Modern Techniques of Adjunctive Pain Control Lower Opioid Use, Pain Scores, and Length-of-Stay in Patients Undergoing Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis

A Thesis submitted to the University of Arizona College of Medicine -- Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Sean J. Nabar
Class of 2013

Mentor: M. Wade Shrader, MD

Dedication

This thesis, along with everything else in life, is dedicated to my parents.

Acknowledgements

There were many people that made the production of this thesis possible. First and foremost, I would like to recognize my mentor, Wade Shrader. Dr. Shrader gave me the opportunity to undertake this very large, but ultimately feasible, retrospective study. As I learned from many of my classmates, finding a supportive mentor with realistic goals is the main hurdle in medical school research. The University of Arizona College of Medicine – Phoenix's "Scholarly Project" requirement, for which this thesis was written, has been the bane of most medical students' existences. I was fortunate to find Dr. Shrader in my first year of medical school and get started on the "SP" early. And it has taken nearly three years to make this final product. Dr. Shrader had a vision for the direction of this project and he never led me astray. He has encouraged me to perform my best and take pride in my research, things that I will carry on into residency and for the rest of my medical career.

In finding Dr. Shrader and this orthopedic research project, my medical school path and career path were also shaped. To gather the mountain of retrospective data (that has been neatly squeezed into 6 tables in the subsequent pages), I was sent to the Pain Department of Anesthesiology at Phoenix Children's Hospital (PCH). There I met Richard Cotugno, the research coordinator and general handyman of the small department. He helped me gather the majority of these tedious data by wading through hundreds of pounds of handwritten, illegible patient charts. In our time together, we have become good friends and I can count on Richard as one of my primary go-to people when I need just about anything.

In the Pain Department, I also met Dr. Emily Parke. Emily is a young, charismatic anesthesiologist who gave this project the pain perspective that it required. She also gave me the opportunity to present some of these results at the American Society of Anesthesiologists' annual meeting in Chicago in 2011. Her mentorship and encouragement almost single-handedly convinced me to pursue Anesthesiology as a career. The fact that she helped me intubate my first patient is just a side bonus. She was gracious enough to write me a letter of recommendation and advise me through the recently ended residency application season. I am very excited to train in anesthesia and be her colleague someday soon.

The last member of the PCH family I would like to thank is Dr. Shrader's former secretary, Ms. Debi Frew. She assisted in many of the early logistical milestones of this project such as setting up meetings and gathering signed documents. But she went FAR beyond her professional duties. In April/May of 2012, she had me as a houseguest during my General Surgery clerkship. By giving me a home for 6 weeks, she made it much more bearable for me to get to the rotation's hospital (40 miles from my downtown apartment) at 5 am. General Surgery was one of my favorite rotations of medical school, largely thanks to Debi.

My parents, to whom this thesis and everything else are dedicated, should also be recognized. They have made my school education from start to finish (now 29 years later) their number one priority. I can only hope to be as positive an influence on my own children someday. In addition, they provided me with an older brother, Neil. Neil and I have grown

much closer over the past 5 years although we now live far apart. I have gone on yearly vacations with him throughout medical school, and these trips have kept me motivated as something to work towards. We will be going on the last of the medical school trips right after graduation – to Spain – but I imagine there will be more in the future. I'm lucky to be going to Boston for my residency where we will be reunited.

Neil certainly belongs in this acknowledgement section as well. He spent several hours during his most recent holiday vacation helping me run the statistical analysis for this project. In a project with such an abundance of data it was a tremendous relief to have the assistance of an east-coast finance/investment mind on my side.

And finally, I would like to thank Dr. Burt Feuerstein and Ms. Nancy Johnson for all their hard work in putting the SP course together. I know that pioneering a research curriculum at a brand new medical school takes a lot of courage and hard work. But by setting high standards for our students, they have been instrumental in the efforts to make our school a leading academic institution in the future.

I am proud of the final product of this project and incredibly grateful to everyone who helped me out. Thank you.

Sincerely,
Sean

Abstract

Study Design. Retrospective analysis.

Objective. To determine if the use of adjunctive pain medications (subcutaneous bupivacaine, dexmedetomidine infusion, and intravenous ketorolac) will reduce the need for opioids, reduce postoperative pain, and shorten length of hospital stay in patients with adolescent idiopathic scoliosis undergoing posterior spinal fusion.

Methods. Retrospective review of children 10 to 18 years with adolescent idiopathic scoliosis receiving posterior spinal fusion surgery over the past 10 years at Phoenix Children's Hospital. Physicians managed the patients' pain postoperatively with adjunctive medications in addition to intravenous and oral opioids. Variables of interest were local anesthetic bupivacaine delivered subcutaneously via elastomeric pain pump, sedative/analgesic dexmedetomidine infused for up to 24 hours postoperatively, and the NSAID ketorolac delivered intravenously. These three medications were used either alone or in some combination determined by the physician's clinical judgment. Primary outcomes analyzed were normalized opioid requirement after surgery, VAS pain scores, and length of stay in the hospital.

