Shriners Hospitals for Children®

TITLE: Sensorial and physiological mechanism-based assessments of perioperative pain

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Initial Version: March 6, 2017

Amendment 1: December 5, 2017

Amendment 2: April 17, 2018

Amendment History of Changes

Version	Description of Changes
March 30, 2017	Original Document
September 20, 2017	• Study table updated (added SDIM data collection; Patient home interview call MDT/PPT & STAI-C questionnaire morning before surgery • Section 9 - Clarified version of NRS to be used for visit • Section 9.2 – updated protocol to include STAI-C & MDT/PPT testing morning before surgery; and also 1 blood draw pre-intubation and 1 additional post-intubation.; Added inclusion of neuromonitoring data to be collected and used in event of ADR • 9.3-Clarified version of NRS to be used for visit; clarified version of PSQI version to be used. • 9.4 -Data collection of neurological assessment at discharge to be used for the study; Patient interview phone call added for at home post-op • 9.5 -Clarified version of NRS to be used for visit • 12.1 – Updated study table to include questionnaires – was missing; added QST/CPM – was missing; added patient home interview call • 13.4 – Updated anticipated ADR section according to new Clonidine supplier`s monograph.
March 15, 2018	• 5.2 Added to the paragraph “Women or girls of childbearing potential should not get pregnant prior to their surgery nor after. The stress of surgery, the general anesthetic and the effect of different medication including clonidine may alter the naturel development of an new born. You should use a proven birth control method (such as Contraceptive Pill, a diaphragm) or abstain from having sex for the 6 months that you are taking part in the study”. • 7.2 Changes to exclusion criteria ○ Children with history of allergies to Clonidine or it’s excipients in either injection or tablet formulation (see respective monograph) ○ Children with history of galactose intolerance ○ Children with history of myocardial disease, arrhythmias, cerebrovascular disease, Raynaud`s/Thromboangiitis obliterans or chronic renal failure diagnosed based on history and physical ○ Pregnancy excluded by an in hospital testing the night before surgery

	○ • 9.1 Clarification of pain rating scale and addition of Medical History Interview Form previously omitted in error; Individual QST tests added in brackets (MDT,PPT,CPM) • 9.2 1 – Clonidine Arm - Administration of study agent given post-surgery and not before surgery; Clarification that Anesthesia Data Collection and SDST Data Collection will be completed at this time point point; Clarification that level of drowsiness will be collected on Sedation Level Form); Clarification that Neurological Deficit Post Op form will be collected at this time; • 9.2.2 – Placebo Arm - Administration of study agent will be given post-surgery and not before surgery. • 9.3 Correction to questionnaires to be completed by patients in-hospital; to be completed on days 1, 2 & 5, not every day; PSQI (In-Hospital questionnaire was previously omitted by error, now added. • 9.3.1 amended to read dosage to 100 mcg Clonidine from Clonidine and removed (between 50 mcg to 100 mcg as prescribed based on the weight of the patient) • 9.5 Added Medical History Interview (Patient History – REVISIT Collection Form) – previously omitted in error • 9.5.1 Additional details for unscheduled visits were added concerning tests/and or data to be collected at unscheduled visits.

PROTOCOL SIGNATURE PAGE

Protocol Title:

Sensorial and physiological mechanism-based assessments of perioperative pain

The signature below provides the necessary assurances that this trial will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality. This is in compliance with the principles outlined in applicable US Federal regulations and Good Clinical Practice Guidelines (ICH E6 Section 4.5.1, 6.2.5, and 8.2.2)

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Site Investigator's Name*: (please print)

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Site Investigator Signature Date Signed

** The protocol should be signed by the local investigator who is responsible for day to day study implementation at his/her specific site.*

List of Abbreviations

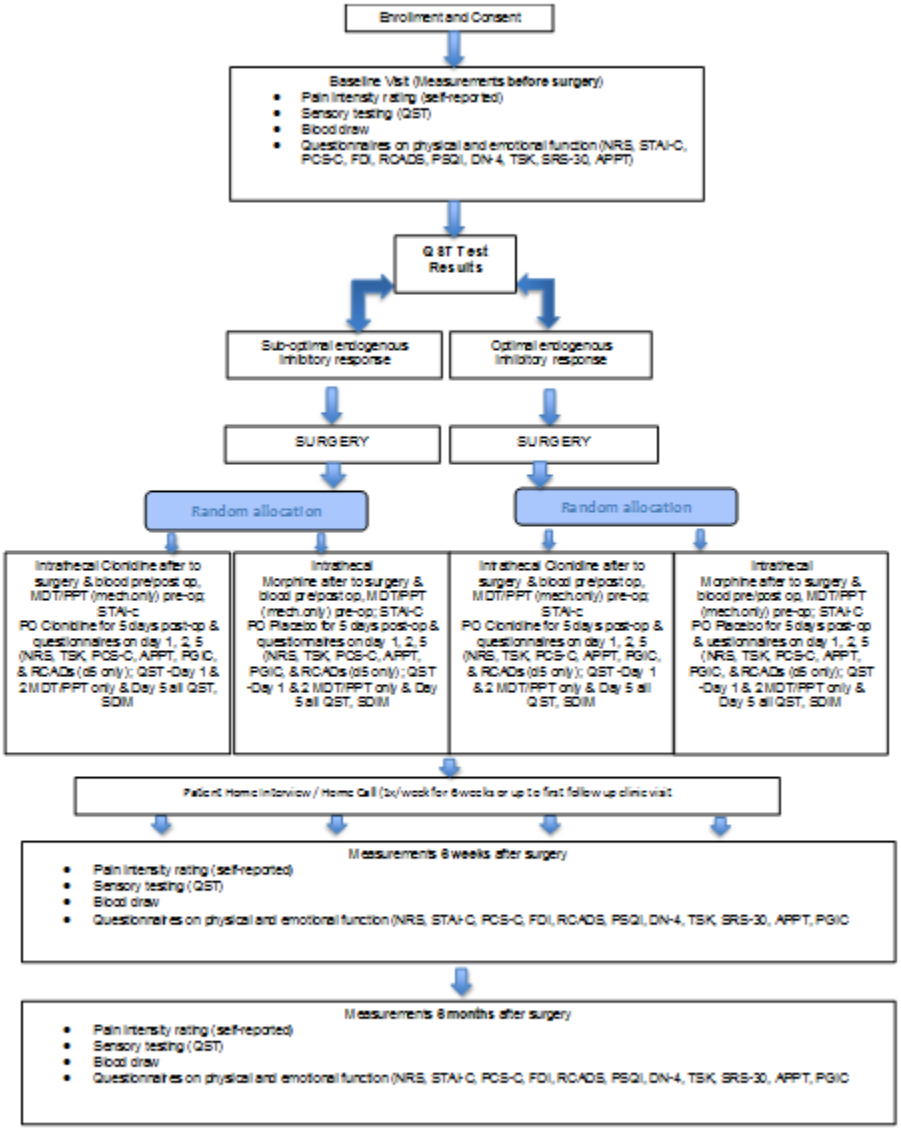
AIS	Adolescent Idiopathic Scoliosis
APPT	Adolescent Pediatric Pain Tool
CPM	Conditioned Pain Modulation
CSF	Cerebrospinal fluid
DN4	Neuropathic Pain Questionnaire
FDI	Functional Disability Index
MSK	Musculoskeletal
NE	Norepinephrine
NME	Normetanephrine
PCS-C	Pain Catastrophizing Scale - Children
PS	Pain Sensitivity
PSQI	Pittsburgh Sleep Quality Index
PT	Pain Threshold
QST	Quantitative Sensory Testing
RCADS	Revised Children Anxiety and Depression Scale
SHC	Shriners Hospital for Children
SRS-30	Scoliosis Research Society Questionnaire
STAI-C	State-Trait Anxiety Scale - Children
TS	Temporal Summation
TSK	Tampa Scale for Kinesiophobia

TABLE OF CONTENTS

Study Summary

Title	Sensorial and physiological mechanism-based assessments of perioperative pain
Short Title	RCT
Methodology	Randomized-controlled double-blind study
Study Duration	5 years
Study Site(s)	Shriners Hospital for Children Canada
Objectives	The overall goal of this proposal is to determine if quantitative sensory testing (QST) assessing pain modulation can be used as a clinical tool to optimize perioperative pain management. The central hypothesis is that the identification of patient's sensory pain profile allows personalizing therapeutic approaches to improve individualized pain management and thus prevents pain chronicity.
Number of Subjects	150 (approximately 75 for each arm)
Diagnosis and Main Inclusion Criteria	Female patients between 10 and 21 years old with a diagnosis of Adolescent Idiopathic Scoliosis (AIS) and no concomitant diseases, who are scheduled for scoliosis surgery at the Shriners Hospital, will be invited to participate in the study.
Study Product, Dose, Route, Regimen	Arm 1 - Intrathecal Clonidine after to surgery & PO Clonidine for 5 days post-op
Duration of administration	Day of surgery and 5 days post-operatively.
Reference therapy	Arm 2 - Intrathecal Morphine after to surgery & PO Placebo for 5 days post-op
Statistical Methodology	Descriptive statistics (means, SD, medians, n, %) will be calculated in order to present baseline characteristics of the different comparison groups and follow-up measures. To better appreciate the evolution of pain intensity (primary endpoint) during the longitudinal follow-up (baseline to six months after surgery), linear mixed models for repeated measures will be achieved for each of the three comparison schemes.

Study Schema



1 INTRODUCTION & BACKGROUND

Thousands of children undergo surgery across the Shriners system each year. These children are at a particularly high risk of suffering significant pain as many of the orthopedic surgical procedures are invasive. Under-treated postoperative pain in children leads to increased postoperative morbidity [1] and can have a negative impact on all aspects of health related quality of life including physical (e.g., reduced quality of sleep, delayed mobilization), emotional (e.g., anxiety, distress, negative thoughts), reduced social interactions with friends and family and school absenteeism [2]. Postoperative pain has immediate consequences leading to postoperative morbidity [1] Moreover, between 10 to 20 % of children undergoing surgery will develop chronic postsurgical pain (CPSP), making this problem the most common surgical complication [3,4]. Preventing CPSP becomes highly relevant as it may predispose children to experience recurrent pain during adulthood [5,6]. The clinical challenge rests in the ability to determine which patient will be at risk of having poor postoperative pain control and the development of CPSP. The challenge is even more relevant as to which analgesic protocol will best relieve pain for a specific patient. In this context, it is of high relevance to provide clinicians a tool to identify patients at risk of having poor postoperative pain control and CPSP. Ideally the tool should provide a rational (physiological/mechanistic based) approach to the establishment of a personalized analgesic perioperative protocol.

