation.

Remifentanil is an excellent medication that possesses an ultrashort half-life, reliable hemodynamic stability, decreased inappropriate patient movement profile under general anesthesia and a favorable effect on the quality of neuromonitoring.[1]

Some detractors of remifentanil has been its association with postoperative hyperalgesia and increased postoperative narcotic consumption which may lead to an increase incidence of postoperative side effects related to narcotic analgesics.

Recent attention to the overall use of narcotics and their social and medical impact has increased interest in narcotic-sparing anesthesia regimens.

Ketamine Low dose infusion, Lidocaine infusion, and Dexmedetomidine infusion are all drugs that have been used successfully as narcotic sparing drugs, and proved to decrease stress response of surgery, improve patient recovery, decrease narcotic consumption and decrease postoperative length of stay, thus overall decreasing hospital costs, and improving patient outcome. The use of these drugs has been investigated in multiple studies as single drug infusion or in a multimodal approach[3,4] .

## Hypothesis

We hypothesize a multimodal approach to intraoperative analgesia, without remifentanil, based on dexmedetomidine and ketamine infusion, provides a safe, and a,

hemodynamically stable anesthesia, with the added benefits of decreased postoperative narcotic consumption.

**Primary outcome:**

1. The incidence of unacceptable movement(UM) that is induced by nociception, or head manipulation and positioning by the surgical or anesthesiology Team or during a Motor evoked potential stimulation and defined as (gross visible movement reported by the Anesthesia or surgical team, bucking, chewing, or reaching to the endotracheal tube).

   The total number of occurrences for each case, and the total number of patients experiencing any UM for each of the study arms will be measured.

**Secondary outcomes:**

1. Heart rate and blood pressure will be recorded from Arterial line. The hemodynamic stability is defined as any increase in the heart rate by more than 20% of the base line. Base line recording will be calculated as the average of the readings taken in the preop- holding area and the reading that is recorded before induction of Anesthesia. Number and length of occurrences will be measured. Heart rate and blood pressure will be assessed per standard of care and the study data will be taken from the medical record.

2. Time to Extubation will be calculated from the time where the attending Anesthesiologist start emergence from Anesthesia till time of Extubation. Extubation Criteria will be eye opening, or toe wiggling or hand squeeze in response to verbal command.

3. Pain Scores will be assessed per standard of care and the study data will be taken from the medical record. Narcotic consumption in PACU, 24 hours will be calculated and transferred to morphine equivalents. Modified Aldrete score will be used as a criteria for readiness of the patient for PACU discharge.

4. Psychometric assessment of recovery from general anesthesia will be assessed using Quality of Recovery score, QoR-15. Assessment will be done twice first time in the preoperative holding area, and second on the following morning after surgery. Answers of the questions are given scores from 1 to 10 on a Likert scale. The score ranges from 0 to 150 and the questionnaire is designed to assess the

emotional state, physical comfort, psychological support, physical independence, and pain.

## Study Design and Procedures

We intend to approach patients scheduled for ACDF surgery, as all of these cases will require neurophysiological monitoring and a subsequent anesthetic technique based on total intravenous anesthesia with no paralysis. Additionally, a majority of these patient group will not have a chronic pain diagnosis which will mandate the use of high doses of intraoperative narcotics.

Study personnel will approach prospective subjects either during their pre-surgery clinic visit (preferably) or the day of surgery, before any pre-operative medications have been administered.

This study will be randomized, controlled trial consisting of two treatment groups:

### *Remifentanil (R) Group*

Remifentanil is a short-acting synthetic opioid analgesic drug structurally related to fentanyl and other piperidine-based analgetics

The remifentanil (R) group will have a remifentanil infusion of 0.05 to 0.2 mcg/kg/min started just prior to induction and stopped at emergence from anesthesia. Remifentanil is a highly hydrophilic narcotic with high potency and short-context sensitive half-life. The remifentanil dose will be adjusted depending on the patient age, weight, blood pressure, and sex as determined by the attending anesthesiologist based on their clinical Judgment.

### *Ketamine and Dexmedetomidine (KT) Group*

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that induces dissociative amnesia and analgesia. Dexmedetomidine is alpha$_2$-adrenergic agonist anesthetic with sedative properties.

The ketamine and dexmedetomidine (KT) Group will receive a dexmedetomidine bolus of 0.5 mcg/kg over 10 minutes starting 5 minutes prior to induction followed by an infusion of 0.2- 0.7 mcg/kg/hr that will be stopped with the start of closing the surgical wound. The ketamine infusion shall be started at induction and will be 2 mcg/kg/min, it shall be stopped at the beginning of emergence from anesthesia, roughly 45 minutes prior to extubation. The dexmedetomidine and ketamine bolus and infusion will be titrated at the clinical judgment of the attending anesthesiologist based on the age, weight, and heart rate of the patient in the same manner he/she would manage those

medications any other clinical situation. The doses used for the study is the normal clinical range that is used within standard clinical practice and the attending anesthesiologist will be manipulating the doses of the drugs within the ranges stated in this protocol

Each treatment group will receive a balanced general anesthesia based on the discretion of the attending anesthesiologist. A propofol infusion titrated to a bispectral index (BIS) of 40-60 combined with 0.5 Monitored MAC of sevoflurane will be used to maintain anesthesia.