Results. One hundred and ninety-six children were analyzed with no significant differences in demographics. Univariate analysis showed that all three adjunct medications improved outcomes. A multivariate regression model of the outcomes with respect to the three medication variables of interest was developed to analyze the effects of the three medications simultaneously. The regression analysis showed that subcutaneous bupivacaine significantly reduced normalized opioid requirement by 0.98 mg/kg ($P = 0.001$) and reduced VAS pain scores by 0.67 points ($P = 0.004$). Dexmedetomidine significantly reduced the average VAS pain scores in the first 24 hours by 0.62 points ($P = 0.005$). Ketorolac had no effect in the multiple regression analysis.

Conclusion. The use of subcutaneous bupivacaine provides good analgesia with low pain scores. A reduction in opioid requirement is beneficial and may be directly related to presence of the bupivacaine pump, although this may be limited by potential treatment bias. The three adjunct medications improve our outcomes favorably and should be studied prospectively.

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1. Introduction

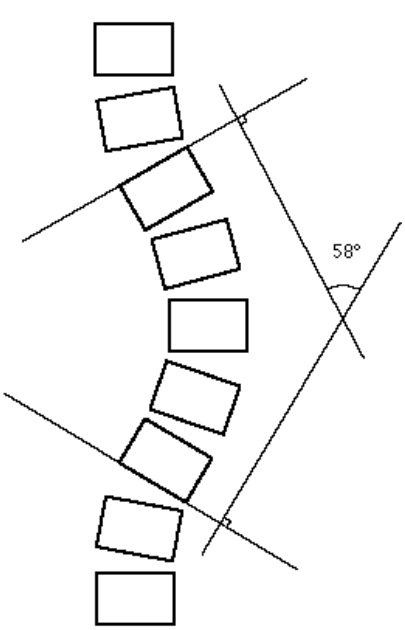
1.1 Scoliosis and Spinal Fusion

Scoliosis is a musculoskeletal condition in which there is an abnormal curvature of the spine. It is a complex three-dimensional deformity involving lateral curvature accompanied by rotation. The lateral curvature of the spine is measured by degrees of the Cobb angle (Figure 1a).[1] There are three etiological classifications of scoliosis: neuromuscular, congenital, and idiopathic. Neuromuscular scoliosis is a result of muscle imbalance that occurs in patients with neurologic or musculoskeletal problems. Congenital scoliosis results from failure of formation or segmentation of the spine during development. Congenital scoliosis is often associated with congenital disorders of other vital organs. Idiopathic scoliosis has no clear etiology and is therefore a diagnosis of exclusion. Adolescent idiopathic scoliosis (AIS) is the most common form of idiopathic scoliosis, comprising 80-85 percent of all cases.[1]

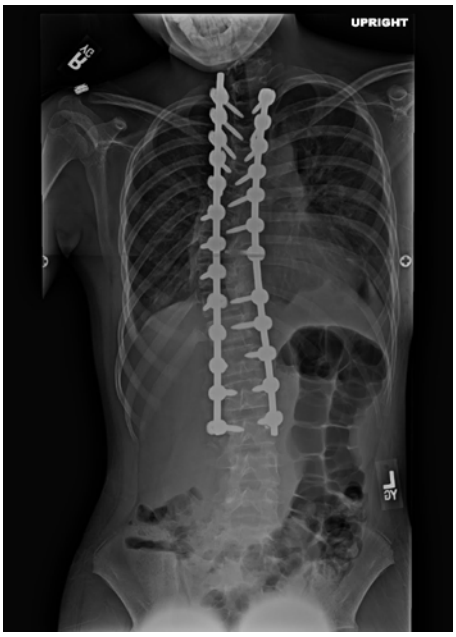
The prevalence of AIS with a Cobb angle greater than 10 degrees is approximately 3 percent.[2] Of these patients, approximately 10 percent will require treatment. Males and females are equally affected when the curve magnitudes are less than 20 degrees. However, when the magnitude of the scoliosis reaches a treatable range, often more than 30 degrees, the prevalence is roughly seven times greater in females. Indications for referral to an orthopedic surgeon may involve a variety of factors regarding Cobb angle, degree of rotation, documented progression, and age. Surgical correction is indicated for skeletally immature patients who with Cobb angles greater than 40 to 50 degrees.[3]

Surgery to correct AIS plays an important role in both physical and psychological health of patients. Invasive curvature of the spine may lead to restrictive lung disease and cardiac complications when left untreated.[4] Additionally, adolescents with deforming scoliosis often experience psychosocial difficulties.[5]

Currently, the most common surgical procedure to correct AIS is posterior spinal fusion (PSF). Both anterior and posterior spinal fusions have been performed safely and specific approach is traditionally chosen according to physician preference and patient anatomy. However, anterior approaches in the thoracic spine can potentially lead to reduced pulmonary



(a)



b)

Figure 1: a) schematic of scoliotic spine with Cobb angle of 58° displayed. b) X-ray of a pediatric patient with adolescent idiopathic scoliosis following posterior spinal fusion correction.

function post-operatively and therefore must be used cautiously.[6] The current "gold standard" surgical treatment for AIS is the posterior spinal fusion.[7] An x-ray of the spine after PSF operation is shown in Figure 1b.

