A Prospective Study Comparing a Multimodal Anesthetic using Total Intravenous Anesthesia (TIVA) with Propofol and Remifentanil vs. Propofol and Dexmedetomidine in Adolescent Idiopathic Scoliosis Patients undergoing Posterior Spinal Fusion and Instrumentation

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1.0 Protocol Summary

Study Purpose	• The purpose of the study is to compare two different total intravenous anesthesia (TIVA) techniques as part of a multimodal anesthetic in pediatric patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion (PSF) and instrumentation for correction of their scoliosis. • TIVA group I is Propofol+ Remifentanil, and TIVA group II is Propofol + Dexmedetomidine (DEX). • The primary outcome to be studied is postoperative opioid consumption for pain control measured in morphine milligram equivalents (MME). • The secondary outcomes are time from skin closure to patient being able to move their feet to command, time from skin closure to extubation, and postoperative visual analog (VAS) pain scores.
Research Procedures	The primary research procedures are: • Medical record review • Recruitment of study subjects • Screening of subjects to ensure subjects meet all inclusion criteria and have no exclusion criteria. • Randomization of patients into the two study groups • Data collection intraoperatively • Data collection postoperatively in the EMR

Subject Population	• The study will enroll randomized patients with the following inclusion criteria:
	  • Age 12-21 years old
	  • ASA 1 and 2
	  • Have diagnosis of AIS
	  • Undergoing PSF with instrumentation for scoliosis correction
	  • Matched on age, sex, and the number of vertebral levels fused

Duration of Subject's Participation	• The duration of subject's participation is the length of their hospitalization for the surgery (2-3 days).

2.0 Background, Rationale

Our institution is a major pediatric spine center performing posterior spinal fusion and instrumentation for the correction of Adolescent Idiopathic Scoliosis (AIS). AIS patients are usually in their teens and are healthy, without other medical problems. They generally do not have significant chronic pain and are opioid-naïve. Scoliosis surgery is painful, so these patients receive a multimodal analgesia regimen as a standard of care (1,2). Our intraoperative regimen uses intrathecal (IT) morphine (3-7) given pre-incision, IV ketamine at induction, and IV acetaminophen at conclusion of case. Postoperatively, patients receive Morphine or Hydromorphone PCA which is quickly transitioned to PO Opioids and NSAIDs. The most common intraoperative anesthetic technique for pediatric scoliosis surgery at our institution is total intravenous anesthesia (TIVA) with Propofol and Remifentanil. TIVA avoids the use of inhalational anesthetic gases and so does not interfere with intraoperative neurophysiological monitoring such as SSEP and MEP. Remifentanil is a popular choice because of its rapid onset, small volume of distribution (Vd), rapid clearance, and brief half-time (1.0-1.5 min) for equilibration between plasma and the effect compartment. Remifentanil's unique hallmarks are its extremely short context-sensitive half-life (3-5 min), its potency (100-200 times more potent than Morphine), and its rapid recovery from drug effect. Remifentanil's ultra-short-acting duration is independent of dose, allowing rapid offset after continuous infusion (8-11). Thus, in the event of intraoperative loss of neurophysiological signals, remifentanil can be turned off to allow for a quick wake up test to be performed.

However, an important concern with intraoperative remifentanil infusion is the possible development of acute opioid tolerance or hyperalgesia. In adults, opioid-induced hyperalgesia (OIH) is a well-documented feature linked to intraoperative remifentanil administration, manifesting as increased postoperative analgesic requirement and paradoxical increase in sensitivity to painful stimuli (12-18). In pediatric patients, the phenomenon is not as well characterized. In one study, a continuous intraoperative infusion of remifentanil, when compared with intermittent morphine boluses, significantly increased postoperative morphine consumption in adolescents undergoing scoliosis surgery (16). The use of

intraoperative remifentanil infusion was shown to increase cumulative postoperative morphine requirements by 30% in the first 24 hours compared to patients not receiving intraoperative remifentanil (16). These findings support the hypothesis that intraoperative remifentanil infusion is associated with the development of clinically relevant acute opioid tolerance or hyperalgesia as seen in adult studies. However, in another study, no association was found between the dose of intraoperative remifentanil and postoperative opioid consumption in the context of a propofol-based TIVA and multimodal analgesia (19).

