

A Randomized Controlled Trial to Compare Pain Medications in Children Undergoing Strabismus Surgery

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Purpose: The purpose of this study was to investigate optimal intraoperative combinations of analgesia for children undergoing strabismus surgery.

Design: A randomized controlled trial was employed to compare the difference in pain after administration of hydromorphone versus fentanyl.

Methods: Participants were randomly assigned to either arm of the study. Pain was measured by the revised Faces, Legs, Activity, Cry, and Consolability Scale (rFLACC) tool postoperatively, and the parent was asked about the presence or absence of pain after discharge.

Findings: A total of 135 children were included in the study. The rFLACC pain score was found to be significantly higher postoperatively among patients receiving fentanyl ($P = .011$). Pain after discharge was reported more often among patients who received fentanyl ($P < .001$).

Conclusions: Results of this study can be used to change practice to minimize the pain levels both postoperatively and after discharge for children undergoing strabismus surgery.

Keywords: strabismus surgery, pediatrics, pain, postoperative.

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EVERY YEAR, MORE THAN 1,100 children undergo eye muscle surgery provided by physicians at this Midwestern pediatric academic hospital.

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For some of these children, this would be their first surgical procedure for eye muscle correction, and for others, it would be a repeat procedure. However, all these children will experience differing degrees of postoperative pain. The pain associated with strabismus surgery in children is due to the manipulation in the conjunctiva, further handling of Tenon's capsule and sclera, and the stretching of the eye muscle.¹ Research has demonstrated that repeated painful procedures result in increased anxiety and pain.^{2,3} Previous studies have also demonstrated that children experiencing preoperative anxiety are more likely to have increased postoperative pain.⁴⁻⁶ This increased preoperative anxiety may contribute to sleep difficulties and increased analgesic consumption.^{3,4} Depending on the age of the child, different methods used to reduce anxiety include distraction, child life services, or antianxiolytic agents such as midazolam.^{4,7,8} In

addition to pain, children undergoing strabismus surgery frequently experience postoperative nausea and vomiting (PONV).^{1,9} This increased incidence of PONV is thought to be related to the use of opiates for pain control. Therefore, the selection of opiates that would minimize the nausea and vomiting needs to be carefully considered.

The purpose of this study was to determine the optimal combinations of analgesia to create a standardized approach for pain management in pediatric patients undergoing strabismus surgery. The following research questions were developed to guide the study:

1. What is the difference in postoperative pain in children undergoing strabismus surgery who are administered hydromorphone and ketorolac as compared with fentanyl and ketorolac intraoperatively?
2. What is the difference in the number of pain medications administered postoperatively in children undergoing strabismus surgery who are administered hydromorphone and ketorolac as compared with fentanyl and ketorolac intraoperatively?
3. What is the association between parent- and child-reported level of anxiety and the experience of prior strabismus surgery?
4. What is the difference in the number of vomiting episodes postoperatively and the morning after discharge in children undergoing strabismus surgery who are administered hydromorphone and ketorolac as compared with fentanyl and ketorolac intraoperatively?

Review of the Literature

Many children undergoing strabismus surgery experience severe postoperative pain.¹ The pain is thought to be associated with manipulation of the ocular muscles with additional discomfort, resulting in blurry vision after the procedure.¹ The child's and parent's level of anxiety is also closely related to the experience of postoperative pain in children with repeated surgeries.⁴ In addition, the adverse effects of anesthesia and analgesia may include excessive nausea and vomiting, which only exacerbates

the child's level of discomfort in the postoperative period.^{10,11}

Assessment and Management of Postoperative Pain

The evaluation of pain in young children is not an easy task. The assessment of the level of pain in young children can differ among parents, health professionals, and the child.¹²

The use of various pain assessment tools can also give different interpretations, resulting in different approaches to pain control.¹² Previous research suggests that health professionals tend to underestimate children's postoperative pain, but the parent's perceptions of pain can be a more reliable surrogate when a child cannot self-report his or her pain postoperatively.¹²

Surgery alone is an experience that can influence children significantly on many levels. Because children can be at varying developmental levels, they may experience pain differently, resulting in long-lasting effects. Those effects can have different manifestations by age groups and cause long-term changes in the sleep pattern, nutrition, and behavior.⁵ To control postoperative pain, it is very important to determine what level of pain is anticipated to be present.¹³ Because pain is subjective and different for each child, this aim varies among patients, parents, and nurses.¹³ To achieve the best results, it is important to make patients and the family aware of the expected level of pain postoperatively and the target for pain control based on the pain score.¹³