1.2 Pain Control

Posterior spinal fusion surgery to correct AIS may result in significant pain postoperatively.[8,9] Poor pain control is not only undesirable for the patient, but also lead to family stress and anxiety, inability to participate fully with prescribed therapies, and longer hospital stays.[10-12] Traditional pain management options are limited to bolus dosing of intravenous and/or intrathecal opioids in the hospital, and later oral opioids as needed at home.[13-15] Because pain relief with traditional approaches may be inadequate, practitioners incorporate less studied adjunct therapies in an attempt to improve care for their patient.[16,17] These therapies include patient or parent controlled analgesia (PCA), intravenous ketorolac, local anesthetic infusions via indwelling catheters, and dexmedetomidine infusions.[18-21] Anecdotally, practitioners observe improvement in pain control with the implementation of these adjunct therapies.[22] Better pain control leads to higher patient and parent satisfaction, better cooperation with prescribed physical therapies, earlier ambulation and shorter hospital stays.[23] However, there are few studies available that corroborate these observations.

Studies addressing pain following PSF for AIS are difficult because treatment strategies are not standardized, physicians have different preferences, and patients may have different pain thresholds. Sucato et al. compared continous epidural analgesia with opioid PCA and found that epidural analgesia resulted in lower and less fluctuation of pain scores. However, that study did not focus solely on PSF operations.[24] Another study by Milbrandt et al. compared PCA with and without intrathecal morphine and epidural analgesia. They found no difference in pain control but did show that epidural analgesia resulted in quicker return to normal diet and that intrathecal morphine injection reduces opioid side effects, requiring less nursing and physician intervention.[25] A recent study by Ross, et al. showed that continuous infusion of bupivacaine reduced postoperative morphine use in AIS following PSF.[26] They did, however, have four different placement locations of the local anesthetic catheter. Additionally,

their study only looked at continuous infusion opioid without considering subsequent oral opioids through the entire hospital stay. The study also used a multivariate regression model to control for variability of anesthesia practice over the study duration.

Because of the differences in anesthesia practice, the areas for analysis are virtually limitless. However, patient pain control and safety remains the most important issue.

1.3 Study Objective

In this retrospective chart review, we focus solely on posterior spinal fusion surgery following adolescent idiopathic scoliosis. All of our patients received postoperative intravenous opioid medications via PCA and subsequent transition to oral opioids. We analyzed the effects of three adjunctive medications (bupivacaine, dexmedetomidine, and ketorolac) on postoperative pain scores, opioid use, and hospital length of stay. Bupivacaine, a medium-acting local anesthetic was administered by continuous infusion via subcutaneous catheters placed in the wound before closure. The medication was delivered by elastomeric pump with a flow restrictor. Dexmedetomidine, a centrally acting α2-adrenergic agonist similar to clonidine, was used as continuous infusion postoperatively for roughly 24 hours. Dexmedetomidine acts as an analgesic and sedative and is noted for its lower incidence of respiratory depression. Ketorolac is a potent non-steroidal anti-inflammatory medication administered intravenously. These three medications were used either alone or in some combination determined by the physician's clinical judgment.

Our hypothesis is that these three adjunctive pain medications can improve post-operative management following posterior spinal fusion for adolescent idiopathic scoliosis. The use of adjunct medications offers a valuable opportunity to reduce systemic opioids and their resultant side-effects. Additionally, improved pain control and quicker patient recovery may have a beneficial economic impact with our increasingly strained healthcare resources.

2. Research Materials and Methods

2.1. Retrospective Data Collection

After obtaining IRB approval from Phoenix Children's Hospital, a retrospective chart review was conducted on 215 children with diagnosis code for AIS who received posterior spinal fusion surgery over the past 10 years. Children with any additional congenital or neuromuscular comorbidities possibly contributing to their scoliosis were removed from the data set. Patients with documented narcotic addiction were also removed from the study. The final study sample included 196 patients. Data collection included patient age, gender, weight, American Society of Anesthesiologists (ASA) physical status, levels of spinal fusion, estimated blood loss, attending surgeon, length of stay in the ICU and hospital, visual analog scale (VAS) score, post-operative opioid requirement, presence of the three adjunctive medications (subcutaneous bupivacaine, dexmedetomidine infusion, intravenous ketorolac), length of surgery, length of time until ambulation, and side effects such as nausea, excess sedation, oxygen desaturation events, and urinary retention.

Data was collected and stored in Microsoft Excel on site at Phoenix Children's Hospital. Only persons included on the hospital IRB had access to patient charts and collected data. All patient identifiers were removed to maintain patient privacy. The patient charts were reviewed as a consecutive series to control for selection bias.

2.2 Treatment Medications

As previously mentioned, all patients had access to opioid PCA for pain management. Patients were started with IV morphine at 10 mcg/kg/demand dose every 10 minutes with a continuous infusion of 10mcg/kg/hr. If the patient was allergic to morphine, PCA with an equivalent dose of hydromorphone or fentanyl was used. Using an opioid conversion calculator the PCA opioid (scheduled and demand doses) and subsequent oral opioids were converted to morphine equivalents for each patient over the duration of hospital stay.[27]

The three adjunctive medications analyzed were bupivacaine, dexmedetomidine, and ketorolac. During the study period, a continuous infusion system for bupivacaine became

available (On-Q Painbuster Post-Op Pain Relief System, I-Flow Corp., Lake Forest, CA). The On-Q device is an elastomeric ball holding 400 mL of fluid and delivering the fluid medication via two 5-inch catheters. Attending orthopedic surgeons using this device placed the catheters subcutaneously in the wound before closure. The infusion of bupivacaine 0.25% was delivered at 4 mL per hour and continued for approximately 100 hours after surgery.

