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Effect of IV Acetaminophen Usage on Opioid Requirements, Outcomes and Costs of Care for Postoperative Children in a Pediatric Intensive Care Unit

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OBJECTIVE Children admitted to the ICU are commonly treated with opioids for postoperative pain. We hypothesized that administration of IV acetaminophen in the immediate postoperative period is effective in lowering cumulative opioid use leading to other benefits.

METHODS This was a retrospective chart review of patients admitted to the PICU between December 2016 and April 2019. For each patient, data including demographics, cumulative opioid usage per kilogram, oral or rectal acetaminophen, x-ray findings, hospital costs, and surgical procedure were collected. Cumulative opioid usage was determined by converting all opioids to morphine equivalents (MEs) per kg. Standard descriptive and comparative analyses were conducted using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS A total of 200 patients met inclusion and exclusion criteria (N = 92 in IV acetaminophen group and N = 108 in no IV acetaminophen group). There was no significant difference in ME per kilogram between the groups (0.3 ME/kg in IV acetaminophen group, IQR 0.5 ME/kg versus 0.4 ME/kg in no IV acetaminophen group, IQR 0.5 ME/kg, adjusted p = 0.38). Rate of atelectasis was not significant between the groups (47.8% in IV acetaminophen versus 45.4% in no acetaminophen group, p = 0.28). There was a significant difference in median total hospital costs between the groups ($22,456 in IV acetaminophen group, IQR $18,650 versus $18,552 in no IV acetaminophen group, IQR $13,361, adjusted p = 0.04).

CONCLUSIONS IV acetaminophen in the immediate postoperative period did not lead to a decrease in cumulative opioid usage or rate of atelectasis. IV acetaminophen usage was associated with increase in overall hospital costs per patient.

ABBREVIATIONS CDC, Centers for Disease Control and Prevention; EMR, electronic medical record; ENT, ear, nose, throat; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LOS, length of stay; ME, morphine equivalent; NSAIDs, non-steroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PICU, pediatric intensive care unit; PIM3, Pediatric Index of Mortality 3; PO, oral; PR, rectal; PRISM3, Pediatric Risk of Mortality 3

KEYWORDS acetaminophen; analgesics; critical care; opioid; pediatrics

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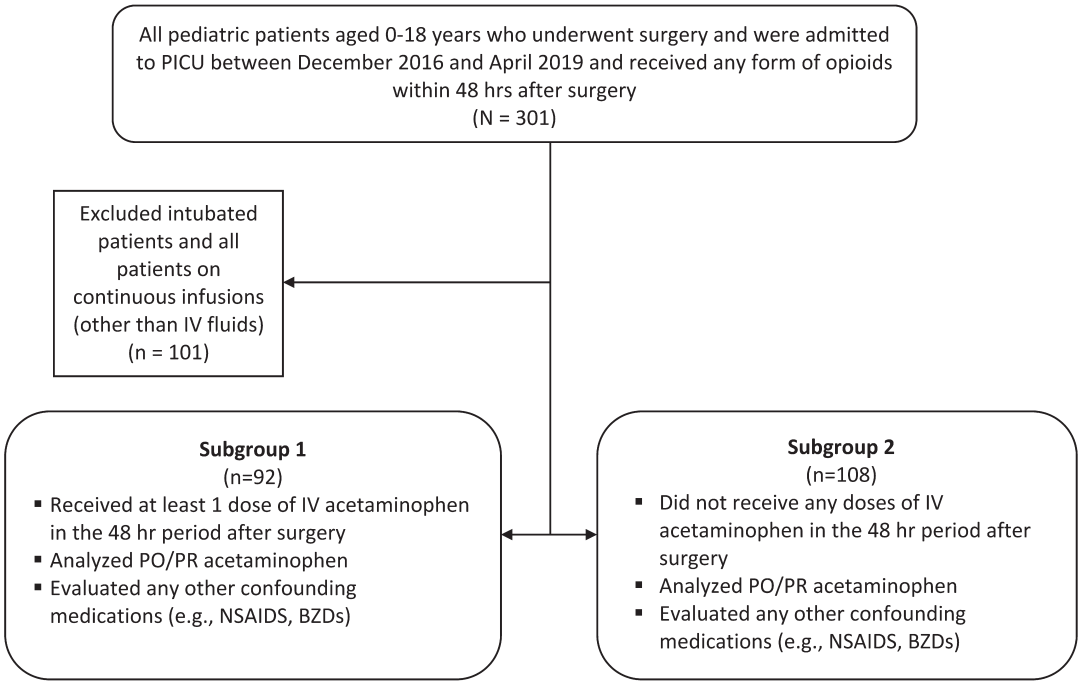
Introduction