Previous research has suggested that a multimodal approach using a combination of pain medications produces optimal results.¹⁴ Combinations of pain medications affect different pain receptors, resulting in better pain control.¹⁴ Evidence shows that children who experience severe postoperative pain achieve better pain control and less side effects with a combination of opiates and nonsteroidal anti-inflammatory medications.³

Level of Anxiety and Pain

Children with higher anxiety preoperatively experience higher postoperative pain and a different

pattern of recovery.⁴ During and immediately after hospitalization, children who present with high preoperative anxiety manifest difficulties in falling asleep, change of appetite, and behavioral problems.⁴ These factors can contribute to a prolonged hospital stay and a longer recovery.⁴

Preoperative anxiety and postoperative pain can often lead to behavioral changes in children.¹⁵ These changes often start immediately postoperatively or during hospitalization and can last several weeks.¹⁵ Increased levels of preoperative anxiety are predictive of behavior changes postoperatively.¹⁵

If children develop a negative painful experience initially, each additional procedure that follows may cause higher levels of anxiety.² This will automatically cause the pain experience to be more exaggerated, and these negative pain memories can lead to phobic reactions to needles and other interventions over time.² These results suggest the need for effective pain management for every encounter with a medical procedure to prevent the development of negative pain memories.²

Postoperative Nausea and Vomiting

PONV is a significant problem for children after strabismus surgery. It is estimated that the incidence of PONV after this surgical procedure can range from approximately 37% to 90% when a prophylactic antiemetic is not administered.^{10,11} The surgical procedure itself may increase the risk for PONV. Manipulation of the medial rectus muscle stimulates the oculometric reflex, resulting in pain, alterations in visual perception, and PONV.^{1,11} Additional factors contributing to the risk for PONV include age >3 years, duration of anesthesia >30 minutes, type of anesthesia administered, female gender, family history, and postoperative analgesia.^{9,11} A recent meta-analysis of 13 randomized controlled trials evaluating 2006 pediatric patients after strabismus surgery found that prophylactic administration of ondansetron and dexamethasone significantly reduces the occurrence of PONV.¹¹ However, the study focused on anesthetic agents and did not address the influence of intraoperative analgesia. Research clearly demonstrates that PONV is also associated with the use of opiates for pain control.^{1,9,16} PONV can significantly increase the

risk for complications such as subconjunctival hemorrhage, loosening of surgical attachments, tension on suture lines, delayed hospital discharge, and even readmission.^{10,11} Although ongoing research is trying to determine the best prophylactic treatment for PONV, the selection of opiates that would decrease PONV needs to be carefully considered.¹⁷

Research Design

A randomized controlled design was used to evaluate pain control after administration of hydromorphone and ketorolac compared with administration of fentanyl and ketorolac during strabismus surgery. The study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02789969) (NCT02789969). Participants were randomized 1:1, and both the nurse and participant were blinded to medication allocation. To randomize participants, the anesthesia attending physician chose from envelopes containing the name of the medication to be administered during surgery. In the documentation by the anesthesiologist, the name of medication was not disclosed to limit the possibility of bias by the nurse in assessing pain after surgery.

Methods

Sample and Setting

This Midwestern academic pediatric hospital performs approximately 1100 strabismus surgeries annually among the targeted age group. Inclusion criteria were as follows: (1) children aged 3 to 10 years having a first-time or repeated strabismus surgery; (2) the child was evaluated as an American Society of Anesthesiologists Physical Status 1 or 2; (3) the caregiver was present in the hospital; and (4) the child and caregiver were English speaking. Exclusion criteria included (1) children evaluated as an American Society of Anesthesiologists Physical Status class 3 or 4; (2) non-English speaking children or parents; (3) additional surgery performed at the same time; and (4) children with documented behavioral disabilities. A review of anesthesia records shows that 480 patients met inclusion criteria for the preceding 12 months, thus validating the availability of an adequate sample size at this institution. The primary outcome measure was pain as measured by the revised Faces, Legs, Activity, Cry, and Consolability (rFLACC) Scale. It was expected that pain scores

would have a mean of five and a standard deviation of two. The goal was to detect a change of one point in rFLACC scores, which was estimated to be clinically significant. With an alpha of 0.10 and power of 0.80, 64 patients in each arm were needed for a one-point decrease in rFLACC scores to be statistically significant.