The attending Anesthesiologist from the UAMS Anesthesiology department will receive a closed envelope 15 minutes before the procedure with the case code and assigned group. The randomization will be computer based. Using MS Excel software, study subject numbers will be entered to spread sheet, numbered from 1 through 80, and the software will be used to randomly assign each number to one of the 2 groups. The Envelopes will be prepared and handed to the attending anesthesiologist by the study personnel.

Any attending anesthesiologist would be asked to do the case, but the consent process will be always done by the research personnel. The study drugs will be then checked out from the operating room pharmacy and prepared for infusion in the regular manner as within the usual clinical situation. All the prepared drugs will be prepared out of site of the blind assessor. The assessor (surgeon, surgical resident, or study personnel) will be blinded to the regimen used and will be asked to monitor for the incidence of inappropriate movements.

We will define inappropriate movements as any movement that is visible by the surgical team. Patient movements under general Anesthesia might occur, and commonly seen by the surgical team during surgical stimulation especially in non-paralyzed Patients, and usually communication between surgical team and Anesthesia personnel will occur. Anesthesia response is usually deepening the Anesthetic level or giving muscle relaxants. In the case of ACDF surgery Muscle relaxants cannot be used as part of the neuromonitoring prerequisites. We are monitoring the incidence of inappropriate movements, and hemodynamic stability as signs of adequate levels of depth of anesthesia and pain management under general anesthetic regimen in the 2 groups.

The attending anesthesiologist, and resident or Certified Nurse Anesthetist (CRNA) will be aware of the study group. The primary surgeon or surgical resident will be functioning as a blinded observer counting the incidence of inappropriate movements. The postoperative evaluators who will be a study staffer (another attending

anesthesiologist, or resident physician) will be blinded of the study group and will be asked to conduct the Quality of Recovery (QoR) questionnaire. All other data collected will be part of the patient chart and will be collected by the study personnel.

The following subject demographics will be collected from the patient record:

1. Age
2. Sex
3. Weight

All patients having ACDF surgery will stay in the hospital as inpatients for at least 24 hours post-operatively as a standard of care. With timing of our QoR questionnaire we will be able to follow up all of our patients and at the same time do not affect their standard postoperative care plan. The QoR questionnaire is completed for research purposes only and is not part of the standard of care. The questionnaire will be administered by study personnel.

**Study Population**

We will include 18-80 year old men and women presenting for an (ACDF) surgery of 1-2 levels. These patients will be required to fall into the Anesthesiology Society of America (ASA) classification 1, 2, or 3 and must consent to their participation. Should the patients have a history of seizure disorder or refuse to participate they will be excluded from the study.

**Inclusion Criteria**

- Men and women 18- to 80-years old
- ASA 1, 2, 3
- 1 or 2 levels ACDF

**Exclusion Criteria**

- ASA 4
- Seizure disorders
- Chronic narcotic use
- Opiate abuse
- Major cardiac comorbidity, or significantly elevated blood pressure
- Known hypersensitivity to fentanyl analogs, ketamine, or propofol injectable

emulsions.

- Known allergy to eggs, egg products, soybeans, or soy products

## Adverse Events

### *Definitions*

### Adverse Event

An adverse event (AE) is any untoward medical occurrence that develops or worsens in severity during the course of the study, whether or not it has a causal relationship to the study treatment. Concurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

### Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event (SAE)** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or

intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

### *Adverse Event Reporting Period*

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as within 1 day following the last administration of study treatment.

### *Pre-existing Condition*

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period (e.g. if behavior worsens).

### *General Physical Examination Findings*

At screening, any clinically significant abnormality should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an AE.

### *Post-study Adverse Event*

All unresolved AEs should be followed by the investigator until the events are resolved, until the events are otherwise stable or the subject is lost to follow-up. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

### *Abnormal Laboratory Values*

A clinical laboratory abnormality should be documented as an AE if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality

- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the investigational product, more frequent follow-up assessments, further diagnostic investigation, etc.

### *Hospitalization, Prolonged Hospitalization or Surgery*

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

### *Recording of Adverse Events*

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and Monitoring in the intraoperative and postoperative period and, as appropriate, by examination. Information on all AEs should be recorded immediately in the Anesthesia Record. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded also on the Anesthesia Record

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that

are still ongoing at the end of the study period must be followed up to determine the final outcome.

### *Reporting Procedures for Adverse and Serious Adverse Events*

All adverse and SAEs will be reported in accordance with FDA and local IRB requirements.