Children undergoing common surgical procedures, such as appendectomies, tonsillectomies, and hernia repairs, experience a great amount of pain as they recover from their operation. Pain is the most prevailing postoperative condition in pediatric patients with both short-term and long-term consequences depending on the physical development of the patient.[1] Management of acute postoperative pain is one of the common reasons for admission to a higher level of care including the ICU or step-down/intermediate status. Although treatments have progressed to improve postoperative pain scores, the pediatric population still remains vulnerable.[2] Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, but the most widely used medications are opioids, which include morphine, fentanyl, codeine, hydrocodone, and oxycodone. Unfortunately, opioid therapy is linked with numerous adverse effects such as respiratory depression, atelectasis, dyspepsia, and constipation.[3] Opioids may also aggravate postoperative ileus. The accumulation of side effects may potentially increase the length of hospital stay, and consequently, the total cost to the patient. It is, therefore, essential that researchers seek to find effective analgesics that are not associated with serious adverse effects.

The "opioid crisis," an issue publicized by the CDC, has been a growing problem in the United States as approximately 400,000 individuals have died from an

Figure. Patient selection flowsheet.



BZD, benzodiazepine; NSAIDs, non-steroidal anti-inflammatory drugs; PO, oral; PR, rectal

overdose involving opioids since 1999.[4] Although American communities seem to be saturated with opioids, health centers are facing a shortage. The shortage stems from manufacturing issues as well as pushback from the government to decrease production.[5] In recent years, governmental organizations, including the CDC, have worked with health care providers and health systems to find alternatives to decrease opioid use and increase patient safety. The societal emphasis on the limitation of these drugs is yet another reason for the importance of identifying a more adequate treatment for pain.

NSAIDs are an effective alternative but have their own adverse effects. In the immediate postoperative period, patients may have oliguria/anuria, which may worsen with NSAIDs. Platelet dysfunction and increased risk of bleeding is another reason for their limited use in the immediate postoperative period.[6] Other common side effects of NSAIDs include gastritis, dyspepsia, nausea, and vomiting.[7] Thus, acetaminophen has been recommended by several studies as the most effective alternative to opioids due to the reduction of serious adverse effects. Ceelie et al[8] reported in 2013 that neonates receiving IV acetaminophen as the primary analgesic in a postoperative setting used significantly less opioids than those receiving a continuous morphine infusion. However, although opioid consumption decreased with the use of acetaminophen, pain scores did not significantly change in this study. This finding may have been due to the very specific patient population as the study only encompassed patients younger than 1 year of age and lists external validity as a limitation.[8]

In our study, we assessed the use of IV acetaminophen in the immediate postoperative setting in pediatric patients to determine if IV acetaminophen decreased cumulative opioid use. Our hypothesis was that IV acetaminophen in the immediate postoperative period is effective in lowering cumulative opioid usage leading to other benefits including decreased atelectasis, ICU/hospital LOS, or decreased overall costs.

Materials and Methods

A retrospective chart review was conducted to identify patients who underwent any surgery at the Children's Hospital of Illinois between December 2016 and April 2019. Inclusion criteria for the study was age between 0 and 18 years, admission to the PICU after surgery, and requirement of any amount of opioid medication during the 48-hour postoperative period. Patients were excluded if they were on mechanical ventilation or received sedation or analgesic continuous infusions in the first 48 hours. Patients who satisfied the above criteria were categorized into 2 groups: those who received IV acetaminophen within the 48-hour postoperative period and those who did not receive IV acetaminophen (Figure).