Instruments

A researcher-developed demographic questionnaire was used to collect information that included patient age, gender, previous surgery, any medication allergies, and the identification of the primary caregiver. The Amsterdam Preoperative Anxiety and Information Scale (APAIS) was used to assess parent feelings of anxiety in the preoperative phase.¹⁸ The APAIS is a short 6-item questionnaire with acceptable reliability of a Cronbach's alpha greater than or equal to 70 and correlated highly (0.74) with the widely used State-Trait Anxiety Scale.¹⁹ Because of its length, the APAIS can be quickly administered to parents in the perioperative area to assess parental preoperative anxiety.²⁰ The measure was completed on all parent participants after consent was obtained. The APAIS took approximately 1-2 minutes to score.

For evaluating anxiety in children, the Modified Yale Preoperative Anxiety Scale (m-YPAS) was used. The m-YPAS is frequently used to measure anxiety before induction and has demonstrated both inter-rater and intrarater reliability (using k statistics) ranging from 0.63 to 0.90 and acceptable reliability ($P = .01$, $r = 0.79$).²¹ This instrument can be administered in less than 1 minute, is reliable in children aged 2 to 12 years, and assesses five areas (activity, vocalization, expression, arousal, and interaction) to rate preoperative anxiety.

Nurses use the rFLACC Scale to measure pain in the postanesthesia care unit (PACU) and in same-day surgery (SDS). The rFLACC has established reliability and validity and is used in the operative units to assess pain in children after receiving general anesthesia in the immediate postoperative period and through phase 1 and phase 2 recovery. In this institution, phase 1 recovery occurs in the PACU, and then the patients return to SDS for phase 2 recovery. The inter-rater reliability revealed intraclass correlation coefficients ranging

from 0.76 to 0.90. Criterion validity ($P = .65$ to $.87$) was supported by correlations between parent and child scores.²²

Procedure

Institutional review board approval was obtained from the university affiliated with the hospital. The protocol was given full board review and approval. Families were informed about the study during a routine preoperative telephone contact the day before surgery and informed they could learn more about the study the next day. After admission to SDS, the researcher approached families of potential candidates who expressed interest and a more detailed explanation of the study was given. At this time, consent was obtained and parents were asked to complete the demographic data form and the APAIS. The researcher evaluated children for preoperative anxiety with the m-YPAS. Upon arrival to the PACU and every 15 minutes during the patient's stay, pain was assessed using the rFLACC Scale. After transfer from the PACU to SDS, the nurse continued to evaluate pain using the same scale on arrival and before discharge. In addition to the patient's level of pain, the need for any additional pain medication was documented. To help ensure study fidelity in regard to pain assessment, all nurses were given additional education on the use of the rFLACC. After discharge, the parent received a telephone call the morning after surgery to evaluate PONV and the presence of pain at home. All patients with strabismus are discharged home with acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg) to be given for the first 12 to 24 hours after discharge and then as needed. The patient is given the option to choose one medication or to alternate the medications every 6 hours.

During the surgery, the anesthesia attending physician administered the pain medication depending on information from the randomly selected sealed envelope. Only the anesthesia attending physician and researcher knew which medication was administered during the surgery. The experimental group received hydromorphone (15 mcg/kg) and ketorolac, and the control group received fentanyl (2.5 mcg/kg) and ketorolac. Both medication combinations were titrated to effect. The documentation during surgery did not disclose