With over 5 million children undergoing surgery yearly, and 25% of adults referred to chronic pain clinics identifying surgery as the antecedent, there is a crying need to elucidate factors that predispose to chronic postoperative pain in children [7]. The nature of orthopedic surgery places our patients at particular risk of experiencing severe pain. Our procedures often consist of detaching and/or cutting muscles, exposing, manipulating and cutting bone. The periosteum, a highly innervated tissue [8] is often stripped, cut and/or crushed, thus inducing significant postoperative pain. In addition, many neural elements are in close proximity of the surgical field placing these patients at high risk of experiencing neuropathic pain. Such tissue manipulation causes a cascade of neurochemical, inflammatory, and hormonal responses that trigger pain and impact physical outcomes such as wound healing and mobilization [9]. Surgery-induced peripheral neural activation and central modulation may determine pain intensity at the early postoperative stage [10]. Thus, tissue injury may set up the neuronal mechanisms for the development of an eventual chronic state. Evidence suggests that acute postoperative pain is a major risk factor for the development of persistent postoperative pain [11,12].

2 INVESTIGATIONAL ASSESSMENT

2.1 QUANTITATIVE SENSORY TESTING (QST)

QST refers to the assessment of the somatosensory function that may be of clinical interest with a great variety of procedures that have specific quantification of one particular aspect of sensory function (Rolke, Baron et al. 2006). QST provides additional information on the mechanisms involved in pain transduction, modulation and in patient's perception and expectation of pain (Goffaux, Lafrenaye et al. 2008, Morin, Marchand et al. 2014), leading to mechanism-based pain management. Two central mechanisms commonly assessed in the experimental setting through QST are the temporal summation (TS) and conditioning pain modulation (CPM). Several studies in various surgical settings have demonstrated a predictive effect of QST parameters. Weissman-Fogel et al. (2009) reported that enhanced pre-surgical TS, a psychophysical correlate of wind-up

and reflecting central sensitization (Arendt-Nielsen and Petersen-Felix 1995), and higher pain scores for mechanical stimulation were significantly associated with greater postoperative intensity in adults after thoracotomy surgery, suggesting that individual susceptibility toward a greater summation response may characterize patients who are potentially vulnerable to augmented postoperative pain (Weissman-Fogel, Granovsky et al. 2009). Preoperative TS level may also be a mechanistic predictor for the development of chronic postoperative pain as studied in adult patients after TKR surgery (Petersen, Arendt-Nielsen et al. 2015). Yarnitsky et al. (2008) demonstrated that efficient preoperative CPM predicted lower risk of chronic post-thoracotomy pain in adult patients (Yarnitsky, Crispel et al. 2008). Furthermore, early postoperative QST testing has also been reported to predict long-term pain outcome. Surgery-induced peripheral neural activation and central neuroplastic changes may determine postoperative pain intensity. Adult patients who developed moderate-to-severe pain following surgery had pronociceptive changes (TS) compared with patients who developed mild pain (Petersen, Arendt-Nielsen et al. 2015).

3 INVESTIGATIONAL DRUG

3.1 CLONIDINE

Clonidine is a selective alpha 2-adrenoceptor agonist used preoperatively for its intrinsic analgesic, sedative and anxiolytic effects. The mechanism of action of Clonidine is thought to not only exert its sedative action via the stimulation of alpha 2 receptors in locus coeruleus, which was responsible for sleep and arousal [20]. When used intrathecally, the primary mechanism responsible for the beneficial effect of alpha-2 agonists is binding to alpha-2 receptors in the dorsal horn of the spinal cord. Clonidine may also interfere with the repolarization process (the hyperpolarization-activated cation current) in the spinal nerves optimizing the endogenous inhibitory descending pain response [21]. Clinically, Clonidine has been extensively studied in pediatric anesthesia, particularly when administered caudally or intrathecally with a local anesthetic agent [22-24]. It also can be used orally or intravenously to decrease the consumption of propofol sedation [25,26], which is quite relevant for this study as propofol is the analgesic of choice for Total IntraVenous Anesthesia (TIVA) required for spinal cord monitoring.

More specifically the use of Intrathecal Clonidine has been demonstrated to prolonged analgesia and decreased morphine consumption postoperatively [27]. Both epidural and intravenous routes achieve postoperative analgesia, but the overall dose required of Clonidine was lower by the epidural route [28].

The administration of 1ug/kg intrathecal Clonidine has been shown to improve the efficacy of postoperative sedation and analgesia and prolong time to first rescue analgesia after surgery and reduce the requirements of propofol for intraoperative sedation [29].

4 PRELIMINARY DATA AND CLINICAL DATA

In a previous study, we have demonstrated that presence of pain before surgery was the best predictor of pain intensity after surgery in Adolescent Idiopathic Scoliosis (AIS) patients undergoing surgery [30]. Pain before surgery was reported by 48% of the cohort (n=50) (Figure 1). We also demonstrated that intensity of pain in the first days after surgery was associated with pain intensity weeks after surgery, thus demonstrating the clinical need to improve preoperative and acute pain management in order to minimize long-term consequences.

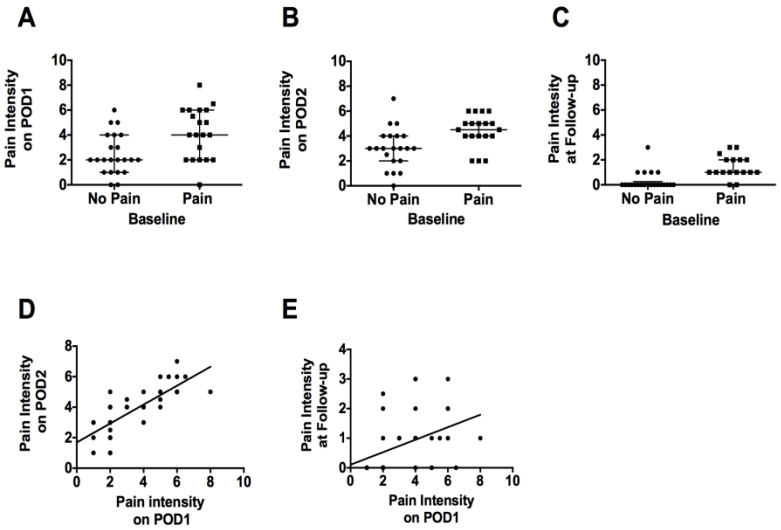


Figure 1. Patients reporting preoperative pain had greater postoperative pain intensity levels during the first postoperative 24 hours (POD1, r=0.47, p=0.001) (A), the second 24 hours (POD2, r=0.35, p=0.025) (B) and at follow-up appointment (4-6 weeks after surgery, r=0.50, p<0.001) (C). The pain intensity during POD1 was also predictive of the pain intensity during POD2 (r=0.74, p<0.001) (D) and at follow-up (6 weeks post-surgery, r=0.43, p=0.005) (E) (Ferland et al. 2016, PMID: 26852092).

In the same cohort, we also quantified neurotransmitters known to be related to pain. The preoperative plasma levels of norepinephrine metabolite metanephrine concentrations revealed to be associated with the postoperative pain intensity (Figure 3). Although preliminary, these results suggested that preoperative inter-individual differences, could explain postoperative pain trajectories.

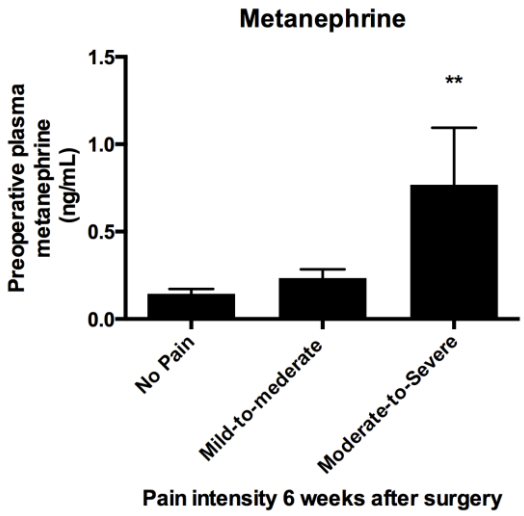


Figure 2. Preoperative monoaminergic levels on postoperative pain intensity. The preoperative metanephrine plasmatic levels of AIS patients scheduled for surgery. Patients who reported greater pain intensity at 6 weeks after surgery had higher metanephrine plasmatic levels before surgery (n=50, P<0.001) (Ferland et al., manuscript in preparation).

In the largest study to examine longitudinal pediatric pain trajectories after spine surgery, Sieberg et al proposed perioperative trajectories of pain experience may be better explained by changes in the central pain modulation rather than in the surgical stimulus itself (Figure 3).

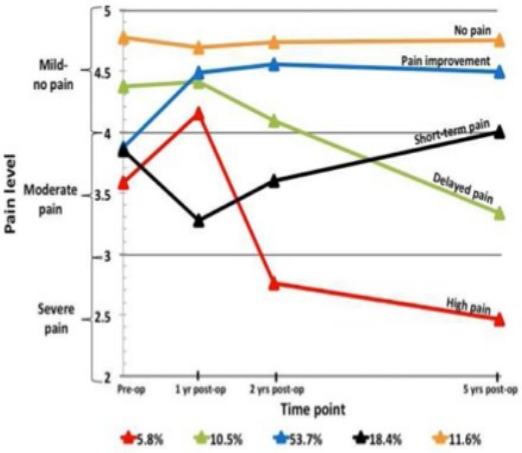
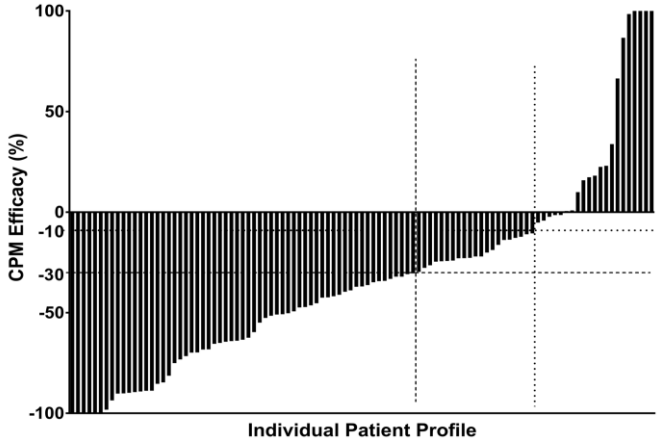


Figure 3. Five empirically derived pain trajectories were identified in a subset of patients with Adolescent Idiopathic Scoliosis (n = 77) (Sieberg CB et al., 2013, PMID: 24290449). Illustrating that patients respond differently to painful surgical stimuli as well as to standardized analgesia regiment. Our hypothesis is that one can identify preoperatively (using QST and or biomarkers) how patient will respond to pain postoperatively.

