Costs and Outcomes Associated with the Administration of Intravenous Acetaminophen in Neonates after Esophageal Atresia and Tracheoesophageal Fistula Repair

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Table 1 is available in the Supplementary Files section.

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Abstract

Objective:
The primary objective was to examine the outcomes and costs associated with the use of intravenous acetaminophen (IV APAP) in combination with opioids versus opioids alone as a pain management strategy after neonatal esophageal atresia (EA) and tracheoesophageal fistula (TEF) repair.

Study Design:
Data from the Pediatric Health Information System was used to examine 1,137 hospitalizations for EA/TEF repair from 2015 to 2018. Neonates administered opioids only, or IV APAP in combination with opioids as pain management were included.

Result:
Neonates receiving IV APAP experienced a longer median length-of-stay (LOS), but a significantly lower mortality rate, a decreased mean daily cost, and reduced opioid use compared to neonates given only opioids. There were no significant differences in pharmacy and total costs.

Conclusion:
Our findings suggest the use of IV APAP alongside opioids in EA/TEF repair is associated with reduced mortality and opioid use, as well as longer LOS.
Introduction

Esophageal atresia (EA) is a congenital malformation manifesting as an incomplete development of the esophagus, impacting approximately 1 in 2,500-4,500 births worldwide. Tracheoesophageal fistula (TEF) is a related condition where the neonatal trachea is connected to the esophagus, occurring in about 90% of cases of EA. Both conditions are caused by an incomplete separation or development of the foregut in utero. Potential surgical repair options include two similarly performed procedures, an open thoracotomy or a video-assisted thoracoscopic surgery, followed by neonatal intensive care with variable length-of-stay (LOS) depending on birthweight, the presence of other congenital anomalies, and post-operative complications. Neonatal care following repair requires significant healthcare resources, with a median post-operative LOS of 23 days and a large interquartile range of 13 to 47 days. While only the above two procedures are generally considered for repair, perioperative management and outcomes of EA and TEF repair vary greatly.

One contributor to this variation is the management of peri-operative neonatal pain. The evaluation and regulation of associated procedural pain are important, as both inadequate pain control and prolonged opioid use have been shown to be associated with worse neurodevelopmental outcomes. To reduce neonatal exposure to opioids while adequately addressing pain, opioid-sparing alternatives, such as acetaminophen, are utilized in conjunction with opioids and have been demonstrated to be effective post-procedural non-opioid analgesics in neonates. Over the last decade, the intravenous (IV) formulation of acetaminophen (APAP) has gained popularity as a safe and effective first-line analgesic in the neonatal intensive care unit and is especially useful in peri-operative settings where oral agents are contraindicated. IV APAP in combination with morphine has been shown to lower the cumulative morphine dose by
66% in neonates undergoing major surgery compared to morphine alone. Through a reduction of morphine consumption, IV APAP has been associated with shorter LOS in pediatric patients undergoing posterior spinal fusion. One advantage to lowering the cumulative opioid dose is to limit the known adverse effects, most commonly sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression, which can have a significant impact on total post-operative costs. Opioids have been shown to increase both median LOS by 10.4% and median total hospital costs by 7.4% in surgical hospitalizations.

The advantages of IV APAP do not come without a cost. Ofirmev® is the patented IV APAP formulation used in the US. Due to its ability to be administered intravenously, Ofirmev® commands a mean wholesale unit price of $0.029 per milligram (mg), nearly 17 times greater than the mean cost of $0.002 per mg of oral APAP. A recent study performed using data from 34 US pediatric hospitals showed that IV APAP is now given in 1 in 8 pediatric hospitalizations. Within that same cohort of hospitals, the total associated pharmacologic costs increased from $2.7 million in 2010 to $18.1 million in 2017. However, to our knowledge, no studies have examined the use of IV APAP in the neonatal intensive care unit population undergoing EA/TEF repair in terms of costs, minimizing cumulative opioid exposure, or reducing LOS. Given the prolonged hospitalizations, in addition to variable LOS and outcomes associated with EA/TEF, we sought to evaluate the use of IV APAP’s impact on the costs and outcomes in EA/TEF repair.