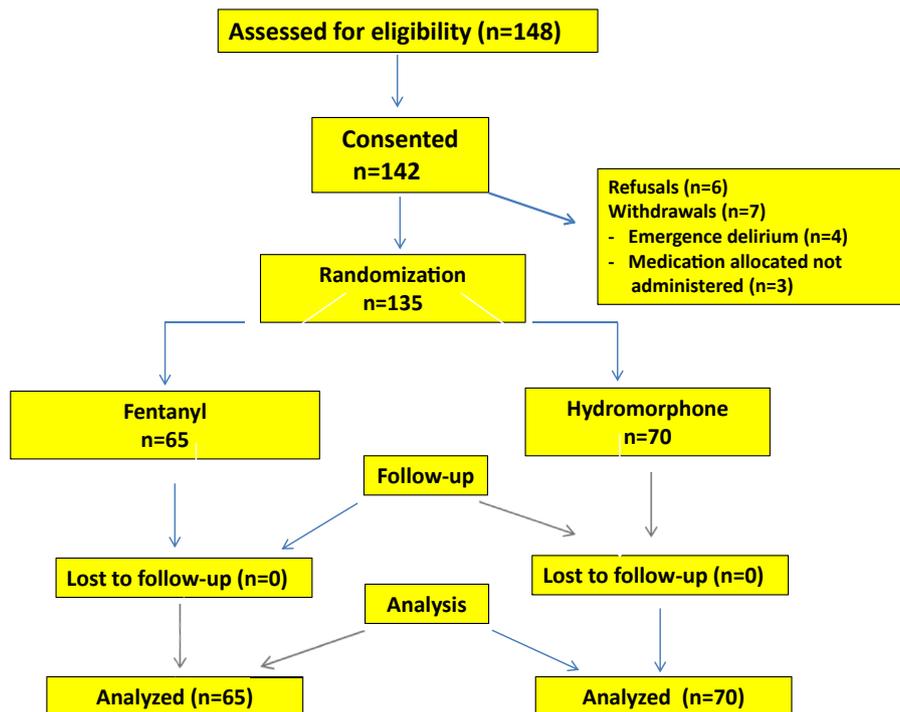


Figure 1. Enrollment data. This image is available in color online at www.jopan.org.

the name of the drug or the dosage to the nurses, which minimized bias during the postoperative care.

Data Analysis

Univariate summary statistics were created for demographic and clinical background variables, as well as pain and anxiety instrument measures, to assess distribution. Categorical variables were compared using a χ^2 tests, including by strata; Fisher's exact tests were used when expected cell sizes of comparisons were too small. Continuous variables were compared by binary predictors using independent samples t tests; nonparametric Mann-Whitney U tests were used when parametric assumptions were not upheld. A Spearman's rank-order correlation was used to determine the association between two ordinal variables. A factorial analysis of variance was used to assess a continuous dependent variable by two categorical independent variables. Alpha was preset at 10% for all testing of significance. Statistical analysis was performed using IBM SPSS Statistics for Mac, version 24.0.²³

Findings

A total of 148 children's parents were called by phone and invited to participate. Six participants did not want further information after the initial phone call. A convenience sample of 142 children aged between 3 and 10 years who were scheduled for strabismus surgery were recruited over a 14-month period. A final sample of 135 participants was analyzed after seven participants were withdrawn as noted in Figure 1. The reasons for withdrawal included emergent delirium necessitating the need for dexmedetomidine or if the anesthesiologist did not follow the medication allocated by randomization. Several variables were recoded into categorical or binary predictors to improve interpretation and analytic power. The rFLACC was recoded as a categorical variable with four levels: 0, 1-3, 4-6, and 7-10. An indicator variable was created to represent the occurrence of either pain medication by the nurse in the PACU or pain medication by the nurse in SDS. The standard pain medication given in the PACU and SDS is oxycodone (0.1 mg/kg) unless

Table 1. Demographic and Clinical Summaries by Medication Allocation (N = 135)

Variable	Fentanyl, n = 65	Hydromorphone, n = 70	Difference			
	Mean (SD)	Mean (SD)	Mean	t	df	P Value
Age (years)	5.38 (2.1)	5.41 (2.3)	0.03	-0.079	133	.938
Variable	n (%)	n (%)	%	χ ²	df	P Value
Gender				0.079	1	.779
Male	30 (46.2)	34 (48.6)	2.4			
Female	35 (53.8)	36 (51.4)	-2.4			
Prior strabismus surgery				2.288	1	.130
First	40 (61.5)	34 (48.6)	-12.9			
Repeat	25 (38.5)	36 (51.4)	12.9			
Pain meds by RN in PACU				0.156	1	.693
Yes	16 (24.6)	15 (21.7)	-2.9			
No	49 (75.4)	54 (78.3)	2.9			
Pain meds by RN in SDS				3.685	1	.055
Yes	18 (27.7)	10 (14.3)	-13.4			
No	47 (72.3)	60 (85.7)	13.4			
Pain meds by RN in PACU and SDS				1.354	1	.245
Yes	29 (44.6)	24 (34.8)	-9.8			
No	36 (55.4)	45 (65.2)	9.8			

PACU, postanesthesia care unit; SDS, same-day surgery; rFLACC, revised Faces, Legs, Activity, Cry, and Consolability; SD, standard deviation; meds, medication.

6 hours has lapsed since the preoperative dose of acetaminophen (15 mg/kg). In this case, acetaminophen is repeated.

As reported in Table 1, age, gender, and prior strabismus surgery were not significantly associated with medication allocation. The recoded binary caregiver variable was also not

significantly associated with medication allocation.