All demographic, disease-specific, and outcome variables were extracted either from the EMRs using health care analytics or database query from virtual PICU systems or pharmacy analytics. Our hospital uses EPIC as EMR with very robust analytics support. Variables that were not amenable for electronic capture were extracted by manual chart review. The variables extracted from the EMR included demographic data including age, sex, race, and the type of procedures. The type of procedure was categorized based on the specialty service such as neurosurgery, cardiothoracic surgery, and other pediatric surgeries, including orthopedic surgeries (e.g., spinal fusions), general surgeries (e.g., chest tube insertions, hemicolectomies), and ENT surgeries (e.g, tonsillectomies). Cumulative opioid doses were tabulated and converted into IV morphine equivalents (MEs) by standard opioid conversion calculations.[9] Morphine equivalents were calculated using opioid conversion factors that were equipotent to 10 mg of IV morphine. Specifically, for these calculations, 10 mg of IV morphine was considered to be equal to 100 mcg of IV fentanyl, 1.5 mg of IV hydromorphone, 30 mg of oral morphine, 20 mg of oral oxycodone, 30 mg of oral hydrocodone, 100 mg of oral tramadol, or 7.5 mg of oral hydromorphone. We do not use codeine at our institution. The number of patients who were on patient-controlled analgesia (PCA) in the 2 groups were counted; cumulative opioid administration through the PCA was included in the overall ME calculations. Similarly, the number of patients who received oral acetaminophen, rectal acetaminophen, benzodiazepines, and NSAIDs as well as the number of patients who were on opioids preoperatively were calculated and compared between the 2 groups. Benzodiazepines were accounted for due to their sedation properties, which may have influenced pain perception. The number of patients who were on any form of supplemental oxygen within the first 48 hours was also extracted from the EMR. Various pain scales including Faces, Legs, Activity, Cry, and Consolability, Pasero Opioid-Induced Scale, CC Pain Observation Tool, FACES, and Numeric Rating Scale were used as appropriate. Presence of atelectasis on chest x-ray was obtained from the formal documentation by the radiologist and was considered to be positive if the radiologist listed atelectasis or collapse of the lung on the report. Pediatric Index of Mortality 3 (PIM3) and Pediatric Risk of Mortality 3 (PRISM3) severity of illness scores were extracted from the Virtual Pediatric Systems database.

Outcome variables compared between the 2 groups included ICU LOS and hospital LOS. We also obtained the total pharmacy cost of medications and total direct cost of hospital care to the patient for the hospital stay. Direct variable pharmacy costs were calculated by using the average wholesale price of medications. Direct fixed costs such as the cost of personnel were not included.

For statistical analysis, we used the groups of IV acetaminophen (yes) and IV acetaminophen (no) as 2 independent variables. The primary outcome variable was MEs divided by weight. We entered 5 independent variables (group, rectal acetaminophen yes/no, use of PCA yes/no, age, and type of procedure) into the multiple regression model. These 5 variables were chosen based on clinical judgment on their effect on the need for opioid analgesia. For this model we categorized age into 3 categories, less than 12 months, 12 to 84 months, and more than 84 months. Similarly, the procedure was categorized into 3 categories: neurosurgery, cardiothoracic surgery, and other surgeries. For sample size calculation, we used the standard rule of linear regression of at least 20 observations per independent variable. Based on this standard we required 140 subjects. To account for 30% missing data/inaccurate data, we determined 192 subjects would need to be included in the study in order to conduct a valid multiple regression analysis.

For statistical analysis, we used Pearson c^2 and Fisher exact test for univariate comparison of categorical variables and Wilcoxon 2-sample test for continuous variables. Data are presented as either mean ± standard deviation or median (IQR) as appropriate. For multivariate analysis, we used a robust regression for continuous outcome variables because normality assumption was not met and used logistic regression for binary outcome variables. Based on the univariate analysis results and clinical judgement, we adjusted for whether the patient had received rectal acetaminophen, PCA, age, and type of procedure for multivariate models. Two-tailed p values were calculated on all tests and p value of less than 0.05 was considered statistically significant. All statistical analysis was conducted on SAS 9.4 (SAS Institute, Inc, Cary, NC).