Dexmedetomidine infusion is normally dosed at 0.4mcg/kg/hr on the day of surgery and through the first 24 hours post-operatively. At our institution, the operating room anesthesiologists started the infusion in the operating room and determined the dose based on clinical judgment. Intravenous ketorolac is generally administered at 0.5 mg/kg every 6 hours for up to 72 hours as needed.

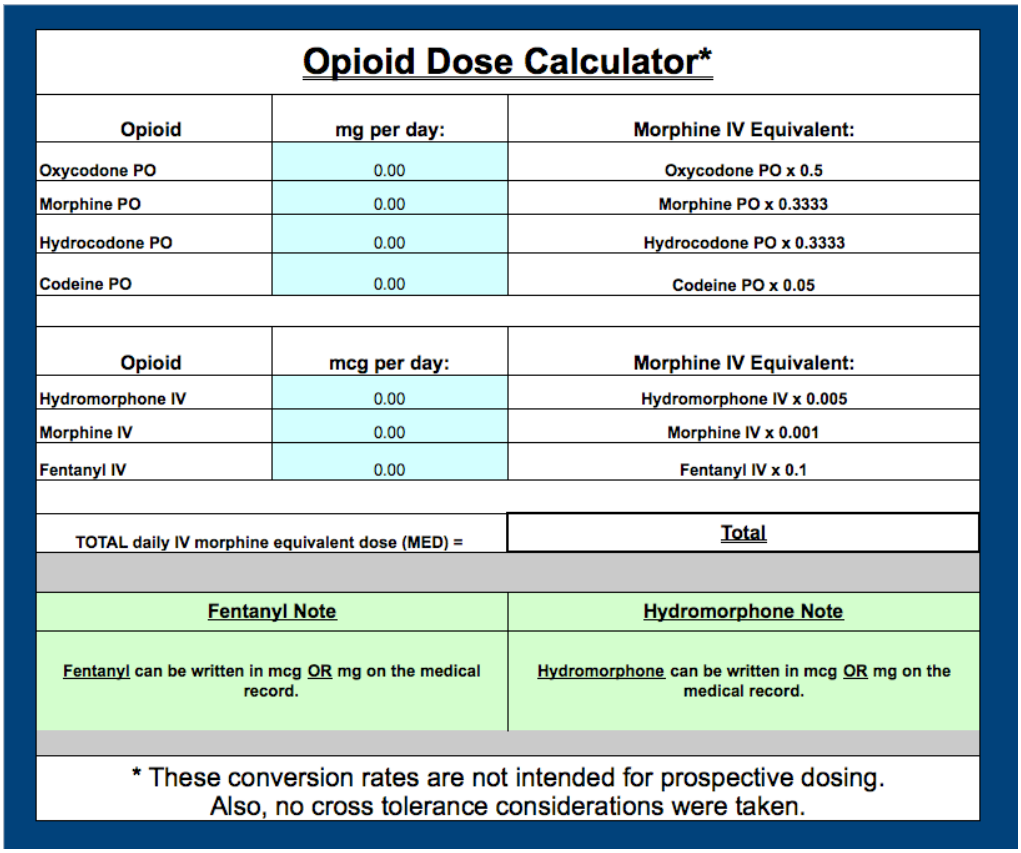
The precise amounts and durations of these adjunct medications were not recorded for this study. Instead, we measured we only recorded the administration of these three medications categorically as present or absent. Additional pain medications such as acetaminophen and ibuprofen were available but not recorded. Medications for the treatment of side-effects (anti-emetics, anti-spasmodics, narcotic reversal, etc.) were also available.

2.3 Data collection tools

Pain scores were recorded every 2 hours over the first 24 hours, and then at the same time of day on postoperative days two through until each patient was discharged. To assess postoperative pain, two 10-point pain scales were used: the Visual Analog Scale (VAS) and a modified Wong-Baker Faces Scale (FACES) for younger children. The FACES scale is shown in Figure 2.

A calculator was developed by our Pain Management department to convert all opioid-containing medications to normalized IV morphine equivalents. Opioid medications included morphine, fentanyl, hydromorphone, hydrocodone, and oxycodone. The relative potencies and bioavailability for opioid medications were used to determine conversion calculations.[27] No cross-tolerance considerations were taken. All IV morphine equivalents were added to calculate the total daily IV morphine equivalent dose. A screenshot of the opioid conversion spreadsheet with conversion formulas is shown in Figure 3.

Figure 2: Wong-Baker modified FACES Pain Rating Scale patient handout.



Opioid Dose Calculator*

Opioid	mg per day:	Morphine IV Equivalent:
Oxycodone PO	0.00	Oxycodone PO x 0.5
Morphine PO	0.00	Morphine PO x 0.3333
Hydrocodone PO	0.00	Hydrocodone PO x 0.3333
Codeine PO	0.00	Codeine PO x 0.05

Opioid	mcg per day:	Morphine IV Equivalent:
Hydromorphone IV	0.00	Hydromorphone IV x 0.005
Morphine IV	0.00	Morphine IV x 0.001
Fentanyl IV	0.00	Fentanyl IV x 0.1

TOTAL daily IV morphine equivalent dose (MED) =	Total

Fentanyl Note	Hydromorphone Note
Fentanyl can be written in mcg OR mg on the medical record.	Hydromorphone can be written in mcg OR mg on the medical record.