A key mechanism of the central pain modulation is the endogenous analgesia system [31]. Efficacy of inhibitory mechanisms can be tested by using the response of conditioned pain modulation (CPM). It is a powerful analgesic mechanism illustrated when a painful stimulus is inhibited by a second painful stimulus delivered at a different body location [32]. In a previous study, we reported the CPM distribution in healthy subjects having no pain condition at the moment of the measurements (Figure 5). Approximately half (42%) of the healthy subjects had a pain reduction of 10% (minimal clinical change) or more [33].



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Poor CPM, or lack of reduction in pain during the presence of the conditioning stimuli was reported in patients with various chronic pain disorders [34-36]. The risk of developing chronic pain following surgical procedure is related to lower efficacy of CPM in humans [37,19]. Although used to assess perioperative efficacy of endogenous inhibition in adults, the use of CPM during the perioperative period surrounding a surgery in pediatric patients has not yet been evaluated.

Considering that the modulatory effects of the endogenous inhibition are largely mediated by descending serotoninergic and noradrenergic pathways [38,39], we further studied

catecholamines as possible biomarkers of pain. Multivariate analyses of perioperative catecholamines levels revealed preoperative plasmatic concentrations of norepinephrine (NE) and normetanephrine (NME) and the cerebrospinal fluid (CSF) concentration of NE were significantly correlated with the presence of pain six weeks after surgery (r = 0.50, 0.49 and 0.50 respectively, p < 0.002), (Figure 6) [30]. These results support the evidence for a potential role of the endogenous inhibitory mechanism and catecholamine levels in predicting postoperative pain intensity and provide clues as to a mechanism-based pre-analgesic approach to perioperative pain management.

Catecholamines	Pain	Plasma (n=50)	CSF (n=38)
NE	Preoperative	r = .05, p = 0.70	r = .11, p = 0.51
	POD1	r = .06, p = 0.70	r = .30, p = 0.07
	POD2	r = .02, p =0.91	r = .18, p = 0.28
	6 weeks	**r = .48, p = 0.0004**	**r = .50, p = 0.002**
NME	Preoperative	r = .06, p = 0.68	r = .008, p = 0.96
	POD1	r = .21, p = 0.14	r = -.18, p = 0.27
	POD2	r = .13, p = 0.39	r = -.26, p = 0.13
	6 weeks	**r = 0.50, p = 0.0003**	r = .25, p = 0.13

Figure 5. Associations between preoperative catecholamine levels and pain. NE: norepinephrine; NME: normetanephrine; CSF: cerebrospinal fluid; POD1: postoperative day 1; POD2: postoperative day 2. (Spearman correlations).

Considering the clinical success of pharmacological interventions that enhance spinal noradrenergic activity in the treatment of chronic pain states [38,40,41], as well as the evidence that optimizing the inhibitory descending endogenous signaling may determine the recovery from hypersensitivity after surgery [42], we believe we are close to achieving a novel personalized pain management approach to perioperative pain in orthopedic surgery by introducing pre-emptive analgesia in the form of an alpha-2 inhibitor. Similarly, You et al. demonstrated in an animal model that pre-emptive analgesia optimizing the endogenous inhibitory mechanism by the use of an alpha-2 adrenergic receptor had better pain control than Fentanyl in preventing mechanical hyperalgesia in the context of surgical insult [43].

Spinal Clonidine before surgery and oral / IV Clonidine after surgery have been extensively utilized in the perioperative setting. Our proposal is to pre-operatively select patients who we believe Clonidine will improve significantly their pre-operative course.

4.1 CLINICAL DATA CLONIDINE

Prior relevant randomized trials, as well as a Cochrane review in 2014, have been published illustrating the benefits of Clonidine as an adjunct to preoperative analgesia. When combined with local anesthetics, intrathecal Clonidine prolongs the regression of the sensory block in a linear dose-dependent way. In addition, Clonidine prolongs the time to the first request of an analgesic with weak evidence of dose-responsiveness. Spinal Clonidine was more potent than intrathecal bupivacaine in the reduction of secondary hyperalgesia in patients recovering from abdominal surgery [45]. Perioperative systemic alpha-2 agonists (including oral Clonidine) decrease postoperative opioid consumption, pain intensity, and nausea without prolonged recovery times in adults [46]. Sixty-six patients undergoing lumbar spinal decompression where

randomized to epidural Clonidine infusion versus a placebo. There was a marked satisfactory analgesic and reduction of PCA morphine by approximately 43% over the first 36 h. Epidural Clonidine produces few side effects of its own (mean reduction of heart rate 11%–17%, and 8%–12% of arterial blood pressure compared with placebo) [47].

There is an enormous experience on the use of epidural and spinal Clonidine in pediatric population around the world. A positive effect of adjunct Clonidine was first reported by Jamali et al. in 1994 [48]. Since then, a large number of clinical studies have been published regarding the use of Clonidine as an adjunct to caudal blockade in children including structured reviews/meta-analysis and in 2014 Cochrane review specifically on Clonidine in children. They concluded that "Oral dose of 4 µg/kg, Clonidine may have reduced analgesia requirements after surgery with no significant side effects of Clonidine that were reported such as severe hypotension, bradycardia, or excessive sedation requiring intervention" [44]. There is no need to combine spinal morphine and spinal Clonidine because "it appears that the addition of intrathecal Clonidine to intrathecal morphine provides only very small clinical benefits in addition to those given by intrathecal morphine alone, especially when balanced with the increased frequency of hypotension [49].

Alpha-2 adrenoceptor agonists currently represent the most versatile and well-tolerated adjunct for the neuroaxial blockade in children. Preservative-free morphine may be indicated in certain situations, but the risk for respiratory depression and other disturbing side-effects must be taken into account [50].

5 RATIONAL AND RISKS/BENEFITS

5.1 BENEFITS

The first goal of this proposal is to determine if quantitative sensory testing (QST) assessing pain modulation can be used as a clinical tool to optimize perioperative pain management. The central hypothesis is that by identifying patients with poor endogenous inhibitory pain pathways, we will be able to personalize the patient`s peri-operative therapeutic approach to optimize pain management by adding an alpha-2 adrenoceptor agonist already identified to improve peri-operative pain management. If successful, the patient will experience less post-operative pain, require less post-operative narcotics, and thus have fewer side effects. In addition, we believe by adding an alpha-2 adrenoceptor agonist, less patients will develop chronic post-operative pain.

5.2 QUANTIFIABLE RISKS

The following risks may be encountered in our patients.

QST: Subjects may suffer mild discomfort to their arm or test site, and potentially have slight bleeding and/or bruising at the blood draw site. It is also possible that some subjects may experience light-headedness or temporary malaise. There is no potential for injury during the QST assessment as the subject can control and stop the testing during the thermal test and mechanical test should he or she feel the stimulus is painful.

Clonidine: After close analysis, we believe that our treatment arm places patients at minimal risk. The most common side effects of this alpha-2 adrenoceptor agonist are: hypotension, bradycardia, and sedation. Such complications are thought to be dose-dependent. In our study we will be using low dose Clonidine which we believe will mitigate the occurrence of these. Intrathecal Clonidine, in combination with intrathecal local anesthetics or morphine, has been associated in a dose-dependent relationship to induce hypotension, bradycardia, and sedation. Almost one-third of adults receiving intrathecal Clonidine (15 to 150 mcg) and local anesthetics presented at least one episode of arterial hypotension (RR 1.81; 95% CI 1.44-2.28; NNH 8) [51]. However, intrathecal Clonidine 1ug/kg in adjunction to bupivacaine in spinal anesthesia in adolescents undergoing orthopedic surgery was not associated with hypotension or bradycardia [52]. In our study will we not be using a combination of intrathecal analgesia, minimizing the risk of side effect of hypotension, bradycardia, and sedation.

Many studies reported minor sedation after Clonidine in children, which was more severe and associated with cardiovascular side effects at higher doses (5 μg/kg) [53]. Case reports of side effects of apnea, oxygen desaturation, and bradycardia have been reported in neonates given doses of caudal Clonidine (1.25–2.2 mg/kg) that are tolerated by older children [54-56]. Systemic Clonidine increased the risk of Intra- and postoperative arterial hypotension. However, the clinical relevance of these hemodynamic effects remains uncertain because none of the trials reported on significant adverse outcomes, such as (adult) patients (analyzed in a recent metanalysis) needing prolonged hemodynamic support with catecholamines [46].

Clonidine intrathecally has even been used and tested in mothers undergoing elective C-Sections with no additional risk. Intrathecal Clonidine 150 mcg combined with bupivacaine had a postoperative antihyperalgesic effect expressed as a significant reduction in the extent and incidence of peri-incisional punctate mechanical hyperalgesia at 48 h after elective cesarean delivery compared with intrathecal bupivacaine-sufentanil and intrathecal Clonidine 75 mcg - bupivacaine-sufentanil [57].

Specific testing as to efficacy and side effects of intrathecal Clonidine have been published. The intrathecal injection of low-dose Clonidine in healthy women resulted in dose-dependent and segmental analgesic effects. The heat pain tolerance of young women increased by 18C after 50 mcg of intrathecal Clonidine and 5 mg of intrathecal bupivacaine. This effect is similar to the analgesic effect of 5 mg epidural morphine or 30 mg epidural fentanyl in previous studies using this experimental heat pain model. Administration of Bupivacaine but not Clonidine resulted in a significant dose-related decrease in HR, but neither drug caused dose-related sympatholytic effects in the doses used [58].