Results

A total of 200 patients met the inclusion and exclusion criteria during the study (Figure). These patients were categorized into IV acetaminophen group (n = 92) and no IV acetaminophen group (n = 108). Median age of the total study population was 59.5 (IQR 127) months. The median age of the IV acetaminophen group was significantly higher (98.5, IQR 58.3 months) compared with the group that did not receive IV acetaminophen (31.5, IQR 114.5 months), p = 0.001. Only 14.1% (13/92) children in the IV acetaminophen group were younger than 12 months of age compared with 31.5% (34/108) of children in the no IV acetaminophen group. There was no difference in the race or gender between the 2 groups. Overall, 43.5% (87/200) of the study population had cardiac/thoracic surgical procedure, whereas 31.5% (62/200) had a neurosurgical procedure. The number of procedures in each surgery category did not significantly differ between the IV acetaminophen group and the no IV acetaminophen group (p = 0.88).

Table 1. Demographic Comparison of Patients Receiving Opioids With No IV Acetaminophen and Patients Receiving Opioids With IV Acetaminophen in the 48-Hour Postoperative Period

	Total	No IV Acetaminophen (n = 108)	IV Acetaminophen (n = 92)	p value
Age, median (IQR), mo	59.5 (13.5–140.5)	31.5 (8.0–122.5)	98.5 (31.5–158.0)	0.001
Age, n (%), mo				0.002
<12	47 (23.5)	34 (31.5)	13 (14.1)	
12–84	71 (35.5)	40 (37)	31 (33.7)	
>84	82 (41)	34 (31.5)	48 (52.2)	
Race, n (%)				0.633
White	156 (78.8)	87 (80.6)	69 (76.7)	
African American	30 (15.2)	16 (14.8)	14 (15.6)	
Other	12 (6.1)	5 (4.6)	7 (7.8)	
Sex, n (%), male	102 (51)	53 (49.1)	49 (53.3)	0.555
Procedure, n (%)				0.881
Neurosurgery	62 (31)	34 (31.5)	28 (30.4)	
Cardiac/thoracic surgery	87 (43.5)	48 (44.4)	39 (42.4)	
Others	51 (25.6)	26 (24.1)	25 (27.2)	
PO acetaminophen, n (%)	139 (69.5)	75 (69.4)	64 (70)	0.985
PR acetaminophen, n (%)	72 (36)	57 (52.8)	15 (16.3)	<0.001
PCA, n (%)	16 (8)	5 (4.6)	11 (12)	0.057
Preoperative opioids, n (%)	17 (8.5)	6 (5.6)	11 (12)	0.105
PIM3	−6.1 (−6.8 to 4.5)	−6.1 (−6.7 to 4.9)	−6.2 (−6.8 to −0.9)	0.431
PRISM3	1 (0.0–3.0)	1 (0.0–3.0)	1.5 (0.0–3.0)	0.818
BZD use, n (%)	145 (72.5)	31 (28.7)	24 (26.1)	0.680
NSAIDs, n (%)	106 (53)	57 (52.8)	49 (53.3)	0.946

BZD, benzodiazepine; NSAIDs, non-steroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PIM3, Pediatric Index of Mortality 3; PO, oral; PR, rectal; PRISM3, Pediatric Risk of Mortality 3

Similarly, there was no statistical difference in the type of surgery between groups and p values were adjusted to include the category of procedure.

There was also no difference within the 2 groups in the proportion of patients who received oral acetaminophen; however, a significantly higher proportion of patients received rectal acetaminophen in the no IV acetaminophen group compared with the IV acetaminophen group (57/108, 52.8% versus 15/92 16.3%, respectively; p < 0.001). For the IV acetaminophen group, a total of 320 doses of IV acetaminophen were administered among 92 patients. Therefore, each patient in this group received, on average, approximately 3.5 doses of IV acetaminophen in the postoperative period. All doses of acetaminophen were within the therapeutic range, which is approximately 10 to 15 mg/kg. Each acetaminophen dose was administered at approximately 12 mg/kg per dose. A higher proportion (11/92, 12%) of patients in the IV acetaminophen group were on PCA compared with the no IV acetaminophen group (5/108, 4.6%). This difference was not statistically significant (p = 0.057). The 2 groups were also comparable in terms of severity of illness as measured by the PIM3 and PRISM3 scores, the use of benzodiazepines, and NSAIDs use in the first 48 hours after surgery (Table 1).