* These conversion rates are not intended for prospective dosing.
Also, no cross tolerance considerations were taken.

Figure 3: Screen-shot of opioid equivalence calculator used to derive IV morphine equivalents

2.4 Primary Outcomes

For this thesis, we focused on five outcomes. They included (1) Normalized opioid (mg/kg), (2) Normalized opioid-LOS (mg/kg/LOS), (3) Average VAS, (4) Average VAS in first 24 hour post-operatively, and (5) LOS in the hospital.

2.5. Statistical Methods

Statistical analysis was performed using Matlab v 7.0 (Mathworks, Natick, MA). Descriptive statistics regarding distribution of variables and population characteristics were performed first. Normally distributed continuous variables were analyzed with the Student's T-test. A Wilcoxon rank sum test (Mann-Whitney U) was used to analyze continuous variables not normally distributed.

Finally, a multivariate linear regression analysis was performed to further examine the impact of treatment variables of interest (bupivacaine, dexmedetomidine, ketorolac) on the five primary outcomes listed in section 2.4.

3. Results

In total, 196 patients were available for analysis. One hundred forty-eight patients (76%) were female and 48 (24%) patients were male. The range of patient ages was 10 to 18 with a mean age of 14.4 years. The mean normalized opioid was 3.11 mg/kg and the mean normalized opioid per length of stay (LOS) was 0.65 mg/kg/LOS. The average VAS score in hospital was 1.84 and the average VAS in the 1st 24 hours was 1.56. The average LOS was 4.65 days in the hospital. Table 1 shows the demographic descriptive statistics of all subjects in the study along with the five outcomes of interest.

Of the 196 patients, 74 (38%) received subcutaneous bupivacaine, 139 (71%) received dexmedetomidine (DEX), and 117 (60%) received ketorolac. We first measured the average difference in the five outcomes univariately with respect to these three treatments. The univariate differences are described in the following sections.

3.1 Subcutaneous Bupivacaine (Bupivacaine)

There were no significant differences between the groups receiving bupivacaine or not regarding age, gender, weight, height, or levels fused. However, the five outcomes were all statistically significant. The normalized opioid was lower in the group receiving bupivacaine (2.4 vs. 3.6 mg/kg, $P < 0.001$) and the normalized opioid per LOS was also lower (0.5 vs. 0.7 mg/kg/LOS, $P < 0.001$). The average VAS was lower in the bupivacaine group (1.4 vs. 2.1, $P < 0.001$) and the average VAS in the first 24 hours was also lower (1.0 vs. 1.9, $P < 0.001$). Finally, the mean length of stay in the hospital was nearly a half-day lower in the group receiving bupivacaine (4.4 vs. 4.8, $P = 0.004$) (Table 2).

3.2 Dexmedetomidine (DEX)

There were no significant differences between the groups receiving dexmedetomidine or not regarding age, gender, weight, height, or levels fused. The only statistically significant differences in the outcomes were the postoperative VAS pain scores. The average VAS score in the group receiving DEX was lower than the group that did not receive the medication (1.7 vs. 2.2, $P = 0.008$). The average VAS in the 1st 24 hours postoperatively was also lower in the group

Table 1. Patient Demographics (N = 196)

	Average	Stdev	25th Percentile	75th Percentile
Age (years)	14.38	1.65	13.0	16.0
Gender (female)	148	NA	NA	NA
Weight (kg)	57.40	14.83	47.9	64.4
Height (cm)	163.38	9.83	158.0	169.0
Levels Fused	10.48	1.49	10.0	11.0
Normalized Opioid (mg/kg)	3.11	1.75	2.0	3.9
Normalized Opioid-LOS (mg/kg/LOS)	0.65	0.31	0.5	0.8
Average VAS	1.84	1.34	0.8	2.7
avg VAS 1st 24 hr	1.56	1.44	0.3	2.5
Mean LOS	4.65	1.11	4.0	5.0

Continuous data presented as mean ± standard deviation and compared with students t test or median (IQR). VAS indicates visual analog scale; LOS, length of stay; IQR interquartile range.

Table 2. Subcutaneous Bupivacaine

	BUP (n = 74)	No BUP (n = 122)	*P*
Age (years)	14.3 ± 1.7	14.4 ± 1.6	0.726
Gender (female)	57 (77%)	91 (75%)	0.702
Weight (kg)	55.6 ± 13.8	58.5 ± 15.3	0.179
Height (cm)	164.4 ± 10.1	162.8 ± 9.5	0.252
Levels Fused	10.7 ± 1.4	10.4 ± 1.5	0.164
Normalized Opioid (mg/kg)	2.4 (1.4,3.2)	3.6 (2.5,4.2)	0.000
Normalized Opioid-LOS (mg/kg/LOS)	0.5 (0.4,0.6)	0.7 (0.6,0.9)	0.000
Average VAS	1.4 (0.5,1.8)	2.1 (1.1,3.0)	0.000
Average VAS 1st 24 hr	1.0 (0.0,1.6)	1.9 (0.7,3.1)	0.000
Mean LOS	4.4 (4.0,5.0)	4.8 (4.0,5.0)	0.004

Continuous data presented as mean ± standard deviation and compared with students t test or median (IQR) and compared with MWU test. Categorical data presented as number and percent of total. BUP indicates subcutanous bupivacaine; VAS, visual analog scale; LOS, length of stay; IQR, interquartile range; MWU, Mann-Whitney U.

receiving DEX (1.3 vs. 2.1, P = 0.002). There were no significant differences between the groups receiving DEX regarding normalized opioid use or length of stay in the hospital (Table 3).

