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Multimodal anesthesia with the addition of methadone is superior to epidural analgesia: A retrospective comparison of intraoperative anesthetic techniques and pain management for 124 pediatric patients undergoing the Nuss procedure

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ABSTRACT

Background: The Nuss procedure corrects pectus excavatum by forceful displacement of the sternum with metal bars. Optimal pain management remains a challenge. Mutimodal anesthesia alleviates pain through blockade of multiple nociceptive and inflammatory pain receptors.

Methods: A retrospective chart review of anesthetic and postoperative mangement of 125 children undergoing the Nuss procedure was conducted. Anesthetic mangement strategies were analyzed in four groups: opioid during general anesthesia (GA), epidural with general anesthesia (Epidural), multimodal anesthesia (MM), and multimodal anesthesia with methadone (MM + M). Data collection included total opioid use (as equivalent milligrams of morphine (Mmg)), pain scores, length of stay (LOS), and adverse effects.

Results: Total opioid use varied by group (median, IQR (in Mg)): Epidural 213 [149, 293], GA 179 [134, 298], MM (150 [123, 281]), and MM + M (106 [87, 149]), as did severe pain (in minutes): Epidural (208 [73, 323]), GA (115 [7, 255]), MM (54 [0, 210]), and MM + M (49 [0, 151]). LOS was shortest for the MM + M group (MM + M = 3.8 + 1.0 days; MM = 4.5 + 1.3 days; GA = 4.9 + 1.4 days, Epidural = 5.5 + 2.3 days).

Conclusion: Multimodal anesthesia is associated with less postoperative pain and shorter LOS compared to epidural or traditional anesthetic techniques for the Nuss procedure. Multimodal anesthesia with a single intraoperative dose of methadone was associated with lowest total opioid use, time with uncontrolled pain, and shortest LOS.

Pectus excavatum is a common chest wall deformity that occurs in approximately 1:400 male children [1]. Surgical correction is performed for children with severe deformities and cardiopulmonary symptoms [1]. The Nuss procedure was first described in 1998, and is now the most common surgical technique for pectus excavatum. This technique involves forceful sternal elevation with implantation of metal bars to keep the sternum elevated until chest wall remodeling takes place. The repair keeps continuous pressure on the sternum, and results in significant postoperative pain sometimes lasting for several weeks [2,3]. Optimal pain management in the early postoperative stages reduces complications, expedites the return to normal function, and increases patient satisfaction [4]. Conversely, poor pain management is undesirable for the patient, and may also contribute to family stress, patient anxiety, inability to participate fully with prescribed therapies, and extended hospital stay [3,5,6]. Common pain management strategies for patients undergoing the Nuss procedure have included epidural or regional analgesia, short and intermediate-acting opioids, nonopioid analgesics, and sedatives [7–9]. These modalities have varying degrees of effectiveness, and each has its own risk of side effects and potential complications [10–13]. Determining the best techniques and strategies for improved analgesia may lead to fewer complications, earlier discharge from the hospital and reduced hospital costs [6,8,15–17].

Opioids are typically used for managing pain, but they have many side effects, all of which may complicate postoperative care. The use of thoracic epidurals has been shown to be safe [20] and may avoid many of these side effects while providing acceptable postoperative analgesia for the patient. However, rare complications that can be devastating are known to occur [29]. Alternative pain management adjuncts have been implemented at many institutions with varying results, including the use of nonopioid analgesics, anxiolytics, and elastomeric infusion pump placement [7–9,14,18].

The primary objective was to determine if a specific intraoperative anesthetic technique and postoperative pain management strategy could help optimize postoperative pain management, specifically by maintaining acceptable patient comfort, reducing opioid requirements and minimizing hospital length of stay. The secondary objective was to determine the prevalence of adverse effects in patients receiving each of the techniques evaluated.

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1. Materials and methods

After approval from the Phoenix Children's Hospital Institutional Review Board, a retrospective chart review was conducted on children diagnosed with pectus excavatum who underwent the Nuss procedure between the years 2007 and 2014. The subjects were identified from the hospital's research registry with the admission diagnosis of pectus excavatum. The need for informed consents was waived because the study only involved a chart review.