Cao JP & al published in 2011, a RCT of fifty-nine children aged 6–8 year undergoing orthopedic surgery [59]. Patients were randomized to 3 groups: group B (intrathecal 0.5% bupivacaine 0.2–0.4 mg/kg and intravenous placibo); group BCit (intrathecal 0.5% bupivacaine 0.2–0.4 mg/kg plus 1 ug/kg intrathecal Clonidine and intravenous 2 ml saline); and group BCiv (0.5% bupivacaine 0.2–0.4 mg/kg) and intravenous 1 ug/kg) Clonidine in 2 ml of saline. The requirements of propofol, time to first rescue analgesia, and postoperative pain or sedation scores were assessed. The duration of motor and sensory blocks and perioperative adverse drug reactions were determined. They found that Clonidine significantly prolonged the time to first rescue analgesia and reduced the requirements of propofol sedation whether administered intravenously or intrathecally. The mean Children and Infants Postoperative Pain Scale scores of children were significantly lower in

Table 3 Perioperative adverse events

	Group B (n = 19)	Group BCit (n = 19)	Group BCiv (n = 19)
Hypotension	3 (16)	5 (26)	5 (26)
Bradycardia	2 (11)	3 (16)	4 (21)
Nausea/Vomiting	1 (5)	2 (11)	1 (5)
Urinary retention	1 (5)	2 (11)	1 (5)
Shivering	2 (11)	1 (5)	0

Data are number of cases (%). Group B, intrathecal bupivacaine; Group BCit, intrathecal bupivacaine plus clonidine; Group BCiv, intrathecal bupivacaine plus intravenous clonidine. There were no significant differences between the groups.

groups BCit and BCiv than in group B. Postoperative sedation scores were higher in groups BCit and BCiv than in group B. Intrathecal Clonidine significantly prolonged the time to regression of the sensory block and recovery of motor block. There were no significant differences among the three groups regarding the incidence of perioperative adverse drug reactions.

The most recent Cochrane review conclude that despite heterogeneity between trials, Clonidine premedication in an adequate dosage (4 µg/kg) was likely to have a beneficial effect on postoperative pain in children. Side effects were minimal, but some of the studies used atropine prophylactically with the intention of preventing bradycardia and hypotension.

To further mitigate the risk associated with the use of Clonidine, the administration of the medication will only be done while patients are in well monitored setting. The intrathecal administration will be done post-operatively with optimal continuous hemodynamique monitoring, as well as the Oral dose will be administered while patient are in Hospital having hemodynamique monitoring every 8 hrs. If required, atropine will be available in the operating room and the ward.

Women or girls of childbearing potential should not get pregnant prior to their surgery nor after. The stress of surgery, the general anesthetic and the effect of different medication including clonidine may alter the naturel development of an new born. You should use a proven birth control method (such as Contraceptive Pill, a diaphragm) or abstain from having sex for the 6 months that you are taking part in the study.

5.3 ALTERNATIVE TO PARTICIPATION

Subject participation is voluntary and should the subject choose to not participate in the study, they will be treated as per the standard of care.

6 OBJECTIVES

The primary objective of this study is to evaluate if pre-operative QST can identify if patients will have high pain intensity peri-operatively and at 6 months post-operatively. We will evaluate the intensity and chronicity of pain and the function of the descending inhibitory system through a short QST procedure before surgery and six months after surgery. In addition, we will evaluate the patient's physical and emotional functioning, and explore the potential biological underlying mechanisms at the same time points.

The secondary objective of this study is to determine if the peri-operative use of an alpha-2 adrenergic receptor agonist enhances the efficacy of the descending inhibitory system of patients with sub-optimal CPM efficacy before surgery by decreasing pain after surgery. Consequently, this pharmacological intervention may also reduce the incidence of acute and chronic pain after surgery. We will evaluate the pain intensity and the function of the descending inhibitory system through a short QST procedure six weeks after surgery and six months after surgery in patients receiving Clonidine or placebo during the perioperative period. We will also evaluate the patient's physical and emotional functioning, and explore the potential biological underlying mechanisms at the same time points.

We will also evaluate the potential biomechanical alterations in 3D related to pain in children reporting presence of back pain pre and post spine surgery.

Our hypothesis is that patients undergoing spine surgery with poor inhibitory pain response will have less pain in the immediate and long-term period when treated prophylactically with Clonidine in the perioperative period.

7 SUBJECT SELECTION

This study aims to recruit 150 female patients, with approximately 75 per group. The scientific rational to exclude male patients is straight forward. Knowing that gender can influence the quantitative sensory testing – knowing that gender can also affect pharmacokinetics, we felt prudent to minimize our variables to ensure our N will be able to show the expected outcome. If and once our hypothesis has been shown, then the protocol will be amended to include males to see if clonidine also improves acute chronic pain management.

7.1 INCLUSION CRITERIA

- Females* aged between 10 and 21 years old
- Scheduled to undergo anterior or posterior spinal fusion surgery for AIS with instrumentation
- Ability to adequately understand and respond to outcome measures
- No previous major orthopedic surgery
- Any ethnic background

*Inclusion of only females is due to inherent gender differences of the parasympathetic activity responsible for the endogenous inhibitory pain response [60].

7.2 EXCLUSION CRITERIA

- Children with history of allergies to Clonidine or it's excipients in either injection or tablet formulation (see respective monograph)
- Children with history of galactose intolerance
- Children with history of myocardial disease, arrhythmias, cerebrovascular disease, Raynaud`s/Thromboangiitis obliterans or chronic renal failure diagnosed based on history and physical
- Children taking antihypertensive agents (diuretics, vasodilators, beta-blockers, ace-inhibitors)
- History of depression
- Inability of the child to speak English or French
- Diagnosed with developmental delay that would interfere with understanding questions being asked (autism, mental retardation)
- Children with major chronic medical conditions (ASA status III or higher)
- Pregnancy excluded by an in hospital testing the night before surgery

8 STUDY DESIGN/PROCEDURES

8.1 GENERAL DESIGN

This study is a randomized-controlled double-blind study. All consecutive female patients who come to the Shriners Hospital for Children – Canada, and who meet the Inclusion/exclusion criteria will be invited to participate in the study throughout the study's specified recruitment period to avoid selection bias.

Subjects will be expected to participate for 6 months. Subjects will be assessed for eligibility, consented and enrolled if they meet all criteria. They will undergo a baseline visit prior to surgery. CPM testing results will determine the subjects to be in one of two arms – 1) Sub-optimal endogenous inhibitory response or 2) Optimal endogenous inhibitory response. The subjects in each of these two groups will be randomized to either be treated with Clonidine arm or the placebo arm. Subjects will be followed in-hospital, and at 6 weeks and 6 months.

All clinicians and researchers involved in the recruitment, consent, data collection, experimental procedures and data analysis will remain blinded to study group allocation for the duration of the study. Blinding will be maintained until the end of statistical analysis, unless un-blinding is required. Although the study will be conducted at the Shriners Hospital for Children – Canada, including analysis of all specimens, the Pharmacy of the McGill University Health Centre will manage the randomization, blinding of medication/placebo as well as the distribution of the medication/placebo on the day of surgery and for 5 days post-operatively.

8.2 RECRUITMENT

Patients will be recruited from outpatient clinics at the Shriners Hospital for Children - Canada. Potential participants will be identified and informed of the study by their attending physician at the time of the examination and that presence of back pain is confirmed. If the subject expresses interest in learning more about the study, the physician and and/or a research assistant will then explain the study and answer any questions the subject or their family may have.

8.3 INFORMED CONSENT PROCESS

Informed consent will be obtained from the participants and/or their legally authorized representative by a member of the study staff authorized to consent for this study. Parents or legal guardians will consent for subjects 17 years and younger. As of the age of 18 years, the subjects may consent as adults. The process will include a thorough discussion, in a private area of the clinic, of all the elements outlined in the informed consent document, including but not limited to what is expected to happen during the study, risks and benefits of the planned therapy, and any possible alternatives. Subjects will be given adequate time to discuss with their family or physician and any questions they may have before deciding to participate in the study. Subjects who agree to participate in the study will be asked to sign the informed consent form. The informed consent form and the Shriner`s "Documentation of Initial Informed Consent Discussion" will be scanned into the subject`s hospital medical record and the originals will be filed, separately from the subject`s study file, in the research coordinator`s office at the Shriners Hospital. The subject and/or family will be given a copy of the signed consent form.

9 STUDY INFORMATION

9.1 BASELINE VISIT

The expected duration for the patient's participation in the research is 6 months and will consist of a baseline visit, In-hospital visit, 6 week post-op visit and a 6 month post-op visit.

At the baseline visit, the subject will be expected to complete the following:

- ✓ Pain intensity rating (self-reported) (Wong Baker Faces Pain Scale)

- ✓ Medical History Interview (Patient History Collection Form)
- ✓ Approximately 10 mL of blood will be drawn and blood pressure will be taken
- ✓ Quantitative Sensory Testing (QST = MDT/PPT/CPM tests)

The subject will be expected to fill out the following questionnaires:

- ✓ Pain numerical rating scale for children (Baseline - 4 questions)
- ✓ State-Trait Anxiety Inventory (STAI-C)
- ✓ Pain Catastrophizing Scale (PCS-C)
- ✓ Functional Disability Index (FDI)
- ✓ Revised Children Anxiety and Depression Scale (RCADS)
- ✓ Pittsburg Sleep Quality Index (PSQI)
- ✓ Neuropathic Pain Questionnaire (DN4)
- ✓ Tampa Scale for Kinesiophobia (TSK)
- ✓ Scoliosis Research Society (SRS-30)
- ✓ Adolescent Pediatric Pain Tool (APPT)

The visit should take approximately 1 hour

Once the subject`s CPM results from the baseline visit have been assessed, the subject will be categorized into one of two arms: 1) Sub-optimal endogenous inhibitory response or 2) Optimal endogenous inhibitory response. The sub-optimal group will then be randomized to either Clonidine or the placebo, and the optimal group will be also randomized to either Clonidine or the placebo.

9.2 SURGERY VISIT

9.2.1 CLONIDINE-RANDOMIZED GROUP

On the day of surgery, just prior to the surgery, a blood draw will be done pre-intubation. The patient will be asked to fill out 1 questionnaire (STAI-C) and undergo MDT/PPT (Mechanical

Detection / Pain Pressure Threshold testing only). Another blood sample will be drawn post-intubation while the patient is still asleep.

At the end of the spinal surgery, both the CPM optimal and sub-optimal subjects who were randomized to the Clonidine group will receive intrathecal Clonidine 1 mcg/kg (up to 75 mcg).