3.3 Ketorolac

There were no differences between the groups receiving ketorolac or not regarding age, gender, weight, height, or levels fused. However, the difference between groups with respect to gender was nearly significant, with more females receiving ketorolac (80% vs. 68%, P = 0.056). Additionally, the five outcomes were all statistically significant. The normalized opioid was lower in the group receiving ketorolac (2.7 vs. 3.7 mg/kg, P < 0.001) and the normalized opioid per LOS was also lower (0.6 vs. 0.7 mg/kg/LOS, P < 0.001). The average VAS was lower in the ketorolac group (1.6 vs. 2.1, P = 0.006) and the average VAS in the first 24 hours was also lower (1.3 vs. 1.9, P = 0.006). Lastly, the mean length of stay in the hospital was shorter in the group receiving ketorolac (4.6 vs. 4.8, P = 0.027) (Table 4).

3.4 Treatment Frequencies

The three adjunct medications of interest were often used in different combinations both to achieve patient comfort as well as dictated by physician preference. Table 5 shows the percentage of patients receiving any combination of these medications. The greatest percentages of patients received either all three medications or dexmedetomidine alone (30% and 26%, respectively). Very few patients received bupivacaine alone or both bupivacaine and dexmedetomidine (2% and 1%, respectively). Twelve percent of the patients in the study received none of the three medications. The implications of these treatment frequencies and combinations are addressed in the discussion section.

3.5 Multivariate Regression Analysis

To analyze the effects of the three adjunctive medications simultaneously, a multivariate regression analysis was performed on all five outcomes (dependent variables) with respect to four independent variables (the three treatments plus number of vertebral levels fused). The results of the regression analysis are shown in Table 6. Number of levels fused was

Table 3. Dexmedetomidine Infusion

	DEX (n = 139)	No DEX (n = 57)	*P*
Age (years)	14.4 ± 1.7	14.3 ± 1.6	0.738
Gender (female)	108 (78%)	40 (70%)	0.268
Weight (kg)	57.5 ± 14.8	57.0 ± 15.0	0.836
Height (cm)	163.3 ± 10.2	163.5 ± 8.5	0.939
Levels Fused	10.5 ± 1.6	10.5 ± 1.3	0.886
Normalized Opioid (mg/kg)	3.0 (2.0,3.6)	3.4 (2.1,4.1)	0.164
Normalized Opioid-LOS (mg/kg/LOS)	0.6 (0.5,0.8)	0.7 (0.5,0.8)	0.132
Average VAS	1.7 (0.7,2.5)	2.2 (1.0,3.4)	0.008
Average VAS 1st 24 hr	1.3 (0.2,2.0)	2.1 (0.7,3.6)	0.002
Mean LOS	4.6 (4.0,5.0)	4.8 (4.0,5.3)	0.104

Continuous data presented as mean ± standard deviation and compared with students t test or median (IQR) and compared with MWU test. Categorical data presented as number and percent of total. DEX indicates dexmedetomidine infusion; VAS, visual analog scale; LOS, length of stay; IQR, interquartile range; MWU, Mann-Whitney U.

Table 4. Intravenous Ketorolac

	KET (n = 117)	No KET (n = 79)	*P*
Age (years)	14.3 ± 1.6	14.5 ± 1.7	0.528
Gender (female)	94 (80%)	54 (68%)	0.056
Weight (kg)	57.1 ± 13.6	57.8 ± 16.5	0.748
Height (cm)	163.6 ± 10.8	163.1 ± 8.0	0.723
Levels Fused	10.4 ± 1.6	10.6 ± 1.4	0.454
Normalized Opioid (mg/kg)	2.7 (1.7,3.3)	3.7 (2.6,4.3)	0.000
Normalized Opioid-LOS (mg/kg/LOS)	0.6 (0.4,0.7)	0.7 (0.6,0.9)	0.000
Average VAS	1.6 (0.7,2.5)	2.1 (1.1,3.0)	0.006
Average VAS 1st 24 hr	1.3 (0.2,2.1)	1.9 (0.7,3.0)	0.006
Mean LOS	4.6 (4.0,5.0)	4.8 (4.0,5.0)	0.027

Continuous data presented as mean ± standard deviation and compared with students t test or median (IQR) and compared with MWU test. Categorical data presented as number and percent of total. KET indicates intravenous ketorolac; VAS, visual analog scale; LOS, length of stay; IQR, interquartile range; MWU, Mann-Whitney U.

Table 5. Adjunct Medication Frequency		
	Count	Percentage
All 3	58	30%
DEX only	51	26%
DEX & KET only	29	15%
None	24	12%
Ketorolac only	18	9%
BUP & KET only	12	6%
BUP only	3	2%
BUP & DEX only	1	1%
Total	**196**	**100%**

BUP indicates subcutaneous bupivacaine; DEX, dexmedetomidine infusion; KET, intravenous ketorolac.