1.1. Inclusion/exclusion criteria and groups

This study included any patient diagnosed with pectus excavatum. Exclusion criteria included any patient with preoperative opioid abuse, and any patient who underwent an open repair of their pectus excavatum in lieu of the Nuss procedure. The standard surgical technique for the Nuss procedure remained similar through the duration of study [19].

The patient charts were separated into four groups based on anesthetic technique and postoperative pain management strategy: (1) opioid analgesia during general anesthesia (GA group), (2) epidural placed in addition to general anesthesia (GA + E group), (3) multimodal anesthesia (MM group), and (4) multimodal anesthesia with a single dose of methadone (MM + M group). Over the course of the study, there was a gradual shift in choice of analgesia from GA to GA + E to MM, and finally to MM + M.

1.2. General anesthesia (GA) group

The GA group received a general anesthetic that included an inhalational agent, intravenous opioids and ketorolac. No other adjuncts, such as benzodiazepines, dexmedetomidine, clonidine, or ketamine were given in this group.

1.3. General anesthesia with epidural (GA + E) group

The GA + E group had the same general anesthetic as the GA group, with the addition of an epidural catheter placed after induction that was used intraoperatively and postoperatively. All epidural catheters in this study were inserted between T4 and T10, and threaded an average of 4.8 cm into the epidural space. The placement was confirmed either by fluoroscopy using neuraxial compatible contrast dye, or by the lack of physiological response after surgical manipulation. Dermatomal levels were determined by the cold test using ice. Lack of a cold sensation from the ice confirmed the level of dermatomal coverage. Average spread was from T4 to T12. Each epidural infusion included a combination of local anesthetic, and opioids. Clonidine was included in some epidural solutions but not all. There were nine different combinations of infusions used throughout the chart review, as seen in Table 1, but each combination provided similarly effective analgesia. These infusions differed between providers because the standard of practice had not yet been established. All opioids used in the epidural infusion, as well as any supplemental parenteral opioids given while the epidural was in place, were included in the total overall opioid use. For calculation, all opioid dosages used were converted to morphine equivalents based on Table 2.

A failed epidural was defined by the following criteria: (1) inadequate analgesia during the first 24 hours after placement. This was identified as an average pain score greater than 4/10 during a 12-hour period, despite attempts to optimize efficacy (e.g., catheter manipulation, boluses, solution adjustments, rate adjustments, etc; (2) inadequate dermatomal coverage at the level of the surgical site, as documented on physical exam; and (3) equianalgesic intravenous morphine bolus requirement greater than 0.3 mg/kg/day.

Table 1
Epidural infusion concentration breakdown.

Epidural infusion concentration	Average continuous rate	Minimum rate	Maximum rate
Bupivacaine 0.125%, clonidine 0.4 μg/mL	15.7	15	17
Fentanyl 2 μg/mL, bupivacaine 0.1%, clonidine 0.2 μg/mL	6	6	6
Fentanyl 2 μg/mL, bupivacaine 0.1%, clonidine 0.4 μg/mL	10.0	5	15
Fentanyl 2 μg/mL, bupivacaine 0.125%, clonidine 0.4 μg/mL	10.2	2	20
Fentanyl 5 μg/mL, bupivacaine 0.1%, clonidine 0.2 μg/mL	6	6	6
Fentanyl 5 μg/mL, bupivacaine 0.1%, clonidine 0.4 μg/mL	12.8	9	16
Hydromorphone 3 μg/mL, bupivacaine 0.125%, clonidine 0.4 μg/mL	10	10	10
Hydromorphone 5 μg/mL, bupivacaine 0.1%, clonidine 0.2 μg/mL	13	13	13

1.4. Multimodal anesthesia (MM) group

The MM group received intraoperative ketamine and dexmedetomidine infusions as part of the general anesthetic. Ketamine 1 mg/kg IV was administered on induction, and 0.25 mg/kg doses were repeated hourly during the procedure. Dexmedetomidine was infused at a rate of 0.7 μg/kg/h. The dexmedetomidine was stopped at the end of the procedure, and a clonidine 0.1 mg/day transdermal patch was applied in the PACU.