Pain, Anxiety, and PONV Results

As displayed in Table 2, the rFLACC pain score upon SDS arrival was found to be significantly higher (more pain) among patients receiving

Table 2. Postoperative Pain Instrument Assessments by Medication Allocation (N = 135)

Variable	Fentanyl, n = 65	Hydromorphone, n = 70	Difference		
	Mean (SD)	Mean (SD)	Mean	U	P Value
PACU rFLACC					
Arrival	0.86 (1.8)	1.31 (2.7)	-0.45	2191.5	.604*
15 minutes	1.18 (2.1)	0.88 (2.0)	0.30	1797.5	.243*
30 minutes [n = 55]	1.10 (2.2)	0.71 (2.2)	0.39	334.5	.405*
45 minutes [n = 20]	0.64 (1.3)	1.22 (3.3)	-0.58	47.5	.842*
SDS rFLACC					
Arrival	1.45 (2.0)	0.93 (2.2)	0.52	1762.0	.011*
Discharge	0.46 (1.2)	0.56 (1.9)	-0.10	1994.5	.296*

PACU, postanesthesia care unit; SDS, same-day surgery; rFLACC, revised Faces, Legs, Activity, Cry, and Consolability; SD, standard deviation.

*Mann-Whitney U Test.

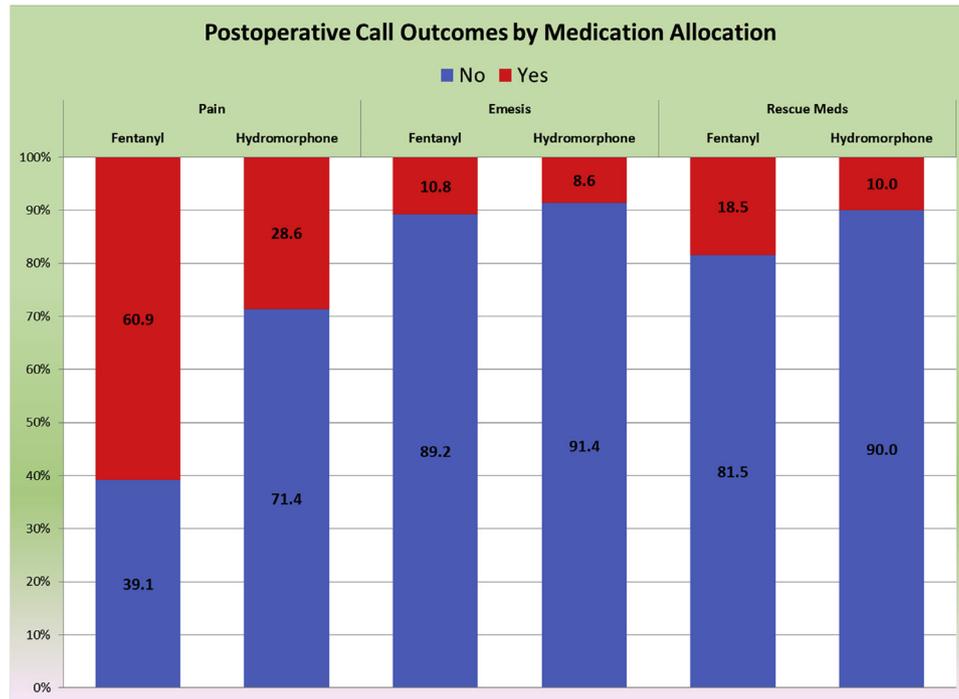


Figure 2. Postoperative call outcomes by medication allocation. Meds, medication. This image is available in color online at www.jopan.org.

fentanyl than among those receiving hydromorphone (1.45 vs 0.93, $U = 1762.0$, $P = .011$).

Postoperative pain medication upon arrival to SDS was reported more often among patients who received fentanyl than among those who received hydromorphone (27.7% vs 14.3%, $\chi^2 = 3.685$, $df = 1$, $P = .055$). The postoperative pain medication given as a standard is oxycodone (0.1 mg/kg). If additional medications were given, they were referred to as rescue medications. These were additional doses of the opiate intraoperatively according to study allocation (fentanyl or hydromorphone).

As shown in Figure 2, postoperative call for the presence of pain was significantly associated with medication allocation. Pain was reported more often among patients who received fentanyl than among those who received hydromorphone (60.9% vs 28.6%, $\chi^2 = 14.212$, $df = 1$, $P < .001$). When stratified by postoperative pain medication administration in the SDS, postoperative call for pain was still reported more often among patients who received fentanyl than among those who received hydromorphone (69.9% vs 28.6%, $\chi^2 = 4.100$, $df = 1$, $P < .043$).