Table 6. Multiple Regression Analysis* (N = 196)

	Subcutaneous Bupivacaine		Dexmedetomidine Infusion		Intravenous Ketorolac	
Dependent Variable	β	*p*	β	*p*	β	*p*
Normalized Opioid (mg/Kg)	**-0.98**	**0.001**	-0.25	0.336	-0.38	0.190
Normalized Opioid-LOS (mg/Kg/LOS)	**-0.19**	**0.001**	-0.03	0.555	-0.05	0.366
Average VAS	**-0.67**	**0.004**	**-0.42**	**0.043**	-0.11	0.633
Average VAS 1st 24 hours	**-0.80**	**0.001**	**-0.62**	**0.005**	-0.07	0.774
Mean LOS	-0.37	0.068	-0.14	0.451	0.06	0.768

**Results of 5 regressions with 5 different dependent variables (Normalized Opioid, etc) using a constant, # of levels fused, and binary variables (with the variable equal to one if used) for the 3 adjunct medications on our dataset of 196 observations. The # of levels was not significant in any of our regressions and is omitted for brevity. Terms which are significant at the 5% level are in bold. VAS indicates visual analog scale; LOS, length of stay.*

included as an independent variable because size of incision and instrumentation could possibly contribute significantly to postoperative pain and recovery. However, there were no significant differences in outcomes with respect to levels fused and therefore this variable is not included in the table.

The presence of subcutaneous bupivacaine was associated with significant reductions in normalized opioid, normalized opioid per LOS, average VAS, and average VAS in the first 24 hours ($P < 0.004$ for all). Bupivacaine may also have had an effect on the reduction of mean LOS in the hospital, although it was not statistically significant ($P = 0.068$).

The use of dexmedetomidine reduced the average VAS pain scores both for the duration of hospital stay and in the first 24 hours ($P = 0.043$ and $P = 0.005$). The presence of dexmedetomidine did not have a statistically significant effect on the other outcomes.

When examined in the multivariate regression analysis, the presence of ketorolac had no significant effect on any of the five outcomes.

4. Discussion

Postoperative pain management can be challenging after posterior spinal fusion for adolescent idiopathic scoliosis. The goal is to provide safe and effective analgesia in the early postoperative period. Because patients have different anatomy, physiology, and inherent requirements, it would be difficult, if not impossible, to create one single postoperative pain control regimen. In this study, we analyzed the current postoperative management following PSF for AIS at our institution. Other studies have looked at continuous infusions of bipuvicaine, adjunct dexmedetomidine, and regional anesthesia techniques to optimize recovery.[24-26] This study demonstrates the effects of three adjunctive medications (bupivacaine, dexmedetomidine, and ketorolac) on pain, opioid use, and length of stay in the hospital after surgery. By defining the specific set of five postoperative outcomes, we are able to draw conclusions from the PSF cases performed at our institution during the study period.

There was no change in opioid protocol during the study duration and each patient had access to continuous infusion of morphine by PCA. However, clinicians prescribing the opioid PCA infusions were not blinded to adjunctive medication use. This potential confounder may have affected study outcomes to some degree. Unfortunately, with a retrospective study design, it is impossible to control for provider treatment bias.

One major advantage of this study is that we looked at all forms opioids used postoperatively, including oral medications until hospital discharge. Use of the opioid conversion table made it possible to calculate the total normalized opioid and normalized opioid per length of stay, two important outcomes. Few orthopedic surgery studies have reported morphine equivalents following PSF and have traditionally only considered opioid drips ran in the immediate postoperative period, days before hospital discharge.

The demographics of the subject groups were well-matched and without significant differences. Only gender difference in ketorolac use approached statistical significance, possibly because of the antiemetic properties of ketorolac and female patients' predisposition to post-operative nausea and vomiting (PONV).[30] Despite a 10-year study period, length of surgery and length of hospital stay did not change. The protocol at our institution is to admit patients to the intensive care unit (ICU) following PSF surgery. We did not take into

consideration the differences in ICU versus hospital ward management in this study and that is a potential area for exploration in future studies.

Bupivacaine administration through the elastomeric pain pump was associated with significant reductions in all five primary outcomes. The opioid use, VAS, and length of stay were all highly statistically significant. Although 1-point difference on a 10-point scale of VAS pain scores may not be clinically significant, the reduction in opioid use supports the idea that the elastomeric pain pump is a useful adjunct to opioid PCA. In the study by Ross, et al. bupivacaine was placed at four different locations (implant, muscle, subfacial, subcutaneous). While they also found that patients with bupivacaine catheter required less postoperative morphine, there was no significant difference in postoperative morphine use based on depth of catheter placement.[26] At our institution, all bupivacaine pumps were placed in the subcutaneous tissue to treat incisional pain, and there is no intention of changing the protocol for now. Regarding hospital length of stay (LOS), the group receiving bupivacaine had nearly a half day reduction (4.4 vs. 4.8). A reduction in hospital stay is both statistically *and* clinically significant and will undoubtedly reduce hospital costs.