1.5. Multimodal anesthesia with methadone (MM + M) group

The MM + M group received the same intraoperative medications and clonidine patch as the MM group with the addition of a single dose of IV methadone at 0.1 mg/kg up to a maximum of 7.5 mg administered on anesthetic induction.

1.6. GA, MM, and MM + M groups

In all three non-GA + E groups, the surgeons inserted bilateral elastomeric infusion pump catheters (Moog Medical Devices Group, Salt Lake City, UT) along the chest wall under the muscles through the surgical incisions used to place the Nuss bars; 0.25% bupivacaine was infused through both catheters for the first 48 hours postoperatively. The non-GA + E groups also received patient controlled analgesia (PCA) with morphine initiated upon arrival to the PACU. A hydromorphone or fentanyl PCA was used in patients with morphine allergy or intolerance. In the MM and MM + M groups, the PCA continuous infusion was stopped on the first postoperative day, and oxycontin 10–20 mg twice a day was started, adjusted to the patient's weight and overnight morphine use.

1.7. Data collection

Data collection included demographics, daily postoperative opioid use, nonopioid analgesic use, numeric pain scores, intraoperative medications, length of hospital stay, days to ambulation, days to tolerating solid food, number of Nuss bars placed, surgical complications, reoperations, adverse effects (nausea, vomiting, sedation, oxygen saturation, urinary retention), and the use of naloxone. Opioid use and pain score averages were collected for five consecutive days following surgery. The opioid use was reviewed on a flowsheet listing all medications given over a five day period. The patient's visual analog scale (VAS) pain scores were recorded by the nurse in the patient's chart at four-hour intervals, and 30 minutes after being given a pain medication as per standard hospital protocol. Any patient with a pain score higher than 7 was reassessed at least every 30 minutes until the pain score was less than 7. Patients who were asleep were assigned a score of zero.

Episodes of nausea or vomiting were monitored by the nurse, surgical team, or pain service and documented on the patient's chart. Any

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Table 2
Ratios for IV morphine equivalent dose calculations.

	Conversion ratio
Oral opioids (Mg)	
Oxycodone PO	2:1
Morphine PO	3:1
Hydrocodone PO	3:1
Codeine PO	20:1
Intravenous opioids (Mg)	
Hydromorphone IV	0.2:1
Morphine IV	1:1
Fentanyl IV	0.01:1
Methadone IV	2:1

Table 3
Descriptive presentation of patient demographic and clinical characteristics.

Characteristics	GA ($N = 31$)	GA + E ($N = 35$)	MM ($N = 28$)	MM + M ($N = 30$)	*p*-Value*
Age (years)	15.2	14.7	15.1	15.7	0.692
Weight (kg)	55.3	53.4	55.9	56.3	0.80
Gender (*n*)					0.613
Male	22	24	22	24	
Female	9	11	6	7	
ASA physical status (*n*)					0.287
I	6	9	2	1	
II	21	21	22	29	
III	4	5	4	1	
IV	0	0	0	0	

With all *p*-values being greater than 0.05, there is no statistical difference among the patient demographics. ASA = American Society of Anesthesiologists.
* Kruskal–Wallis test was used for continuous measures. chi-square tests were used for categorical measures. Cochran–Mantel–Haenszel tests were used for ordinal qualitative variables. $p < 0.05$, statistically significant difference.

medications given to relieve the episodes of nausea or vomiting were noted and reviewed from the chart. Respiratory depression was defined as a respiratory rate of less than eight breaths per minute requiring opioid reversal with naloxone. Oversedation was defined as the inability to arouse patients solely with verbal stimulus.

1.8. Statistical methods

Descriptive characteristics for quantitative variables were determined based on the underlying distribution. For normally distributed variables, mean and standard deviation were computed, otherwise median and interquartile range were used. Relative frequencies were given for quantitative variables.