**Methods**

This study was approved by the institutional review board at the Children’s Hospital Los Angeles (IRB ID STUDY CHLA-20-00182). This retrospective study utilized data from the Pediatric Health Information System, a database that collects admission, diagnostic and treatment data from 47 freestanding children’s hospitals in the United States. For this analysis,
we used data from the 1,137 neonates who underwent EA/TEF repair in participating hospitals from October 2015 to September 2018. Diagnoses included atresia of the esophagus with tracheoesophageal fistula, atresia of the esophagus without fistula, and congenital tracheoesophageal fistula without atresia. Only patients who were given opioids or opioids and IV APAP during their hospitalization were included. We excluded 36 patients who were not given opioids.

Quantitative patient outcomes studied included birthweight, gestational age, age at admittance, days on total parental nutrition (TPN), cumulative opioid dosage, mean daily opioid dosage, cumulative IV APAP dosage, number of comorbidities, and costs. Costs included the total adjusted estimated costs, which standardizes cost accounting from the hospital perspective based on geographic region. Costs were categorized into clinical, imaging, lab, pharmacy, supply, and other. All costs were converted to 2023 U.S. dollars using the U.S. Medical Consumer Price Index. The categorical patient characteristics evaluated were gender, ethnicity, race, and payer type. We examined the categorical patient outcomes of diagnosis, discharge type, and mortality, as well as the presence of flags for extracorporeal membrane oxygenation, infections, medical complications, surgical complications, premature and neonatal, and technology dependence. The sole categorical hospital characteristic analyzed was the region. P-values for continuous characteristics were calculated using the two-tailed Mann–Whitney U test, while p-values for categorical variables were obtained with chi-squared tests.

**Results**

A total of 1,101 neonates were included in the study, with 537 neonates receiving only opioids, and 564 neonates receiving both opioids and IV APAP. The patient’s ages ranged from 0 to 28 days at the time of admittance. The opioids administered included Alfentanil, Fentanyl,
Hydromorphone, Meperidine, Methadone, Morphine, Nalbuphine, Oxycodone, Remifentanil, Sufentanil, and narcotic analgesic combinations. The cohort consisted of predominantly white (67.7%), non-Hispanic or Latino (74.1%) males (58.3%). 90.3% of patients were diagnosed with atresia of the esophagus with tracheoesophageal fistula. The IV APAP group received a mean cumulative dosage of 2,974 mg of IV APAP during their hospitalization. The median day of the first administration of IV APAP was 2 days after admittance. Neonates had a median LOS of 38.0 days and averaged 41.9 days on TPN, with a 9.4% mortality rate. The patients had 34.2 comorbidities on average. 8.5 of those comorbidities were congenital, and 2.4 were congenital cardiac comorbidities. They were born prematurely at a mean gestational age of 36.0 weeks with a low mean birth rate of 2,420 grams. Most patients (69.2%) were routinely discharged home, while 15.1% were discharged to home under the care of an organized home health service organization in anticipation of covered skilled care.

The median LOS in the group receiving only opioids was 32.0 days, compared to the 47.5 days in the group receiving opioids and IV APAP (p<0.001) (Table 1). The group receiving IV APAP had a mean 58.7 days on TPN, higher than the 24.4 days in the opioids only group (p<0.001) (Table 1). Neonates administered IV APAP were routinely discharged home at a rate of 76.6% compared to 61.5% in those given opioids only (p=0.03) (Table 1). The mortality rate in patients given IV APAP was 4.1%, significantly lower than the 15.1% experienced by patients that did not receive IV APAP (p=0.03) (Table 1).