The effect of dexmedetomidine on reduction of postoperative opioids has been studied extensively in the anesthesiology literature. Although dexmedetomidine is not FDA approved for children, it is commonly used by pediatric anesthesiologists for sedation and analgesia following surgery.[28] Sadhasivam et al. described the possible morphine-sparing effect of dexmedetomidine following spinal fusion as evidenced by increased morphine PCA use on postoperative day 2. They did not see a difference in VAS pain scores on any postoperative day due to dexmedetomidine infusion.[29] In this study, we did not look at individual postoperative days' opioid use and we found no difference in opioid requirement with respect to dexmedetomidine. However, we did see a statistically significant reduction in VAS pain scores averaged over the hospital stay and over the first 24 hours postoperatively. This is likely due to the fact that dexmedetomidine infusion is continued for roughly 24 hours after surgery in the ICU. Dexmedetomidine had no effect on hospital LOS.

The presence of ketorolac was significant for reductions in all five postoperative outcomes. As a potent anti-inflammatory, it is clearly a useful adjunct to opioids after posterior spinal fusion and may be used barring contraindications.

To analyze the differences in outcomes with respect to the three adjunct medications used simultaneously, we performed a multiple regression analysis (Table 6). In the multiple regression analysis, subcutaneous bupivacaine is the most promising of the three adjunct medications, as it was statistically significant for nearly every dependent primary outcome. Total normalized opioid reduction was not just statistically significant, but the coefficient was a clinically meaningful value with a difference of 33% of the base. Dexmedetomidine's effect was statistically significant for both VAS measures, yet another expected outcome due to its administration in the first 24 hours postoperatively. Interestingly, ketorolac did not have any significant impact on the primary outcomes in the multivariate regression analysis. This is an unexpected result, considering the univariate analysis of ketorolac's effect demonstrated significant reductions in all of the primary outcomes.

A limitation to the multivariate model is the possible multicollinearity of the three adjunct pain medications. We attempted to determine if there was an association between the three adjunct medications usage by calculating the treatment frequencies (Table 5). Since subcutaneous bupivacaine (On-Q) became available during the study period, the earlier patients in the study did not receive the medication. In the data set, the most common combination of the drugs was all three being present (30% of patients). Overall, we were not able to find a significant trend in use over time or combination of the drugs. Choice of adjunct medication was often due to clinician preference or patient contraindication, information not readily available at the time of retrospective review.

The major limitation to this study is that it is retrospective and not a randomized control trial. Analysis was performed to control for confounding variables, but there may be other confounders not identified. In various institutions, there have been changes in clinical practice over the past 10 years with regard to ketorolac use and diazepam use for prevention of muscle spasm. For this study, we did not analyze the effect of benzodiazepines use although that data is available for future studies. Another limitation was that we treated the three adjunct

medications as categorical variables being either present or absent rather than analyzing the exact dosages of medication. While the three medications are usually prescribed similarly between patients and dosed per body weight, there differences almost certainly remain. Anesthetic technique involving adjunctive medications and opioids could be further standardized at our institution.

5. Conclusions and Future Directions

Pain control following major spine surgery remains an important topic in pediatric orthopedic surgery and anesthesia. With the favorable results of this study, we hope to continue optimizing treatment. This study demonstrates that adjunctive medications in the postoperative management of posterior spinal fusion for adolescent idiopathic scoliosis results in reduced opioid use, reduced hospital stay, and good analgesia with low pain scores.

Bupivacaine local anesthetic delivered subcutaneously via elastomeric pain pump is associated with significant reductions in postoperative opioid requirement and pain scores. Although bupivacaine has notable cardiotoxicity and has been associated with deaths when the epidural anesthetic has been inadvertently administered intravenously, this is not a major concern with our practice of placing the catheters subcutaneously before wound closure. Given its favorable effect on primary outcomes and the safety profile of the local anesthetic, subcutaneous bupivacaine should become a mainstay of postoperative management for AIS where not contraindicated.

Dexmedetomidine's effects on VAS pain scores were positive but not overwhelming. Additionally, dexmedetomidine is not FDA approved for children therefore a prospective study involving dexmedetomidine would require an exemption. Also, dexmedetomidine, at this point in time, is an expensive medication and may not be warranted for such a modest effect on pain score reporting. Ketorolac showed no effect on outcomes in the multiple regression model and but was very favorable in the univariate model. Therefore, there is no reason to avoid its use when not contraindicated.

Further work needs to be done to completely evaluate postoperative pain management of PSF surgery for AIS in our sample data. We collected information regarding estimated blood loss, use of benzodiazepines, adverse effect including nausea and oxygen desaturations, as well as recovery measures such as return to normal diet and ambulation. These data were not analyzed in this paper, but they are available to be studied for further correlations. The effect of different doses of each adjunctive medication used should also be addressed in future works.

There were some significant limitations in this study. This was a retrospective study performed over 10 years by multiple surgeons. Inherent bias in treatment strategies could

significantly affect the results. Clinician blinding of treatment medications would be ideal to eliminate observation bias but is not practical and possibly dangerous. The multiple regression analysis controlled for treatment bias within the three adjunctive medications and produced favorable results. Given these favorable results, a prospective, randomized control trial is warranted to more accurately characterize the effect of adjunctive medications on pain and recovery following posterior spinal fusion.

6. References

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