The overall outcomes of the four groups were compared using the nonparametric Kruskal–Wallis test. Subsequent pairwise comparisons were computed using the the Dwass, Stell, Critchlow–Fligner method. For the comparison of the repeated measurements over the 5 days in the four groups a mixed model with unstructured covariance matrix was applied.

Outcomes of qualitative variables were analyzed using the chi-square test or for ordinal qualitative variables, a Cochran–Mantel Haenszel test was used. A *p*-value of ≤0.05 was assumed to be significant.

2. Results

2.1. Demographic Data

Of the 131 charts that were reviewed, 124 charts met the inclusion criteria for this study. One patient was excluded because of a history of drug abuse and known drug seeking behavior. Six patients were excluded because they had an open procedure for repair of their pectus excavatum. Of the patients included in the review, 31 patients were in the GA group, 35 patients were in the GA + E group, 28 patients were in the MM group, and 30 patients were in the MM + M group. Patient ages ranged from 7 to 22 years with an mean of 15.2 ± 1.9 years for the GA group, 14.7 ± 2.7 years for the GA + E group, 15.1 ± 2.1 years for the MM group, and 15.6 ± 2.4 years for the MM + M group. In the GA + E group, 97% of the epidurals were successful based on epidural failure criteria stated above. There were no significant differences for patient age and gender between the groups (Table 3). The distribution of the ASA scores was comparable in the 4 groups ($p = 0.50$). The number of bars placed was higher in the MM + M group as shown in Table 3 ($p = 0.009$).

2.2. Outcomes

The MM + M group had the lowest total opioid administered during the five days after surgery, closely followed by the MM group ($p < 0.0001$). There appeared to be no difference between the GA and the GA + E group, as shown in Table 4. The most significant differences in opioid use between the groups occurred during the first 24 hour period after surgery (Table 4, $p = 0.03$). The frequency of VAS pain scores ≥7 was significantly lower in the MM + M group (Table 4, $p = 0.004$). A multivariate comparison of all five consecutive days also revealed the MM + M group to have the lowest average VAS score ($p < 0.0001$).

2.3. Patient's hospital length of stay

The mean length of stay was significantly shorter in the MM + M group compared to the other groups (Table 4, $p < 0.0001$).

2.4. Perioperative complications

Adverse events such as pruritus, nausea, vomiting, or sedation requiring naloxone were not statistically significant. Urinary retention and constipation were significantly lower in the MM + M group (Table 5, $p = 0.01$).

3. Discussion

Multiple anesthetic techniques and postoperative pain management strategies have been used over the years for patients undergoing the Nuss procedure at our institution. We postulated that intraoperative anesthetic technique could optimize postoperative analgesia, and that identifying the best strategy and standardizing that technique would yield positive benefits for our patients. We observed that patients who received a multimodal anesthetic seemed to have a high level of comfort after what is traditionally a very painful procedure. In following these patients postoperatively, we recognized that these patients remained comfortable throughout the rest of the hospital stay. We coordinated our pain management strategy with our surgical colleagues, and as our postoperative care plan evolved, we found that patients were ready for discharge earlier than before. A formal retrospective review has validated our observations. The MM group showed reduced opioid use in every time period analyzed when compared to both the GA and the GA + E groups. Adding methadone to the multimodal anesthetic reduced the total opioid use and the length of stay over multimodal anesthesia alone.

Nationally, many pediatric centers implement thoracic epidural analgesia as a standard postoperative pain regimen for patients undergoing the Nuss procedure. However, despite advances in regional anesthetic techniques, including fluoroscopic confirmation of epidural catheters, failure rates up to 32% have been reported [7–9,21]. Technical risks and variable provider skill can negatively impact the delivery of safe and successful epidural analgesia [10,22] although very rare, thoracic epidural placement is associated with neurological injury [29]. It is therefore important to identify a pain management technique

Table 4
Descriptive presentation of primary and secondary outcomes.