An alternative TIVA that is very commonly used for adult spine surgery at our institution is propofol + dexmedetomidine (DEX). Notably, pediatric patients undergoing scoliosis correction surgery have also safely received propofol + DEX TIVA at our institution. DEX is a highly selective alpha2-adrenergic receptor agonist with sedative, analgesic and sympatholytic properties. Its sedative effects are dose-dependent. The locus ceruleus of the brain stem is the principal site for its sedative action, and the spinal cord is the principal site for its analgesic action, both acting through alpha2-adrenergic receptors. Side effects are mainly hypertension, hypotension and bradycardia as a result of vasoconstriction, sympatholysis, and baroreflex-mediated parasympathetic activation (20, 21). A meta-analysis of randomized placebo-controlled trials testing systemic alpha2 agonists like clonidine or dexmedetomidine administered in surgical patients showed that perioperative systemic alpha2 agonists decreased postoperative opioid consumption, pain intensity, and nausea, and did not prolong recovery time (22).

Despite the lack of FDA approval for pediatric use, DEX is widely used off-label in pediatric patients and has previously been shown to be safe and efficacious for various clinical indications including procedural sedation, craniotomy-awake-surgery, cardiac surgery, and posterior spinal fusion for scoliosis (23-30). A meta-analysis of 11 randomized controlled pediatric trials revealed a lower risk for postoperative pain and the need for postoperative opioids following intraoperative DEX in comparison with placebos or opioids in children undergoing surgery; however, the influence of DEX on postoperative opioid consumption was

less clear (31). The most common adverse event in patients treated with DEX was intraoperative bradycardia (32). DEX does not affect intraoperative neurophysiologic monitoring (33,34). The use of DEX has been shown to not affect the intraoperative wake up time in patients undergoing spine surgery (35-38).

Are there studies comparing remifentanil to DEX? A recent meta-analysis of 21 randomized trials comparing intra-operative analgesia with remifentanil and DEX demonstrated that intra-operative DEX for general anesthesia was superior to remifentanil administration, with lower pain scores during the first 24 hours and with less hypotension, shivering, and postoperative nausea and vomiting (39). However, time to extubation and length of stay in the recovery room were significantly longer in the DEX group by a mean difference (95% CI) of 4.9 min (0.8-9.1), $I^2 = 99\%$, $p=0.02$, and 8.9 min (4.4-13.4), $I^2 = 97\%$, $p<0.0001$, respectively. Though statistically significant, the authors viewed the differences as clinically negligible. Of note, most of the operations in this meta-analysis were laparoscopic surgery and ENT surgery.

There is a paucity of studies comparing TIVA with propofol + remifentanil and propofol + DEX in spine patients. In one study of adult patients having posterior lumbar interbody fusion (PLIF) surgery under propofol-based TIVA, DEX was demonstrated to lower the VAS pain score and reduce PCA requirement compared to remifentanil for the first 48 hours (40).

Our study proposes to compare these two TIVAs in the setting of pediatric AIS patients having posterior spinal fusion and instrumentation to see if the use of DEX instead of remifentanil will result in less hyperalgesia, lower opioid consumption, and lower VAS pain scores in the post-operative period. We also hope to demonstrate that the use of DEX will not significantly prolong extubation time when used appropriately.

In an age where ERAS protocols seek to improve post-operative pain control, decrease opioid consumption, and achieve quick discharge home after posterior spinal fusion for pediatric scoliosis patients, we believe our study could have a positive societal impact.

3.0 Study Purpose and Objectives

The proposed study is a prospective, randomized comparison of propofol + remifentanil TIVA vs. propofol + DEX TIVA on postoperative opioid requirements and pain in AIS patients undergoing PSF and instrumentation for scoliosis correction. All other perioperative anesthetic management, including post-anesthesia care and pain management, are standardized.