The administration of the medication will only be done while patients are in well monitored setting. The intrathecal administration will be done post-operatively with optimal continuous hemodynamic monitoring. If required, atropine will be available in the operating room and the ward.

The anesthesia monitoring process and details of the surgical procedure will be collected for research purposes on the Anesthesia Data Collection and SDST Data Collections forms, respectively.

All Patients receiving the oral dose of clonidine or the placebo will undergo hemodynamic monitoring every 8 hours. Neuro-monitoring data as per standard of care (pain level assessments, level of drowsiness (Sedation Level Form), hemodynamic stability q2hr for the first 48hr, vital signs q1hr for 12h, then q2h for 12h, then q4hr for 24hr, then q8hr for 72hr) will be used for study purposes, as well, neuromonitoring surgical data will be collected on the SDIM (Spinal Deformity Intra-Operative Monitoring) worksheet and the Neurological Deficit Post-op form.

9.2.2 PLACEBO-RANDOMIZED GROUP

Both the optimal and sub-optimal groups who were randomized to the placebo group will receive intrathecal spinal morphine (5 mcg / kg) at the end of the spinal procedure in the operating room.

9.3 IN-HOSPITAL VISIT

Post-operatively, subjects will have their blood drawn on post-operative Day 1, 2 and 5. On Day 1 and 2 subjects will also undergo only the Mechanical Detection and Pressure Pain Threshold portion of the QST testing. On day 5, subjects will undergo the full QST testing. The subjects will be asked to fill out the following questionnaires on post operative day 1, 2 and 5 while they are in the hospital:

- ✓ Pain numerical rating scale for children (In-hospital – 7 questions)
- ✓ Tampa Scale for Kinesiophobia (TSK)
- ✓ Pain Catastrophizing Scale (PCS-C)

- ✓ PSQI (In-hospital)
- ✓ Adolescent Pediatric Pain Tool (APPT)
- ✓ Revised Children Anxiety and Depression Scale (RCADS) (Post Op Day 5 only)
- ✓ Patient`s Global Impression of Change (PGIC)

These tests should take approximately 45 minutes.

9.3.1 CLONIDINE-RANDOMIZED GROUP

On Post-operative Day 1 through Day 5, both the CPM optimal and sub-optimal subjects who were randomized to the Clonidine group will be instructed to take 100 mcg pill three (3) times a day. Patients and treating team will be blinded to which pills they will be taking.

9.3.2 PLACEBO-RANDOMIZED GROUP

On Post-operative Day 1 through Day 5, both the CPM optimal and sub-optimal subjects who were randomized to the Placebo group will be instructed to take the placebo pill three (3) times a day. Patients and treating team will be blinded to which pills they will be taking.

9.4 DISCHARGE VISIT AND AT HOME PATIENT DIARY CALL - 1X/PER X 6 WEEKS

On the day of discharge, patients are assessed for any neurological deficits. These will be recorded on the SDIM Discharge form and included in the patient`s study analysis.

Patients will be contacted by phone once a week for 6 weeks (or up until their 6 week visit). They will be asked about pain levels, medication intake, activity levels and their sleeping habits for the week in question. Their interview will be recorded on Patient Home Interview / Phone Call Form.

9.5 SIX (6) WEEKS AND SIX (6) MONTH FOLLOW-UP VISITS

At the 6-week and 6 month visits, the subject will be expected to complete the following:

- ✓ Pain intensity rating (self-reported)
- ✓ Approximately 10 mL of blood will be drawn and blood pressure will be taken
- ✓ Medical History Interview (Patient History - REVISIT Collection Form)

- ✓ Quantitative Sensory Testing (QST)

The patient will be asked to complete the following questionnaires:

- ✓ Pain numerical rating scale for children (6 questions)
- ✓ State-Trait Anxiety Inventory (STAI-C)
- ✓ Pain Catastrophizing Scale (PCS-C)
- ✓ Functional Disability Index (FDI)
- ✓ Revised Children Anxiety and Depression Scale (RCADS)
- ✓ Pittsburg Sleep Quality Index (PSQI)
- ✓ Neuropathic Pain Questionnaire (DN4)
- ✓ Tampa Scale for Kinesiophobia (TSK)
- ✓ Scoliosis Research Society (SRS-30)
- ✓ Adolescent Pediatric Pain Tool (APPT)
- ✓ Patient`s Global Impression of Change (PGIC)

The visit should take approximately 1 hour

9.5.1 UNSCHEDULED VISITS

If subjects present for any unscheduled visits during the course of the study for any reasons, primary data sets will be collected in a prospective fashion. A separate data point will be added to ensure good documentation of any adverse event as the unscheduled visit may be related to the enrolment from the medications. Any additional pertinent outcome questionnaires or testing limited to the type of tests scheduled at the visit as described in section 9.5 are judged relevant by the PI or the coordinator. At minimum, the following data points will be collected:

a) Cause of unscheduled visits
b) Medications
c) The subject will be expected to complete the following:

- ✓ Pain intensity rating (self-reported)

d) The patient will be asked to complete the following questionnaires:

- ✓ Pain numerical rating scale for children (6 questions)

9.5.2 PREMATURE STUDY TERMINATION

Participation of the subject in the study may end for any of the following reasons:

- The subject/subject`s representative withdraws informed consent for any reason
- Occurrence of an AE or SAE that prevents the subject from continuing in the study.
- Death
- The subject does not meet eligibility criteria / fails the screening process
- Physician discretion (e.g. Patient is non-compliant with protocol)
- The subject is lost to follow up
- The Sponsor/Investigator terminates the study

Documentation of reason(s) for subject`s discontinuation in the study will be detailed and explained on a File Note and entered into the patient`s study file.

10 STUDY AGENT INFORMATION

QST results will show that subjects either have an optimal or a sub-optimal response. The subjects who fall into the optimal category will be randomized to either Clonidine or placebo and the subjects who fall into the sub-optimal category will also be randomized into either Clonidine or placebo. The hospital pharmacy will do 1:1 randomization using online software.

Randomization and blinding of the medications and placebo will be performed by the hospital pharmacy. The pharmacy will be sent the list of patients participating in the study. They will maintain the trial treatment randomization codes, and procedures for breaking codes will be also carried out by the pharmacy.

For each study patient, the physician will supply the pharmacy with a prescription ordering medication for the Clonidine arm OR the placebo arm according to what the patient is randomized to. The pharmacy will prepare the appropriate medication kits, according to the randomization assignment, either containing vials of Clonidine or intrathecal morphine. For the day of surgery, the pharmacy will prepare a blinded kit containing the medication, preparation materials and instructions. Either the evening before, or the morning of the surgery, the research assistant will go to the pharmacy and pick up the blinded study medication kit and deliver it to the OR. The respiratory therapist will prepare the medication contained in the kit in the operation room just prior to surgery and then give it to the anesthesiologist who will administer it to the patient.

The 5 days of post-operative medication, either Clonidine or placebo, according to patient`s randomization prescription, will be dispensed daily from the hospital`s pharmacy, along with their regular routine medications.

As per Standard of care, concomitant therapy will be provided for pain, anti-nausea and for any other reasons that may occur. These therapies will be given in addition to the study medications.

All medications given to the patient will be noted in the patient`s medical chart by the nurse. The patient`s medical chart will then be verified daily by a research assistant for study drug compliance. In the event of non-compliancy, a Note File will be added to the patient`s study file listing the reasons why, and the action taken and filed in the patient`s study file. Providing patients wish to remain in the study, they will not be discontinued from the study for non-compliant medication intake.

The hospital pharmacy will be responsible for the storage and stability of all medications and placebos and preparation of the blinded study kits. They will maintain the patient identification code list, randomization, drug accountability, and temperature logs.

Any unused medications will be returned to the hospital pharmacy for accountability purposes and for destruction as per hospital policy.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Any remaining drugs will be destroyed as per on site will be documented in the study files.

11 STUDY MEASURES

The following procedures are experimental and performed exclusively for research purposes.

11.1 SPECIMENS

11.1.1 BLOOD DRAW AND BLOOD PRESSURE READING

The nurse will blood draw approximately 10mL of venous blood and take the subject's blood pressure. The data will be recorded on the Blood Information Form.

10ml of blood will be drawn at various time points and will be processed for further analysis.

Although the role of inflammatory cytokines in pain sensitization is well-known, there relevance is yet to be fully understood (Clark, Old et al. 2013). Using antibody-based immunoassays, these inflammatory markers will be measured throughout the perioperative period.

More and more, the importance of epigenetic modifications in the development of chronic and/or neuropathic pain is being recognized (Denk and McMahon 2012, Sukenaga, Ikeda-Miyagawa et al. 2016, Chidambaran, Zhang et al. 2017). Global DNA methylation in blood will therefore be analyzed to see if any changes occurred following surgery and methylation state on the promoter of specific genes that have either been shown to be altered in chronic neuropathic states or that could be implicated in the pathology will be analyzed.

A genomic anaylsis of the sample will also be carried out. Chronic pain development after surgery results from complex biochemical and pathophysiological mechanisms that differ in type, although inter-related, among different surgical procedures [40]. Another explanation to understand why some patients do develop CPSP and others don't may reside in susceptibility factors that might be inherited and/or environment-related and can be assess with a genomic approach [41]. According to the PainGene Database, about 300 genes are known to be relevant to pain and hundreds of pain-regulated genes have been identified by gene expression profiling studies [42]. Genetic variations may provide useful information to predict the intensity of postsurgical pain. Moreover, these variations may inform us on the sensitivity to anesthetics and analgesics regimen. Changes in the transcriptomes of patients undergoing major orthopedic surgery may also reflect anesthesia and analgesia-related expression profiles of various types of neurons, and information on such changes may contribute to personalized post-operative pain management. Furthermore, chemical modifications of DNA are epigenetic marks that constitute the functional genome and are key to generating diverse cellular phenotypes from the same genotype. These modifications and the cellular machineries that regulate them are essential for maintaining tissue-specific and timing-specific expression profiles for normal functioning [43] and can be altered in the post-operative context."

Ultimately, we hope to have a thorough understanding of the molecular alterations leading to pain while help developing more targeted line of treatments.