Outcomes	GA ($N = 31$)	GA + E ($N = 35$)	MM ($N = 28$)	MM + M ($N = 30$)	p-Value
Total opioid (mg)	178.8 (54.8, 467.1)	212.2 (56.3, 545.4)	150.4 (75.2, 438)	106.3 (49.1, 270.6)	<0.0001*
24-hour opioid (mg)	56.2 (13.3, 134.5)	55.2 (17.6, 139.1)	44.9 (20.1, 133.1)	42.2 (11.9, 88.8)	0.0342
Minutes pain score greater than 7	115 (0.0, 770.0)	208.3 (0.0, 2173.5)	54.3 (0.0, 926.0)	48.8 (0.0, 2260.0)	0.0044*
Total LOS (days)	4.9 ± 1.4	5.5 ± 2.3	4.5 ± 1.3	3.8 ± 1.0	<0.0001*
Average pain scores	2.3 (0.5, 4.5)	2.7 (0.9, 4.8)	2.3 (0.4, 4.4)	2.2 (0.3, 5.0)	0.4073

Median (minimum, maximum) are given for continuous measures; LOS was given as mean ± standard deviation. POD = postoperative day, LOS = length of stay.
* Kruskal–Wallis test was used for continuous measures. $p < 0.05$, statistically significant difference.

that provides effective analgesia, subjects patients to minimal risk and does not depend on procedural precision to deliver reproducible results.

Our failure rate was significantly lower than reported failure rates; we limited epidural placement to a few skilled anesthesiologists, which we believe was responsible for our high success rate. Higher opioid use in this group was caused by a combination of continuous opioid administration used in the epidural infusion, and supplemental parenteral opioids administered as needed. Parenteral opioid use went up significantly in some patients soon after the epidural was discontinued because of acute worsening of their pain. We believe this may have contributed to a lengthened hospital stay in some patients. Other factors may have contributed as well, such as the lack of a formal protocol for the advancement of activity and diet.

Several studies have shown the safety and efficacy of a single dose of intraoperative methadone in controlling postoperative pain and reducing opioid use beyond the initial 24 hours following surgery [23–25]. Since methadone has been shown to cause cardiac conduction abnormalities [26], electrocardiogram (ECG) screening is required before the patient receives methadone. For pectus excavatum patients, an ECG is routine in the workup to evaluate for conduction abnormalities. Although methadone can have a varying half-life among individuals, delayed respiratory depression is less frequent in patients receiving a single dose therapy as compared to chronic therapy [28]. In our review, there were no cases of respiratory depression in the MM + M group. In addition, the group that received 0.1 mg/kg of methadone on induction had less total opioid use and shorter hospital stays when compared to the other groups.

The multimodal anesthetic technique (Table 6) has evolved over the years at our institution, and is based on the known synergistic analgesic effect of medications that exploit multiple pain pathways [24]. In addition to inhalational anesthetics, opioids, and ketorolac used in the GA group, dexmedetomidine, ketamine, and methadone alleviate pain through blockade of multiple nociceptive and inflammatory pain receptors that contribute to better postoperative analgesia. By utilizing this protocol, many of our patients no longer require IV opioids after postoperative day two, and the majority of our patients are now discharged on postoperative day three.

The Nuss procedure has already been described as more cost effective when compared to an open repair because of shorter surgical times, decreased length of stay, and reduced perioperative morbidity [16,27]. Cost savings have been attributed to both shorter operative times and reduced length of stay when compared to the open procedure. To date, there are no studies evaluating the potential cost savings of more effective pain management techniques, however, it is not unreasonable to postulate that removing the cost of a regional blockade and reducing hospital length of stay provides cost savings to both the patient and the healthcare institution [16].

3.1. Limitations

As our study was a retrospective review of patient's medical records we acknowledge its limitations and potential biases. Individual patient characteristics such as high anxiety, low pain tolerance, or previous thoracic surgery not documented in the patient's chart may have led to increased postoperative opioid use.

Other potential variability may have existed during the VAS assessments performed by the nurses. Since the nurses perform the pain assessment, it is up to their discretion when pain medication should be administered. This could cause a varying threshold for opioid administration because different nurses do not assess the patient in the same way. As a result, some patients may have been treated more or less aggressively than others who demonstrate similar levels of discomfort.