The number of patients who required supplemental oxygen was comparable between the 2 groups (p = 0.86) as was the percentage of patients who had a diagnosis of atelectasis on chest x-rays within the first 48 hours (p = 0.73). Pain control was also similar with the 2 groups as shown by the percentage of patients who had an average pain score of 2 or less for the first 48-hour postoperative period (p = 0.96). The primary outcome variable of ME per kilogram in the first 48 hours did not show any difference in the 2 groups with a median ME of 0.3 mg/kg (IQR 0.5) in the IV acetaminophen group compared with 0.4 mg/kg (IQR 0.5) in the no IV acetaminophen group (p = 0.598). On univariate analysis, the 2 groups were similar in terms of median ICU LOS and median hospital LOS. Adjusting for type of procedure, use of PCA, use of rectal acetaminophen, and patient age, those who received IV acetaminophen had a significantly longer ICU LOS (median 2.5 days [IQR 1.9]) and hospital LOS (median 4.3 days [IQR 3.6])

Table 2. Outcome Differences Between Patients Receiving Opioids With No IV Acetaminophen and Patients Receiving Opioids With IV Acetaminophen in the 48-Hour Postoperative Period

	Total (N = 200)	No IV Acetaminophen (n = 108)	IV Acetaminophen (n = 92)	p value	
				Unadjusted	Adjusted*
Morphine equivalents, median (IQR), mg/kg	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.3 (0.2–0.6)	0.598	0.389
Atelectasis on CXR within 48 hr, n (%)	46 (46.6)	49 (45.4)	44 (47.8)	0.729	0.289
ICU LOS, median (IQR), days	1.9 (1.1–3.0)	1.4 (1.1–3.0)	2.5 (1.1–3.1)	0.148	0.022
Hospital LOS, median (IQR), days	4.2 (3.1–6.3)	4.1 (2.9–6.1)	4.3 (3.2–6.8)	0.205	0.011
Direct variable pharmacy amount, median (IQR), USD	437.6 (246.3–770.2)	394.7 (211.0–615.8)	503.6 (317.7–895.5)	0.015	0.021
Total cost, median (IQR), USD	19,665 (14,756–29,403)	18,551 (13,652–27,012)	22,455 (15,774–34,423)	0.023	0.041

CXR, chest x-ray; PCA, patient-controlled analgesia; USD, US dollars

* Adjusted for PCA, patient-controlled analgesia, rectal acetaminophen, age, and categories of procedure.

when compared with the group that did not receive IV acetaminophen (respectively: median 1.4 days [IQR 1.9]; 4.1 days [IQR 3.2]) with adjusted p values of 0.021 and 0.011, respectively. Multivariate analysis indicated that patients without IV acetaminophen were discharged from the ICU 12 hours sooner when compared with patients who received IV acetaminophen (p = 0.21, regression coefficient = −0.5). Patients who did not receive IV acetaminophen were discharged from the hospital 24 hours sooner than those who did (p = 0.011, regression coefficient = −1). Analysis of the cost-related outcome variables showed that patients who received IV acetaminophen had a significantly higher median direct pharmacy cost ($503.6 [IQR 577.8] versus $394.7 [IQR 404.8], p = 0.014) as well as total hospital cost during their LOS ($14,493 [IQR 12,413] versus $12,016 [IQR 8665], p = 0.016) when compared with patients who did not receive IV acetaminophen (Table 2). This difference remained significant after adjusting for the confounders described above.

Discussion

In our study, IV acetaminophen in the immediate postoperative period did not lead to a decrease in the cumulative opioid usage. Patients who received IV acetaminophen in this study were older than previously conducted studies. At our institution, IV acetaminophen guidelines during the study period suggest avoiding rectal administration in patients older than 13 years as erratic rectal absorption may diminish the ability to attain pharmacodynamic goals. Interestingly, patients in this study who did not receive IV acetaminophen received more rectal acetaminophen. Therefore, it may be theorized that we were unable to elicit a significant difference as patients in both groups received acetaminophen in one form or another. However, we were unable to identify a significant difference after multivariate regression. Mortality scores are less likely to affect this primary outcome because there was no difference between the 2 groups (Table 1). Our results reinforce similar findings as seen in the study conducted by Hiller et al,[10] which concluded that the administration of IV acetaminophen did not decrease postoperative opioid consumption. In contrast, the study conducted by Ceelie et al[8] demonstrated a decline in opioid consumption in neonates who received IV acetaminophen. This variation might be due to a difference in study populations or therapeutic interventions. In this particular study, subjects were younger than 1 year of age and did not receive rectal acetaminophen. Administration of acetaminophen by any route may diminish the need for opioids.