11.1.1.1 ALIQUOTING AND SPECIMEN RETENTION

The blood sample will be centrifuged, aliquoted and stored at -80°C pending biochemical analysis. The samples will be analyzed within 1 year. The samples are stored in a locked laboratory and only authorized research personnel are permitted to access this area. Sample accountability and storage location is tracked by research personnel on a spreadsheet maintained in a password-protected computer.

11.1.1.2 LABELING

All samples will be labeled with a study identification number and the time and date of collection. They will be stored in the laboratory`s -80°C freezer pending analysis.

11.1.1.3 SPECIMEN ANALYSIS

Biochemical Assessment: Modulatory effects of the nociceptive transmission are largely mediated by descending monoaminergic pathways. A molecular assessment of monoamines involved in the dopaminergic and adrenergic pain pathways related to the endogenous pain inhibitory system (dopamine, serotonin, epinephrine, norepinephrine) will be performed. Analyses will be performed by liquid chromatography coupled with tandem mass spectrometry on TripleTOF 5600 mass spectrometer (AB Sciex Pte Ltd, Concord, Ontario, Canada) equipped with DuoSpray (AB Sciex) source. Data integration and analysis will be performed by selecting the appropriate ion

transition with a mass range of 0.05 0.05 0.05 MultiQuant software, version 2.0, with the signal finder algorithm (AB Sciex)

Genomic analysis: DNA will be extracted from the buffy coat containing the white blood cells of collected blood samples through the QIAGEN DNA Mini Kit. The DNA will then be further analyzed for specific single-nucleotide polymorphisms (SNPs) (rs4633, rs4680, rs4618 and rs165774) via TaqMan Genotyping Assay. This process involves amplification of specific DNA fragments by PCR followed by analysis on an optical plate for specific genetic polymorphisms, to identify which patients carry such polymorphisms.

11.1.1.4 DESTRUCTION OF SPECIMENS AT STUDY COMPLETION

All specimens, at the end of the study, will be destroyed as per the hospital's biohazard waste management policy.

11.2 QUANTATITIVE SENSORY TESTING (QST)

11.2.1 MECHANICAL DETECTION THRESHOLD (MDT)

The Research Assistant will use TouchTest Sensory Evaluators (filaments) with varying diameters (forces ranging between 0.008-300 grams) and apply stimulation on the forearm, which will serve as the control site, as well as on the painful segment (affected area – where back pain is located).

11.2.1.1 DATA COLLECTION AND TOUCH TEST SENSORY EVALUATOR PREPARATION

The Research Assistant will start by entering the required information on the MDT Data Collection Form, as well as setting up the 5 TouchTest Sensory Evaluators (filaments) that will be used during testing (1g, 0.6g, 0.4g, 0.16g, 0.07g). The Research Assistant will demonstrate the procedure using the subject`s palm of their hand.

11.2.1.2 CONTROL TEST SITE

The subject will rest their arm on a comfortable surface and be instructed to keep their eyes closed throughout the duration of the test. On the subject`s left forearm, one inch from the crook of their elbow, with a washable marker, a 1 inch by 1 inch square box is to be drawn and a dot placed in the middle of the box. Using the filaments, and starting with the smallest filament, stimulation will be applied from a 90 degree angle to the dot, not exceeding 1 second of stimulation. With each application of stimulation, inform the subject you will be touching them by saying "now". The subject should respond yes or no to feeling the touch. The results are to be recorded on MDT Data Collection Form.

11.2.1.3 PAIN SITE

For this test, the subject is to wear a hospital gown so that their bare back and affected site can be seen. The subject will be asked to bend forward keeping their legs straight and to touch their toes. The Research Assistant will locate the apex of the curve. On the right side of the apex, a 10 cm dot from the middle of the back will be made. The subject may then sit down for the test. The subject will be asked to keep their eyes closed throughout the test. Using the filaments, and starting with the smallest filament, stimulation will be applied from a 90 degree angle to the dot, not exceeding 1 second of stimulation. With each application of stimulation, the subject will be informed that you will be touching them by saying "now". The subject should respond yes or no to feeling the touch. Record results on MDT Data Collection Form.

During the test, periodically (once every 3-4 times) the patient should be presented with a "false positive" by saying "now" without touching their skin. If the subject says they felt the touch, report this as a false positive on the collection form.

Between each stimulus, the filament is put down even if even if repeating the same stimulus.

11.2.1.4 MDT DETAILED TEST PROCEDURE

Procedure - Descending

This test procedure should be followed for both the control and pain test site.

1. Begin at filament (1g) (higher if the subject does not feel this force) on marked location.

2. If the subject feels the filament, present the next thinner filament, (0.6g). Continue to present thinner and thinner filaments until the subject no longer detects the touch.

3. Record the LAST DETECTED FORCE in grams (the filament above the one the subject did not feel).

Procedure - Ascending

4. Begin with the filament that was noted as last detected force, and begin moving up to next thicker filaments, augmenting the force each time.

5. Continue until the subject feels the touch again.

6. Note the FIRST DETECTED force in grams.

7. Repeat the descending and ascending procedures for a total 3 times of each.

NOTE: If the subject does not feel the initial (1g) filament, move up 3 filaments (e.g. 4g). Keep repeating this until the patient feels the touch. Then proceed with the protocol using the newly selected filament.

11.2.2. PRESSURE PAIN THRESHOLD WITH JTECH ALGOMETER

The JTech Algometer should be connected to the pressure reading device using the 1cm probe. Ensure the mark on the subject`s left forearm is still visible and the area is clean. The procedure will be explained to the subject and the test will be demonstrated to them on the palm of their hand. The test is to be performed on the control site and pain site.

Procedure

1. Turn on the Pressure Reading Device and note the test number down on the data collection sheet.
2. Apply the pressure device to the subject`s previously designated areas that were used for MDT testing. Ensure you watch the device read out as you are applying pressure.
3. Begin to slowly increase pressure at a rate of ~1 N/s.
4. Stop when the subject says "STOP" and immediately write down the read out of the force (in N) displayed on the pressure device screen on your data collection form that was indicated when the patient said stop.
5. Wait 1 minute between each trial.
6. Repeat this procedure 3 times on the left upper forearm (control site) and on the subject`s affected site (pain site).
7. Review the device`s readings of the test and transcribe them to the MDT Response Form.

11.2.3 QUANTATIVE SENSORY TESTING (QST) THERMAL

The Research Assistant is to set up all required equipment.

1. Set up Chiller and water bath.
2. Set up Laptop with Software, Q-Sense and CoVAS, Thermode.
3. Ensure CoVAS is calibrated.
4. Ensure Q-Sense has performed its calibration test.
5. Ensure new subject file is created in software and is ready for testing.
6. Ensure CPM response form is ready to be completed.

11.2.3.1 INSTRUCTIONS FOR THE SUBJECT

The following instructions are to be explained to the subject prior to starting the study tests.

11.2.3.2 COVAS (COMPUTERIZED VISUAL ANALOG SCALE)

The Research Assistant will explain the CoVAS device to the subject. The CoVAS device is a sliding scale which is connected to the laptop`s software. The subject is instructed to use the scale slider to indicate the intensity of their pain on a scale of 0 to 10. It is important that the subject understand that this device will not control the temperature of the test.

11.2.3.2.1 UNPLEASANT FACTOR OF PAIN

The Research Assistant will describe various experiences or sensations the subject will feel throughout the test. The subject needs to understand the temperature will continue to increase – going from warm to hot, then to a point they will feel pain, and eventually to the point it will be too painful at which point they should stop the test. The subject should be instructed to indicate – "warm" as they feel the increase in temperature; "pain" due to the heat, and "stop" when it is too painful.

11.2.3.2.2 RELATIONSHIP BETWEEN COVAS AND UNPLEASANT FACTOR OF PAIN

The Research Assistant will describe the correlation of the pain the subject is experiencing to their indication of it on the CoVAS scale – thus rating their pain on the scale from "0" being no pain at all to "10" being worst pain tolerable.

11.2.4 QST THERMAL FAMILIARIZATION PRE-TEST

1. Set up the new subject in the software on the laptop; fill out the required information and save it.

2. Select the program "Pain Threshold Pretest", select (Hand Palmer Middle). This test will be used to explain and familiarize the subject with the procedure, to demonstrate how hot the Thermode will get and how to use the COVAS device to assess their pain intensity. It is important that the patient understands that as soon as they say "stop", the temperature will decrease immediately. The Thermode has a cut off temperature of 50 degrees.

    - Place the Thermode on the palm of the subject`s hand. Start the pre-test. The subject should indicate three things to the Research Assistant – that the Thermode is "warm", that it`s "painful" and finally "stop" when it is too painful to continue. If the subject understands the test, repeat the test and ask them to rate their pain intensity on the CoVAS throughout the test. If the subject does not understand the test, repeat the test.

    - Record the subject`s Threshold for pain and Threshold for Tolerance on the CPM response form.

11.2.4.1 QST THERMAL VAS50% DETERMINATION PRE-TEST

Once the patient understands, move to New Test and change the body site to “Forearm Medial” and save the changes. The forearm “pre-test” is used to determine the temperature corresponding to the patient`s VAS50%. The pain and threshold tolerance temperatures are also noted.

- Place the Thermode on the subject`s forearm approximately 1 inch below the crook of their elbow. Start the pre-test. The subject should indicate three things to the Research Assistant – that the Thermode is “warm”, that it`s “hot” and finally “stop” when it is too painful to continue. The subject will rate their pain intensity with the CoVAS throughout the test. If the subject seems to not understand the test, or the Research Assistant feels there was an issue with the test, repeat the test.

Once the Thermode Pre-Test is successfully completed, proceed to the Thermode Test.

11.2.4.2 THERMODE TEST BEFORE BATH

The Research Assistant will prepare the Software for the Thermode Test. The subject`s VAS50% score will be used to personalize the Thermode Test.

1. For the Thermode test, the subject`s “Left Forearm Medial” will be used. Select the site just below the site used for the pre-test.

2. This Thermode Test is for a duration of 2 minutes and the temperature remains at the subject`s VAS50% temperature throughout. Although the temperature remains constant at the subject`s VAS50%, the subject is instructed that the temperature will vary throughout the test. The subject should indicate their pain intensity with the COVAS device with “0” being no pain at all and “20” being the worst pain imaginable. Assistant feels there was an issue with the test, repeat the test.