Two intervention groups will include:

1. Propofol + Remifentanil group: Maintenance TIVA will be started after induction using propofol at standard doses (100-200 mcg/kg/min) and remifentanil (0.2-0.5 mcg/kg/min); TIVA is titrated to keep BIS < 55-60 to ensure patient is asleep.
2. Propofol + Dexmedetomidine group: Maintenance TIVA will be started after induction using propofol at standard doses (100-200 mcg/kg/min) and DEX (02-0.7 mcg/kg/hr); TIVA is titrated to beep BIS < 55-60 to ensure patient is asleep.

The following persons are blinded:

a. Surgeon
b. PICU staff (attending MD, NP, RN)
c. Patient and family

The following persons are unblinded:

a. Patient's anesthesiologist
b. This same anesthesiologist will accurately record the time from skin closure to patient moving feet to command, and the time from skin closure to extubation. (Note: the anesthesia spine team comprises a small core group

of pediatric anesthesiologists who work exclusively with the spine surgeons and will be trained on the accurate collection of these data.)

c. Investigator accessing EMS to collect the following patient data:
   i. MME
   ii. VAS Pain scores

Summary of Perioperative Multimodal Analgesia

Propofol + Remifentanil Group	Propofol + DEX Group
At Induction	
Ketamine 1 mg/kg (max 50 mg) at induction	Same
TIVA to maintain BIS < 55-60	
Remifentanil + Propofol (remifentanil dose 0.2-0.5mcg/kg/min)	Dexmedetomidine + Propofol (DEX dose 0.2-0.7 mcg/kg/hr)
Pre-Incision	
Intra-thecal (IT) Morphine pre-incision 4 – 5 mcg/kg (max 250 mcg)	Same
Conclusion of Case	
IV Acetaminophen 15 mg/kg (max 1000 mg)	Same
Post-op (Peds ICU)	
Per multimodal analgesia Protocol	Same

The primary outcome to be measured is the total opioid consumption (IV and PO in MME) on POD 0 and 1 because this is when our patients experience the most acute postoperative pain. By POD 2, most of our patients are discharged home. The secondary outcomes to be measured are time from skin closure to patient being able to move their feet to command (mins), time from skin closure to extubation (mins), average VAS pain scores on POD 0,1 and 2, and total MME on POD 0,1 and 2. Skin closure is defined as when the last stich is placed by the surgeon thus concluding the surgery. POD 0 = first 24 hours after surgery, POD 2 = 48 hours after surgery, POD 3 = 72 hours after surgery.

Primary Outcome	
Opioid Consumption on POD 0 and 1	MME
Secondary Outcomes	
Time from skin closure to patient being able to move their feet to command	Mins
Time from skin closure to extubation	Mins
Average VAS Pain scores on days 0,1 and 2	Numerical rating scale
Opioid consumption on POD 0,1 and 2	MME

Patients will be sent directly from the OR to the pediatric ICU for their post-operative recovery. They will be continued on a multi-modal analgesia regimen including opioid PCA and oral opioids as needed (PRN) based on the Visual Analog Scale (VAS) pain scores.

4.0 Study Population

The study population will be randomly drawn from AIS patients of spine surgeons Dr David Skaggs and Dr Kenneth Illingworth undergoing PSF and instrumentation for scoliosis correction.

Enrollment numbers: A total of 120 patients randomly assigned to one of two study groups.

TIVA Group I	Propofol + Remifentanil TIVA (n=60)
TIVA Group II	Propofol + Dexmedetomidine (n=60)

a. Inclusion criteria include:
    i. Age 12-21 years old

ii. ASA 1 and 2
iii. Have diagnosis of adolescent idiopathic scoliosis
iv. Undergoing posterior spinal fusion with instrumentation for scoliosis correction
v. Matched on age, sex, and the number of vertebral levels fused.

b. Exclusion criteria include:
    i. Neuromuscular scoliosis
    ii. Allergy to any of the multi-modal analgesia regimen drugs
    iii. Use of serotonergic drugs, MAOIs, mixed agonist/antagonist opioid analgesics

c. Withdrawal criteria include:
    i. Intraoperative loss of motor evoked potentials necessitating a wake up test to monitor for neurological deficits
    ii. Allergic reaction to any medications administered during the surgery.