A shorter time to ambulation and hospital length of stay may have been influenced by a lack of standardized protocol for diet advancement and return to physical activity in the earlier years. Subsequent implementation of a more standardized effort to mobilize patients earlier in their hospital course in later years may have introduced a bias toward the most recent group of patients.

The surgical techniques changed somewhat during the time period, but none of the modifications from the original technique would have been expected to reduce the pain of the procedure. The chest wall program at Phoenix Children's Hospital was started by two surgeons who did the first cases together. Together they created a standardized approach that is now used by all five surgeons. Rules are in place at the hospital requiring every Nuss procedure to have two surgeons which also ensures a consistency of technique. One of the core pectus surgeons were present for every one of the cases early in the series. Whenever a new surgeon was added to the program, there was a period during which the standard technique was passed on. While the techniques have changed significantly, the procedure is associated with significant pain regardless of the technical variation. Evolution of the technique over time is a potential confounding variable, and should be noted as a possible limitation.

For the epidural group, the continuous infusions contained opioids, which were added to their opioid totals. While epidural dosages are significantly lower than intravenous dosages, the potential for a continuous epidural infusion to inflate the opioid use of those patients may be a confounding variable. Additionally, there may have been confounding effects of the significance of other medications on the effects of postoperative opioid usage.

Table 5
Descriptive presentation of adverse events.

Adverse events	GA ($N = 31$)	GA + E ($N = 35$)	MM ($N = 28$)	MM + M ($N = 30$)	p-Value
Nausea/Vomiting	13 (41.9)	16 (47.1)	15 (53.6)	9 (29.0)	0.2626
Pruritus	13 (41.9)	13 (38.2)	5 (17.9)	8 (25.8)	0.1601
Respiratory depression	1 (3.23)	2 (5.71)	0	0	0.3644
Urinary retention	7 (22.6)	6 (17.1)	9 (32.1)	0	0.0105*

Frequencies (percentages) are given for categorical measures.
* Chi-square tests were used for categorical measures. $p < 0.05$, statistically significant difference.

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Table 6
Intraoperative and postoperative protocol.

MEDICATION	DOSE	FREQUENCY	TIMING
Methadone	0.1 mg/kg	Once	At Induction
Ketamine	1 mg/kg then 0.25 mg/kg/hr	Once	At Induction, Intraoperative Only
Dexmedetomidine	0.7 mcg/kg/hr	Once	Intraoperative Only
Ketorolac	0.5 mg/kg	Once	Prior to extubation
PCA Morphine	0.01mg/kg/hr basal rate 0.015 mg/kg q8 min	Once	Postoperatively Discontinue basal rate after 24 hours
Oxycodone SR	10 mg PO	BID	Start after 24 hours, once PCA basal discontinued
Oxycodone	5–10 mg PO	Every 4 hours PRN	Start after 24 hours
Ketorolac	0.5 mg/kg	Every 6 hours x 12 doses	Start in PACU
Diazepam	0.1 mg/kg up to 5mg	Every 6 hours PRN	Start in PACU
Clonidine	0.1 mg/day patch	Replace every 5 days	Start in PACU

Shaded section is intraoperative; nonshaded section is postoperative.

We now use long-acting oxycontin and clonidine patches routinely to help with the management of postoperative pain. This may introduced bias toward the more recent populations of patients included in the analysis, especially with the aggressive multimodal approach to treating postoperative pain. However, patients who received a multimodal anesthetic without standardized postoperative pain management strategies still showed reduced opioid use and shorter hospital stays than those in the GA or GA + E groups.

4. Conclusion

This retrospective analysis suggests an association between the multimodal anesthetic techniques and lower total opioid use, time with severe pain, lower average pain score and decreased LOS when compared with patients receiving GA or GA + E. Multimodal anesthetic techniques with the addition of a single intraoperative dose of methadone were associated with the lowest total opioid use, least time with severe pain, and shortest hospital LOS. This pain management strategy appears safe and has the potential to improve measurable and meaningful care outcomes.

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