The APAIS subscale surgery-related anxiety was found to be significantly higher among parents whose children had no prior history of strabismus as compared to those with a repeated surgery (5.91 vs 5.00, $U = 1764.5$, $P = .027$). A factorial analysis of variance of surgery-related anxiety was assessed by medication allocation and prior strabismus surgery. The overall model was statistically significant ($F = 5.086$, $P = .002$). None of the subscale APAIS scores were significantly correlated with rFLACC pain scores, either in SDS or upon arrival or discharge in the PACU. This was also true for the presence of postoperative call pain; no significant associations were reported. Neither postoperative emesis nor postoperative call for emesis the day after discharge was significantly associated with medication allocation.

Discussion

This is the first study to compare the effect of two different opioid analgesics used routinely in strabismus surgery on postoperative pain and PONV. The nurses performing assessments of pain within the PACU observed different effects depending on the type of opioid analgesic used intraoperatively. The multimodal approach as far as

delivering a combination of opiates and nonsteroidal anti-inflammatory medications was upheld for both arms of this study, allowing the effect of the opioid analgesic to be assessed. Previous literature cites the importance of the multimodal approach for effective management of postoperative pain and other adverse effects.¹⁴ The findings in this study supported the initial hypothesis that the use of hydromorphone resulted in less pain immediately postoperatively and on the morning after discharge in this sample of patients undergoing strabismus surgery. In addition, the amount of additional pain medication needed postoperatively was higher in patients receiving fentanyl as opposed to those receiving hydromorphone.

However, findings from this study also differ in what has been reported previously regarding the experiences of children undergoing repeated surgery. In this study, parents of children reported a higher level of anxiety with the initial rather than repeated surgery. This is different than what was previously reported by Kain⁴ who found the reverse to be true; repeated surgeries resulted in higher parent and child anxiety. One explanation for this difference could be the initial strabismus surgery for the children in this sample, while not analyzed by the type of analgesic used, could have resulted in what the parent and child perceived as an acceptable level of postoperative pain and resulted in less anxiety upon return for subsequent surgeries. This finding would give credence to empirical findings that initial negative pain experiences result in higher anxiety.² Higher anxiety levels have also been reported to be associated with higher levels of postoperative pain.^{4,15} This finding was not supported in the present study because no correlations were found between anxiety and pain in any point during the hospitalization or after discharge.

Although vomiting is reported to be a common symptom postoperatively in children undergoing strabismus surgery, no significant difference in vomiting was detected by the allocation of pain medication in this study.^{1,11} However, this does not preclude that there was no vomiting; there was just not a significant difference depending on medication allocation. The initial hypothesis that hydromorphone would result in a significant

reduction in postoperative vomiting was not upheld.

Several limitations were noted in the present study. The investigators would have liked to analyze the effect of medication allocation on hospital length of stay. However, during the study, it was found there was significant variation in how nurses scored and interpreted the transition from phase 1 and phase 2 recovery which could have affected discharge times, so this association could not be established. Although a multimodal approach was implemented in this study, previous research regarding pediatric strabismus surgery involved the use of a topical anesthetic such as bupivacaine in the sub-Tenon muscle intraoperatively. Some children in this study received bupivacaine intraoperatively depending on surgeon preference. In a recently published randomized control trial, children who received the bupivacaine injection had a significant reduction in postoperative pain scores with mean scores reduced to 2.8 as opposed to 5.9 on a 10-point scale in the control ($P < .001$). In the study sample, the use of bupivacaine was not analyzed, so this is a known confounder to the results. In addition, the surgical technique was somewhat varied and not analyzed with all the children in the study. Depending on surgeon preference, sometimes, the eye muscle was cut and sometimes simply stretched, and this could have resulted in a further confounding variable for postoperative pain. An additional limitation is that the anesthesiologists who administered the allocated medication were not blinded, which could have resulted in bias.

Conclusion

This is the first study to analyze pain medication allocation in children undergoing strabismus surgery and subsequent effect on postoperative pain and vomiting. Postoperative pain differed between agents. Higher pain ratings were detected among patients receiving fentanyl than among those receiving hydromorphone both postoperatively and the day after discharge. Furthermore, higher use of pain medications was observed among those patients receiving fentanyl than among those receiving hydromorphone. No effect was found between the agents on vomiting. Future research should replicate the study while controlling for known confounders such as the use of topical

anesthetic and surgical technique. Additional studies could also measure the concept of nausea

to assess for differences based on medication allocation.

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