Subject Identification, Recruitment, and Consent

I. Subject Identification and Recruitment
    a. Medical records of upcoming preoperative visits at APEC will be reviewed for the purposes of recruitment.
    d. At APEC, Eligible patients and parents will be provided introductory study material packet by APEC staff. The study material packet contains a study recruitment letter, an informed consent form, and a child assent form. There is no need to explain the study at this stage, but the intent is for parents and potential subjects to be able to read the information in the comfort of their home in an unrushed manner. Parents will be told that a study investigator will call them to tell them about the study and give them an opportunity to participate.
    e. If patients are seen virtually at APEC, staff will provide parents of potential subjects with introductory study material packet via email or via mail, and a study investigator will call them about the study.
    f. A study investigator will call these patients and their parents after their APEC appointment and before the surgery to explain the study

protocol including the potential risks, benefits, and alternatives, and address any questions/concerns.

II. Day of Surgery
   a. Preoperative evaluation by the Anesthesiologist
      i. In the preoperative holding area, patients and their parents will provide a detailed medical history, demographic information, anesthetic complications such as postoperative nausea and vomiting, baseline VAS pain scores, and current pain medication regimen.
   b. Consenting performed by the Anesthesiologist
      i. Only patients indicating that they have been introduced to the study prior to meeting with the anesthesiologists on the day of surgery will be able to participate, undergo screening, and be consented.
      ii. Screening will ensure subjects meet all inclusive criteria.

After consents have been signed, patients will be randomized to one of two study groups according to a computer-generated randomization number table.

5.0 Study Design and Procedures

5.1 Schedule of Events and Procedures

Legend
- **R** = Research item/procedure done only for research purposes and their costs are covered by the study.
- **S** = Standard of care item/procedure that is part of regular care and billed to the patient/insurance.
- **sBNA =** item/procedure is not billable separately. It is a bundled service.

Procedures	Recruitment	Treatment	Follow Up	Follow Up	Follow Up
	3-15 days before Surgery	Day of Surgery	POD #1	POD #2	POD #3

Introductory Study material packet	R				
Written Parental Consent		R			
Randomization		R			
Inclusion/Exclusion criteria		R			
Complete Medical History		S(BNA)			
Demographics		S(BNA)			
Weight		S(BNA)			
BMI		S(BNA)			
Preoperative Cobb Angle		R			
Number of levels fused		R			
Number of osteotomies		R			
Anesthetic complications		R			
Visual Analog Pain Scores (VAS)		R	R	R	R
Current pain medication regimen		R			
Physical Exam		S			
Dexmedetomidine/Remifentanil dispensing IV		S			
Dexmedetomidine/Remifentanil administration IV		S			
Propofol dispensing IV		S			
Propofol administration IV		S			
Midazolam IV		S			
3-lead EKG		S(BNA)			
NIBP		S(BNA)			
Pulse Oximeter		S(BNA)			
EtCO2 capnography		S(BNA)			
Urinary Temp		S(BNA)			
Bispectral index (BIS) monitor		S(BNA)			
Radial Arterial		S			
Scoliosis Correction Surgery		S			
Ketamine IV		S			
Morphine IT		S			
Acetaminophen IV		S			
Rocuronium IV		S			
Dexamethasone IV		S			
Cefazolin		S			
Gentamycin		S			
Tranexamic acid (TXA)		S			
Deliberate hypotensive anesthesia (using nitroglycerin)		S			
Vasopressor (using phenylephrine)		S			