3. The pain threshold, VAS50% and the pain tolerance should be recorded on the CPM response form.

11.2.4.3 WATER SUBMERSION BATH TEST

Prior to starting the Water Immersion Bath Test, the subject`s blood pressure is to be taken and recorded on the CPM response form. After this, the subject will be asked to submerge their arm (the opposite one from the one used for the Thermode tests) into a bath of 12 degree water. The Research Assistant will verbally ask the subject to rate their pain every 15 seconds on a scale from “0” being no pain to “10” worst pain tolerable. The subject`s blood pressure will be taken and

again after 1 minute of submersion. Their responses and the blood pressure readings should be indicated on the CPM response form.

11.2.4.4 THERMODE TEST AFTER BATH

For the Thermode test, the subject`s "Left Forearm Medial" will be used. Select the site just below the site used for the previous test.

This Thermode Test is for another duration of 2 minutes and the temperature remains at the subject`s VAS50% temperature throughout. Although the temperature remains constant at the subject`s VAS50%, the subject is instructed that the temperature will vary throughout the test. The subject should indicate their pain intensity with the CoVAS device with "0" being no pain at all and "10" being the worst pain tolerable. If the Research Assistant feels there was an issue with the test, repeat the test.

The pain threshold and the pain tolerance should be recorded on the CPM response form.

12 PAIN ASSESSMENT QUESTIONNAIRES

The following questionnaires used for this study:

- ✓ The Faces Pain Scale – Revised (FPS-R) [61-63]
- ✓ State-Trait Anxiety Inventory - (STAI-C) [64]
- ✓ Pain Catastrophizing Scale (PCS) [65]
- ✓ Functional Disability Index (FDI): measures physical functioning in school age children and adolescents. This measure asks about being able to do a range of everyday physical activities (Walker and Greene 1991).
- ✓ Revised Children Anxiety and Depression Scale (RCADS): is a 47-item scale intended to assess children's report of symptoms corresponding to selected DSM-IV anxiety disorders and depression (Chorpita, Yim et al. 2000).
- ✓ Pittsburgh Sleep Quality Index (PSQI): designed to assess different clinically derived domains of sleep difficulties (Buysse, Reynolds et al. 1989).
- ✓ Neuropathic Pain Questionnaire (DN4): consists of both sensory descriptors and signs related to bedside sensory examination (Bouhassira, Attal et al. 2005).
- ✓ Tampa Scale for Kinesiophobia (TSK) [70]
- ✓ Scoliosis Research Society Questionnaire- Quality of Life Tool (SRS-30) [71]
- ✓ The Adolescent Pediatric Pain Tool (APPT): measures the location, intensity and quality of pain (Savedra, Holzemer et al. 1993).
- ✓ Patient`s Global Impression (PGIC)

12.1 IN-HOSPITAL ADDITIONAL MEASURES:

As analgesics may influence reported pain score, as may the anesthetic during the surgery, all perioperative medication intake will be recorded. Patient`s medical charts will be reviewed to document patients demographics. Vital signs will be recorded on admission, measured throughout the surgical procedure as well as during the post- operative period. To minimize variability our care plan has been standardized and implemented over the last 3 years. No changes to standard care will be required as a result of participation in this study on the day of surgery. In the operating room, general anesthesia and pharmacological pain management will be induced and maintained in a manner consistent with the standard of care standardized perioperative protocol established and respected by the anesthesiologists collaborating in this study. Following the surgical procedure, postoperative pain management is controlled in a standardized fashion by the Acute Pain Service (APS). As per standard care, the patient's pain is monitored continuously and as needed the APS adjusts the level of narcotics given. Tracking of self-reported pain scores and all analgesics given are reported in the patient's charts and accessible to the research team. A mean of all numerical pain scores for the first 48 hours after surgery will be calculated. The cumulative intake (mg/kg/hr) of each analgesic agent will be calculated for the first 48 hours after surgery as well.

Patients x-rays will be reviewed and spinal deformity will be quantified using standard Cobb angle measurements and using EOS technology will have 3D rendering of their spinal deformity.

Patient`s radiographic imaging will be used to generate individual anatomical spinal profiling. 3D imaging using EOS technology will be used to define patient`s spinal deformity. Each 3D rendition will be analyzed for: identification of the plane of maximal deformity in 3D using 3D vectors; identification of relative change from one segmental deformity to the adjacent segmental deformity across the entire spine; defining the plane of maximal correction and its impact on the other segmental deformities of the spine. In addition, relative findings of spinal imbalance will also be correlated to the presence or absence of pain which may influence overall spinal balance. Subsequently, patients with postoperative loss of normal sagittal alignment will be identified. Each case will then be illustrated on a DaVinci Diagram (axial 3D representation of the spinal deformity) providing clues as to why these individual patients have aberrant spinal alignment and possible postoperative spinal imbalance. 3D rendition will also be used to generate finite element models estimating anatomical forces across the intervertebral discs and the facets.

12.1 STUDY PLAN TABLE

	Baseline	*Surgery*	*In-Hos Day 1*	*In-Hos Day 2*	*In-Hos Day 3*	*In-Hos Day 4*	*In-Hos Day 5*	*Patient Diary call*	*6 week*	*6 month*
Blood Sample	*X*	*X*	*X*	*X*			*X*		*X*	*X*
Randomization	*X (After QST results obtained)*									
Clonidine or Placebo Intrathecal/Spinal		*X*								

Clonidine or Placebo PO			X	X	X	X	X			
dnadPaQST- Mechanical (MDT)	X	X	X	X			X		X	X
QST – Pressure Pain Threshold (PPT)	X	X	X	X			X			
QST-CPM	X						X	X	X	X
Questionnaires	X	X	X	X	X	X	X	X	X	X
X-rays	X	X	X	X	X	X	X		X	X
Medication	X	X	X	X	X	X	X		X	X
Vital signs	X	X	X	X	X	X	X		X	X

13. SUBJECT SAFETY

13.1 SAFETY AND TOXICITY ASSESSMENT

The experimental procedures in this study are the additional blood test, the QST testing and the use of Intrathecal Clonidine.

During the blood test the patient may suffer malaise, slight bleeding and/or minor bruising at the blood draw site.

In terms of QST, the patient may suffer some mild discomfort and reddening of the test site. The thermode will shut off after 50°C so there is no risk to burn the patient. The patient is always in control of their pain level and can stop the test at any time.

There are potential risks to patients the use of Clonidine. These are listed in section 5.2. Patients are followed for 6 months in this study and will be assessed for AEs at each follow up visit.

Additional risks associated with the study are in relation to confidentiality and data collection.

The benefit of using Intrathecal Clonidine is that patients may suffer less pain during the peri-operative period.

13.2 ADVERSE EVENT AND ADVERSE DRUG REACTION (ADR)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reaction.

13.3 SERIOUS ADVERSE EVENT OR ADVERSE DRUG REACTION

A serious adverse drug reaction (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

13.4 ANTICIPATED ADVERSE DRUG REACTIONS

An anticipated AE is any event, which is described below and can be clearly connected to one of the treatments. It is consistent with the specificity or severity and/or the risk information described in the product monographs for Clonidine Hydrochloride injection, and for Clonidine Hydrochloride Tablets.

Endocrine disorders:

≥0.01% and <0.1%	gynaecomastia

Psychiatric disorders:

≥1% and <10%	depression, sleep disorder
≥0.1% and <1%	delusional perception, hallucination, nightmare
Not known	confusional state, libido decreased

Nervous system disorders:

≥10%	dizziness, sedation
≥1% and <10%	headache

≥0.1% and <1%	paraesthesia
Eye disorder:	
≥0.01% and <0.1%	lacrimation decreased
Not known	accommodation disorder
***Cardiac disorders**:*	
≥0.1% and <1%	sinus bradycardia
≥0.01% and <0.1%	atrioventricular block
Not known	bradyarrhythmia
Vascular disorders:	
≥10%	orthostatic hypotension
≥0.1% and <1%	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders:	
≥0.01% and <0.1%	nasal dryness
Gastrointestinal disorders:	
≥10%	dry mouth
≥1% and <10%	constipation, nausea, salivary gland pain, vomiting
≥0.01% and <0.1%	colonic pseudo-obstruction
Skin and subcutaneous tissue disorders:	
≥0.1% and <1%	pruritus, rash, urticaria
≥0.01% and <0.1%	alopecia
Reproductive system and breast disorders:	
≥1% and <10%	erectile dysfunction
General disorders and administration site conditions:	
≥1% and <10%	fatigue
≥0.1% and <1%	malaise
Investigations:	
≥0.01% and <0.1%	blood glucose increased

Most adverse effects are mild and tend to diminish with continued therapy.

Occasional reports of abnormal liver function tests and cases of hepatitis have also been reported.

13.5 SERIOUS ADVERSE EVENT AND ADVERSE DRUG REACTION REPORTING

All adverse events and all adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. As soon as study staff become aware of an ADR, it is this person`s responsibility to notify the PI. The PI will ensure that SHC Headquarters and all applicable regulatory organizations are notified per regulatory guidelines.

Shriners Hospitals for Children must be notified of any unexpected ADR, via the OnCore reporting mechanism, within 10 days of occurrence.

The study PI will notify all participating investigators of any adverse drug reaction associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

Documentation of serious adverse drug reactions requires the investigator to collect the following data in order to report to the sponsors and IRB; Subject`s demographics, date event occurred, description of the event and how serious and severe it was, and whether or not it was related to the study treatment. If not related to the study treatment, what the possible causes may have been, if there is any relevant past medical history, if any tests were carried out and the results, if any concomitant medications were taken.

All data is to be documented on the AE/ADR form and filed in the patient`s medical record and study file. All follow up information surrounding the event will also be documented and sent to the sponsor and IRB.

All adverse events and all adverse drug reactions will be followed up until resolved, or until the end of the patient`s study participation.

13.6 NOTIFYING HEALTH CANADA

For drugs used in clinical trials in Canada, only adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting to Health Canada. Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is not required for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

During a clinical trial the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada. ADR report must be filed in the cases:

- where the ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- within 8 days after having informed Health Canada of the ADR, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings

Each ADR which is subject to expedited reporting should be reported individually in accordance with the Health Canada / ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (77).

Ongoing safety information respecting a drug should be conveyed to Investigator(s) and their Research Ethics Board(s). For further information refer to the Health Canada / ICH Guidance Documents E6: Guideline for Good Clinical Practice and E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

A completed ADR Expedited Reporting Summary Form should be attached to the front of the completed ADR report (suggested ADR report format: Suspect Adverse Reaction Report - CIOMS form of the Council for International Organizations of Medical Sciences (CIOMS)).