Median ICU and hospital LOS were both greater for patients in the IV acetaminophen group than the no IV acetaminophen group. These outcomes contradicted our hypothesis that IV acetaminophen would decrease ICU and hospital LOS due to a decrease in opioid related adverse effects associated with decreased opioid use. A possible explanation is that patients administered IV acetaminophen may have undergone more complex surgical procedures than their counterparts in the no IV acetaminophen group. Our classification system was broad and did not account for the complexities of each individual procedure. For example, in the neurosurgery category, a patient undergoing a ventriculoperitoneal shunt placement might not have received IV acetaminophen, but a patient undergoing a tumor resection might have. Therefore, more involved procedures in each category might have included an administration of IV acetaminophen and a longer ICU and hospital LOS due to their complexities. More specifically, a study by Baichoo et al[11] had a similar

conclusion that the addition of IV acetaminophen may not decrease LOS in pediatric patients admitted for sickle cell pain crisis.

In our study, there was also no significant rate of atelectasis between the 2 groups. This finding is in contrast to our hypothesis that a decrease in the cumulative opioid usage would decrease the risk of adverse effects such as lung collapse. Despite the reported adverse effects of IV acetaminophen being rare in clinical practice, premarketing trials of the medication reported that a common adverse effect was atelectasis in greater than or equal to 5% of the total 355 pediatric subjects.[12] To our knowledge, no other studies assessing rates of atelectasis in children receiving IV acetaminophen in postoperative period exist in the literature. There have been other associations between IV acetaminophen and serious adverse effects such as hypotension and cardiac arrest. A rapid infusion of IV acetaminophen may cause a significant decrease in systolic blood pressure.[13] To achieve a more detailed explanation, more studies should include data on specific adverse effects in the analysis of acetaminophen and other analgesics.

The total costs for patients in the IV acetaminophen group were significantly higher than those in the no IV acetaminophen group. This outcome contradicted our hypothesis that a decrease in cumulative opioid consumption would decrease total costs. Our hypothesis was based on previous studies including Subramanyam et al[14] in which the average total cost for the IV acetaminophen group was significantly less than the no IV acetaminophen group due to reduced adverse effects. Although IV acetaminophen can be considered expensive, it is observed that the cost of hospital stay outweighs the cost of this medication. However, because there was a significant difference in the length of hospital stay between the 2 groups, the total cost was higher in the IV acetaminophen group due to the additive effects of this medication and hospital LOS costs.

This is one of the first studies focusing on the role of IV acetaminophen in postoperative children admitted to ICU and included a population of pediatric patients undergoing a variety of procedures. However, our study has several limitations. Our study only encompassed medication usage for the first 48 hours of the postoperative period. This was due to the feasibility of the study and because the first 48 hours is when a patient presents with pain after a surgical procedure. It is possible that patients in either group received IV acetaminophen after this period for other reasons including fever. Our methods also included a broad categorization of procedures. There might have been a difference between the 2 groups on subcategorization that may explain why patients in the IV acetaminophen group had a longer LOS and higher total cost. Finally, the retrospective nature of the study can limit the findings. Additional prospective studies and randomized control trials encompassing concomitant opioid use, adverse effects, and costs are needed to understand the role of IV acetaminophen in controlling pediatric postoperative pain.

Conclusions

IV acetaminophen in the immediate postoperative period did not lead to a decrease in the cumulative opioid usage or the rate of atelectasis in children. IV acetaminophen usage was associated with increase in overall hospital costs per patient. Future prospective studies are needed.

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Ethical Approval and Informed Consent Given the nature of the study, it was exempt from committee approval and was exempt from informed consent.

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