Glycopyrrolate IV		S			
Atropine IV		S			
Ephedrine IV		S			
Fentanyl IV		S			
Diazepam IV		S			
Ketorolac IV		S	S	S	
Patient controlled analgesia (PCA)			S(BNA)		
Oxycodone PO			S	S	S
Diazepam PO			S	S	S
Acetaminophen PO		S	S	S	S
Ibuprofen PO					S
Type of Narcotic given on transport to PICU (Fentanyl IV, Morphine IV, Dilaudid IV. If applicable)		S			
Dose of Narcotic given on transport to PICU (As clinically applicable)		S			
Type of PCA Medication (Dilaudid IV PCA, if applicable)		S	S	S	
Total dose of PCA Medication (As clinically indicated)		S	S	S	
Type of PO Narcotic (Oxycodone PO)		R	S	S	
Dose of PO Narcotic (As clinically indicated)		S	S	S	
Type of IV rescue narcotic (Morphine IV, Diaudid IV, if applicable)		S	S	S	
Dose of IV rescue narcotic (As clinically indicated)		S	S	S	
Total MME		R	R	R	
Time from skin closure to moving feet on command		R			
Time from skin closure to Extubation		R			

5.2 Study Design and Duration

The total study duration for the subject's participation is the length of their hospital stay at Cedars-Sinai Medical Center (2-3 days).

5.3 Description of Study Procedures

The study involves the study procedures listed below. The timepoints of the procedures are outlined in the previous section 5.1 Schedule of Events.

Study Procedures	Description
Introductory Study Material Packet	Parents of potential study subjects will be handed the introductory study material packet during their child's preoperative visit at APEC, or mailed if preoperative visit was virtual. Parents are informed that a study investigator will call them to tell them about the study and give them an opportunity to participate.
Written Parental Consent	The anesthesiologist will answer any outstanding questions and address any concerns subjects and their parents may have about the study in the preoperative area on day of surgery. Written parental consent is obtained at this time.
Randomization	After consents have been signed, patients will be randomized to one of two study groups according to a computer-generated randomization number table. The anesthesiologist will open the sealed envelope containing the subject's randomized group assignment, and instructions for drawing up the study drugs. From this information, the anesthesiologist will prepare the study TIVA medications. Both remifentanil and DEX are within the standard of care and routinely used in anesthetic care at our institution. Remifentanil is obtained by the anesthesiologist ordering the medication from the pharmacy, and DEX is obtained by the anesthesiologist from the core Pyxis.
Monitors	Standard ASA monitors include 3-lead ECG, non-invasive BP, pulse oximetry, end-tidal CO2 capnography, temperature. In addition, bispectral index (BIS) and radial arterial BP are routinely used for all spine cases.
Multimodal Analgesia	Multimodal analgesia is used intraoperatively and postoperatively as standard of care to help improve pain management. It prescribes the use of more than one pharmacological class of analgesia medication targeting different receptors along the pain pathway with the goal of improving pain management while reducing individual drug-related side effects. Medications used are listed in previous section 5.1.
Data Collection and Management	See section 6 below

5.4 Medical Record/Clinical Record Review:

This study involves an electronic medical record review. Data will be abstracted from the electronic medical record perioperatively and within 3 months of surgery. The data points to be abstracted are outlined in Section 6 of the protocol.

6.0 Data Collection and Management

6.1 Data Procurement

- **Identification/Access/Abstraction**

  ☒ Members of the study team will require access to the electronic medical record (clinical data source) to identify eligible data and to conduct data abstraction.

- **Source(s) of Data:**

  The source of the data to be analyzed is the electronic medical record which includes pertinent medical information, demographics, anesthesia record, operative note, flowsheets for postoperative opioid use, and visual analog scale (VAS) pain scores.

6.2 Time Period of Data under Review

- Data will be collected from/at the following timepoints: Perioperatively, Day of Surgery (DOS), 1-week to 3 month postoperative.
- Information will be kept indefinitely.

6.3 Data Elements

- Age
- Sex
- Weight
- Body Mass Index (BMI)
- Preoperative Cobb Angle
- Current pain medication regimen
- Number of levels fused
- Number of osteotomies
- Anesthetic complications
- Postoperative opioid MME (DOS, POD#1, POD#2, POD#3)
  - PCA opioids IV
  - Rescue opioids IV
  - PO opioids
- Visual analog scale (VAS) pain scores (DOS, POD#1, POD#2, POD#3)

- Time from skin closure to moving feet on command
- Time from skin closure to extubation

6.4 Confidentiality

HIPAA Identifiers
Name
Medical Record Number
Age in years
Date of Surgery

Confidentiality will be maintained in the following manner:

- **Secure Storage**: Data will be housed in a HIPAA-compliant secure storage system, like Box, within the Cedars-Sinai network with access restricted to approved members of the research team.
- **Limited Access:** Private identifiable information will be accessible only to IRB approved study team members with current IRB training.
- **Unique ID Numbers and Coding:** Each patient will be assigned a unique ID number. The linking list will be kept secure. Direct identifiers listed in section 8 will be separated from the study materials (data and/or specimens) as soon as possible. During data abstraction, name and/or MRN are required for data verification purposes. After data abstraction is complete and data have been verified, the name will be removed (if collected). Only the MRN will be used to link the study ID/code to the individual after that point until the linking list is destroyed.
- **Destroying Identifiers:** The identifiers and the linking list will be destroyed as soon as scientifically possible and maintained only as long as necessary to abstract, analyze and verify data.
- **Storage of Physical Records:** Physical records will be maintained for this study at a secure location where access is limited to approved personnel. The records will not be removed from Cedars-Sinai premises.

7.0 Data and Safety Monitoring

7.1 Data and Safety Monitoring Plan

The study will be monitored by the PI to ensure appropriate study conduct, including obtaining proper access to data/specimens, compliance with the HIPAA Privacy Rule, compliance with Cedars-Sinai policy, and adhering to the plans outlined in the protocol for all study procedures,

abstracting and recording data, data and/or specimen security and maintenance, and data accuracy and integrity. Any adverse events, deviations, protocol exception requests, potential unanticipated problems involving risks to subjects or others, or other events will be submitted to the IRB in accordance with IRB reporting policy. All study procedures will be conducted in accordance with standard clinical practice.]

7.2 Quality Control and Quality Assurance

- The PI will delegate a study team member to conduct QC/QA activities on a quarterly basis who will be responsible for the evaluation of data quality. Data will be evaluated for adherence with the protocol and for accuracy in relation to source documents.

8.0 Sample Size and Statistical Considerations

8.1 Statistical Sample Size Justification

The main hypothesis to be tested is whether the primary outcome of Mean Total MME for POD 0 and POD 1 is different between the Propofol + Remifentanil group and the Propofol + DEX group. For sample size, we performed a pilot study of 15 AIS patients who underwent PSF with instrumentation by our study surgeons at our institution using Propofol + Remifentanil TIVA in the last two years. We performed a power analysis with the following assumptions: Power of 80%, estimated SD of 33.3, and level of significance (alpha) of 0.05. We considered a difference of 17.2 as an important Group Difference in Mean Total MME for POD0 and POD1. The sample size necessary after the power analysis was 60 per group using a two-sided two sample t-test.

8.2 Statistical Analysis Methodologies

The primary outcome variable (total MME) will be summarized using mean and SD and using median and IQR (interquartile range). Differences between the two groups at each time point will be analyzed by t test or Wilcoxon rank sum test. The normality assumption will be verified by the Shapiro-Francia test[ref] and homogeneity of variance by the Levene test[ref].

The secondary outcome variables are VAS pain score (scale of 1-10), time from skin closure to moving feet to command, time from skin closure to extubation, and total MME for POD 0, 1 and 2. VAS pain score is an ordinal variable that generally is treated as a continuous variable in analysis. We considered an important difference in a pain scale of 1-10 to be 2 units, VAS will be compared between groups on POD 0, 1 and 2 using t test and/or Wilcoxon tests. Time from skin closure to moving feet to command and time from skin closure to extubation will be compared between groups on POD 0, 1 and 2 using t test and Wilcoxon rank sum test.

A spaghetti plot will be presented for MME across all time points (POD0,1,2). We will then perform multivariable generalized linear mixed effects regression for the continuous MME outcome with treatment group, time point, and the interaction between treatment group and time point as fixed effects. In addition, relevant demographic and baseline variables will be considered as candidate covariates. Adequacy of assumptions will be assessed by the analysis

and visualization of residuals. All tests of hypotheses will be two-sided with a significance level of 5%. All calculations will be performed using R, version 4.3.0.

9.0 References

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