All forms can be found on Health Canada`s website and reports should be submitted by fax to the appropriate Directorate.

See Health Canada Website for more information: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_post_approval-eng.php#adr

13.7 UNBLINDING PROCEDURE

An investigator whose participant experiences side effects can be un-blinded if knowledge of the participant treatment is necessary in order to deliver appropriate treatment.

Should any events occur during surgery, whereby, the surgeon or anesthesiologist feel it is necessary to unblind the treatment, a call will be placed to the hospital`s pharmacist who will advise which treatment the patient is receiving and the patient will be treated medically as dictated by the event.

Should any events occur during the 5 day post-operative period, whereby it is felt that it is necessary to unblind the treatment, the patient`s surgeon will be contacted and will make the final decision to unblind the treatment or not. Should the response be affirmative, a call will be

placed to the hospital`s pharmacist who will advise which treatment the patient is receiving. There is no need to taper off the medication as the dosage given is very small.

If un-blinding occurs and medication is stopped immediately. No dose modifications will be made. The patient will be asked to remain in the study as we can still collect valuable information through blood samples, QST and questionnaires; however, no further medications or placebos will be given.

At the conclusion of the study, all investigators will be unblended with respect to their participant`s treatments.

14 DATA HANDLING AND RECORD KEEPING

14.1 CONFIDENTIALITY AND SECURITY

Data handling and protection are in accordance with the guidelines of ICH-GCP and applicable regulations. Validated outcome measures are used. Data collection for this study will primarily be through an online data management system housed on SHC servers. Members of the SHC research team will enter data into SHC system with unique user IDs and passwords. All secure web-based information transmission is encrypted and complies with HIPAA security guidelines and 21 CFR 11.

14.2 QUALITY CONTROL AND QUALITY ASSURANCE

The PI is responsible for all data and specimen management of all aspects of the study. The PI and the study project coordinator will be responsible for evaluating the data and ensuring the study team adheres to the protocol. Monthly meetings with the research team will be held to review and ensure the data is accurate and complete.

Investigators, approved study staff, collaborators, Shriners Hospital for Children, Health Canada, and McGill University Institutional Review Board may review records for research, quality assurance, and data analysis.

14.3 DATA STORAGE

For this study, source data will be collected by way of paper data collection forms. Patient data will be de-identified and given a unique numerical identifier. Data from the questionnaires and the data collection forms will be transcribed into a password protected electronic database housed on a SHC-Canada server using only the unique identifiers. A separate patient study log will be kept by the Principle Investigator linking the unique identifier to the patient data. All study data and the patient study log will be stored in a locked filing cabinet in a locked office at the SHC-Canada located at 1003 boulevard Décarie, Montreal, QC, H4A 0A9. Only authorized research personnel will have access to the documents and research computer.

14.4 CONFIDENTIALITY AND SECURITY

Privacy and confidentiality of the patient's medical data will be maintained through the study. Case report forms and all other documents pertinent to the study will be de-identified and carry only the numeric patient's identifier code. The site will maintain the link between the patient identifier code and the patient's names.

Personal medical information will at all times be treated as confidential. The informed consent document will contain information about the confidentiality of the medical information and approval for the access.

In the event that a subject revokes authorization to collect or use their personal medical information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

14.5 SOURCE DOCUMENTATION

The following outcome measures will be used to collect data and will be considered source documents:

The above questionnaires are all considered source documents in addition to the following:

- ✓ The Faces Pain Scale – Revised (FPS-R)
- ✓ State-Trait Anxiety Inventory - (STAI-C)
- ✓ Pain Catastrophizing Scale (PCS)
- ✓ Functional Disability Index (FDI)
- ✓ Revised Children Anxiety and Depression Scale (RCADS)
- ✓ Pittsburgh Sleep Quality Index (PSQI)
- ✓ Neuropathic Pain Questionnaire (DN4)
- ✓ Tampa Scale for Kinesiophobia (TSK)
- ✓ Scoliosis Research Society Questionnaire- Quality of Life Tool (SRS-30)
- ✓ The Adolescent Pediatric Pain Tool (APPT)
- ✓ Patient`s Global Impression (PGIC)
- ✓ Blood Sample Collection Form
- ✓ MDT/PPT Data Collection Form

- ✓ CPM Data Collection Form
- ✓ Surgical Data Collection Form
- ✓ Concomitant Medication Form
- ✓ AE & SAE Form
- ✓ Spinal Deformity Intra-Operative Monitoring Work Sheet (SDIM)
- ✓ Patient Home Interview / Phone Call Form

14.6 RECORD RETENTION

Source data, clinical data and other essential documents will be retained according to the SHC Standard Operating Procedure on Clinical Research Records Retention.

Study data will be kept for 25 years after the results have been published in a healthcare journal.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 DATA SAFETY MONITORING BOARD (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be assembled. Composition and details of the DSMB will be compliant to Health Canada requirements and will be in place prior to the initiation of the study.

15.2 STUDY MONITORING PLAN

Monitoring Plan

Monitoring will occur at 3 time points in throughout the study; 1) After the first 10 patients have been recruited; 2) After half the study patients have been recruited; 3) At close of study.

Source Data Verification (SDV) of critical data will be performed all on all patients in the study. A minimum of 25% or 10 patients recruited at the time of the monitoring time point will undergo 100% SDV. Patients study numbers will be randomly drawn from a box.

Critical data is defined below:

- Informed consent
  - Signature and dated by patient
  - Signature and dated by person consenting the patient (study team)
  - Inclusion criteria met
    - Females* aged between 10 and 21 years old

- Scheduled to undergo posterior spinal fusion surgery for AIS with instrumentation
- Ability to adequately understand and respond to outcome measures
- No previous major orthopedic surgery

- Exclusion criteria met
- Children with history of myocardial disease, arrhythmias, cerebrovascular disease, Raynaud`s/Thromboangiitis obliterans or chronic renal failure
- Children taking antihypertensive agents (diuretics, vasodilators, beta-blockers, ace-inhibitors)
- History of depression
- Inability of the child to speak English or French
- Diagnosed with developmental delay that would interfere with understanding questions being asked (autism, mental retardation)
- Children with major chronic medical conditions (ASA status III or higher)
- Pregnancy
  - Verification that all QST was completed
  - Verification that study medications were taken as per protocol

100% Source Data Verification

- Verification of medical records for AE and SAE occurrence
- Verify and compare all data collected to medical records and worksheets

If unreported AEs, SAEs or SDRs are found in any study files, the study files of the 3 consecutive patients will undergo 100% SDV.

16 STATISTICAL CONSIDERATIONS

16.1 PRIMARY STUDY ENDPOINTS

Average pain intensity over the past 7 days (0–10 numerical rating scale where 0 indicated “no pain” and 10 “worst possible pain”) six weeks and six months after surgery [73].

16.2 SECONDARY ENDPOINTS

Chronicity of postsurgical pain: Six months after surgery, CPSP will be defined in a dichotomous way (yes/no) as the presence of symptoms 6 months after surgery is reported.

16.3 SAMPLE SIZE DETERMINATION AND POWER / ACCRUAL RATE

The sample size was calculated for the primary outcome (average pain intensity over the past 7 days six months after surgery). Assuming that a 2-point change on the 0–10 pain intensity scale constitutes a clinically meaningful difference [74,76], a standard deviation of 2.0 units, a study design with 3 repeated measurements having a compound symmetry covariance matrix, a power of 90%, a two-sided alpha level of 0.05 and a conservative autocorrelation coefficient (rho) of one,

a minimum of 22 patients per comparison group is required. To prevent reduced power because of patient loss to follow-up and to minimize cofounding effects, 35 patients per group will be enrolled (35 x 4 groups = 150 patients in total).

16.4 STATISTICAL METHODS

Primary End Point: Average pain intensity over the past 7 days (0–10 numerical rating scale where 0 indicated "no pain" and 10 "worst possible pain") six weeks and six months after surgery (Dworkin et al., 2005).

Secondary end points: Chronicity of postsurgical pain: Six months after surgery, CPSP will be defined in a dichotomous way (yes/no) as the presence of symptoms 6 months after surgery are reported.

Descriptive statistics (means, SD, medians, n, %) will be calculated in order to present baseline characteristics of the different comparison groups and follow-up measures. To better appreciate the evolution of pain intensity (primary endpoint) during the longitudinal follow-up (baseline to six months after surgery), linear mixed models for repeated measures will be achieved for each of the three comparison schemes described above with the inclusion of the following variables as independent variables to obtain adjusted effects: age, functional outcome score and psychological profile (STAI and PCS scores). This type of analysis is justified by its flexibility in regard to missing data caused by patients lost to follow-up [75] and the possibility to adjust for potential confounders (e.g. patients' demographics, physical and emotional functioning, clinical characteristics such as medication use or scoliosis parameters). Continuous secondary outcomes will be compared between study groups using similar models. Categorical secondary outcomes such as the presence of chronic postsurgical pain measured 6 months after surgery will be compared between study groups using Chi-square tests. The investigator that will be in charge of the statistical analyses will be blinded to group assignment. As a secondary analysis aiming at understanding the underlying changes over time in QST, pain intensity and catecholamine concentrations will be examined using repeated measures analyses.

16.5 STRATIFICATION FACTORS

The chosen study design (Figure 7) will test different hypotheses and comparisons between the following groups:

1) Placebo group of patients with sub-optimal endogenous inhibitory response vs placebo group of patients with optimal response to test whether patients with inadequate endogenous inhibitory response before surgery are more at risk to develop chronic postsurgical pain (CPSP) than patients with optimal response.

2) Clonidine vs placebo group of patients with sub-optimal endogenous inhibitory response to test whether a pharmacological intervention focused on restoring the normal function of the descending inhibitory system reduces the incidence of acute and chronic pain after surgery.

17 FINANCE

This study is funded by Shriners Hospital for Children.

Subjects will not incur any expenses by participating in this study as all study visits are conducted in line with the regular standard of care visits and follow up visits.

Any costs incurred by the study such as supplies (blood collection tubes, supplies for analysis, or analysis of specimens) will be paid through the SHC grant.

In the event of opportunities to present the study and / or results, key individuals related to the study will be permitted to travel incurring expenses to cover flight, accommodations and meals up to $2000.00)

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