All SAEs that meet the IRB's Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO) requirements must be submitted to the IRB within 10 working days. All other SAEs will be submitted to the IRB at continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

### *Data Safety and Monitoring Plan*

All safety data will be reviewed by the Medical Monitor after each patient and after the completion of each cohort. A Data Safety and Monitoring Board will not be appointed.

### *Medical Monitor*

A Medical Monitor (MM) will be selected. The MM will be a licensed physician who is familiar with cardiovascular disease, neurological assessment, and adverse neurological outcome. For this study, the medical monitor will be the Principal Investigator. The MM will review the data collected after each patient. As part of the review, the MM will review all AEs and assure that any SAEs have been reported appropriately.

## Risks and Benefits

We do not anticipate any increase in risk using the multimodal KD anesthetic regimen as compared to the R regimen and others. Narcotic-sparing anesthesia has been documented in multiple studies with a favorable clinical outcomes.[2,3,4] The attending anesthesiologist will always have the ability and prerogative to withdraw the subject from the study, stop the study medication and / or administer narcotics if he feels by his clinical judgment this is better for the patient.

Common risks associated with the use of remifentanil include but are not limited to: bradycardia, hypotension, pruritus, nausea, vomiting, and apnea. Contraindications to its use would include hypersensitivity to it or its components, intrathecal or epidural

administration.

Common risks associated with the use of ketamine include but are not limited to: prolonged emergence, confusion, delirium, hallucinations, irrational behavior. Contraindications to the use of ketamine would include but not be limited to hypersensitivity to it or its components, conditions in which an increase of blood pressure would be hazardous, increased intracranial or intraocular pressure (relative).

Common risks associated with the use of dexmedetomidine include but are not limited to: bradycardia, hypotension, hypertension, agitation, constipation, respiratory depression. Contraindications to the use of dexmedetomidine would include but not be limited to hypersensitivity to it or its components.

Should a participant experience any adverse reaction to the medications in the study, the medication will be stopped, patient will be treated appropriately as the case with any other patient who is outside the study .

Both of study arm infusions has been used in clinical Practice safely, but if any persistent repeating event is occurring with one group, we will stop the whole study.

As with all clinical research, there exists the risk to the study participants' privacy violated in the form of a loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

**Data Handling and Recordkeeping**

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code (the instrument associating the data with subject identity) will be kept in a locked file in the principal investigator's office, if hardcopy, or on a password-protected UAMS server, both located behind locked doors in a restricted access area of the UAMS campus. Only Mohamed Abdeldayem, M.D. PhD. Principal Investigator of this protocol will have access to the code and information that identifies the subject in this study.

Once all of the study data have been validated, it will be de-identified by destroying the key associating the assigned study number and the subject identity. The resulting de-identified data will be retained, and then, ultimately destroyed per UAMS Policy.

## Data Analysis

We are expecting to recruit 80 patients to our study, and including 60 to 70 patients in the data analysis. Sample Size is based on being able to detect non-inferiority on both inappropriate movements, and postoperative narcotic consumption. The samples size estimation is based on our experience from similar studies. We defined hemodynamic instability as a 20% increase in the heart rate from base line. The Quality of Recovery questionnaire will be scored for every patient. Our primary outcome is the incidence of intraoperative inappropriate movements, and postoperative narcotic consumption. Means(M) and Standard Deviations(STD) will be calculated for each group. We will test the non-inferiority of Dexmetetomidine/Ketamine group to Remifentanil group on narcotic consumption & inappropriate movement incidence using a 1-tailed Wilcoxon rank sum test. Independent t test will be used to compare quality of recovery scores, between 2 groups. Non-inferiority on the hemodynamic stability will be assessed using a 1-tailed t test from a repeated measures ANOVA model. Treatment effect will be calculated using difference in means between groups with interim-adjusted 95% confidence intervals (CIs).

## Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study.

The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record. The consent will be done by the

Principal investigator, attending anesthesiologist or one of the trained study personnel. The consent will be done before the patient has received any preoperative sedation or medications.

**Dissemination of Data**

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

**References**

1. Beers R, Camporesi E. Remifentanil update: clinical science and utility. CNS Drugs. 2004;18:1085–1104.
2. Shobana Rajan, MD, Matthew T. Hutcherson, BS, Daniel I. Sessler, MD, Andrea Kurz, MD, Dongsheng Yang, MS, Michael Ghobrial, MD, Jinbo Liu, MD, and Rafi Avitsian, MD: The Effects of Dexmedetomidine and Remifentanil on Hemodynamic Stability and Analgesic Requirement After Craniotomy: A Randomized Controlled Trial. JNS. 2016:28.
3. Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, Salihoglu Z.: Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. Braz J Anesthesiol. 2015 May-Jun;65(3):191-9.
4. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT.: Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014 May;112(5):906-11

**Appendices**

1. QoR15 questionnaire V2 04.24.2019