The neonates in the IV APAP group were born at an older gestational age of 36.3 weeks as opposed to 35.7 weeks in the opioids only group (p=0.04) (Table 1). The IV APAP group also had a significantly lower number of Black patients (44 vs 69) and a higher number of Pacific Islander (6 vs 0) patients in the cohort (p=0.007) (Table 1). The IV APAP group had higher
mean number of comorbidities at 35.7 compared to 32.6 (p=0.003) (Table 1). There were no statistically significant differences between the groups’ congenital or cardiac comorbidities, or birthweight. The IV APAP group experienced more medical complications, surgical complications, and infections (p=.02, p<0.001, and p<0.001, respectively) (Table 1). Opioid use was decreased in the IV APAP group which received a mean cumulative dose of 235.2 mg of opioids, less than the 262.9 mg mean in those that did not receive IV APAP (p=0.007) (Table 1). Mean daily opioid use also decreased in the IV APAP group (2.6 mg vs 2.8 mg) (p<0.001) (Table 1).

Despite a longer median LOS, mean daily costs were decreased in the IV APAP group ($8 233 vs. $28 150) (p<0.001) (Table 1). The opioids only group also had a higher mean adjusted total cost of $284 516 versus $274 827 in the IV APAP group (p=0.37) (Table 1). The opioids only group’s hospitalizations resulted in a mean $21 794 pharmacy cost, higher than the $19 175 cost incurred by the neonates receiving IV APAP (p=0.79) (Table 1).

**Discussion**

The results of this retrospective study suggest the use of IV APAP in neonates undergoing EA/TEF repair is correlated with a longer LOS but decreased daily costs and mortality. Our study also shows a significant decrease in the use of opioids with the administration of IV APAP. Our results differ somewhat from existing literature, which indicates the use of IV APAP is effective in reducing overall costs in pediatric hospitalizations when used in combination with opioids, due to a reduced LOS and minimal adverse effects. IV APAP’s association with an increased LOS in our study could be due to a higher likelihood of administration in patients with a greater severity of illness and care intensity. In a national review
of IV APAP use in pediatric patients, the treatment has been associated with a longer LOS, increased mortality rates, and higher proportions of ICU admissions and positive pressure ventilation. The significantly greater number of infections and medical and surgical complications seen in the IV APAP group would support this rationale. However, we would also expect a greater number of comorbidities, lower birthweights and gestational ages, as well as higher mortality rates, none of which were present in our study. In fact, the substantial decrease in the mortality rate seen in patients given IV APAP opposes this potential explanation.

The decrease in mortality rate of over 11% in patients who received IV APAP may be explained by the greater opportunity to be administered the analgesic during additional days spent hospitalized. The neonates who did not receive IV APAP before they expired had a median LOS of 7.0 days, much shorter than the median 76.0 day LOS before death in those who did receive the analgesic. Moreover, 46 of the 81 expired patients in the opioids only group died within 10 days of admission. Only two of the 23 in the IV APAP group expired within this timeframe.

With a longer hospitalization, clinicians have a greater opportunity to utilize IV APAP after the escalation of opioids. The neonates who expired shortly after birth had a reduced opportunity to receive IV APAP, potentially inflating the mortality rate in the opioids only group. The longer duration to potentially be administered IV APAP could also provide an explanation for the longer median LOS in the IV APAP group. However, IV APAP is commonly administered early by clinicians before opioids in an effort to reduce subsequent opioid requirements. In fact, the median day of first administration of IV APAP in the neonates who expired was 4.0 days after admittance, only slightly higher than overall median of 2.0 days. It is likely the greater number of infections and medical and surgical complications had a larger impact on the increased LOS than the timing of IV APAP.
While IV APAP was not correlated with a significant decrease in overall hospital costs, the IV APAP group incurred mean daily costs that were less than a third of the opioids only group’s. This may be explained by a decrease in daily costs in longer hospitalizations. Studies have shown that shorter stays account for higher per-day costs, and mean daily costs will gradually decline as the LOS increases.\textsuperscript{16,17} The lack of a significant decrease in overall costs suggests that IV APAP’s association with a lower mean daily cost could be partly a result of longer LOS. The absence of a significant difference in pharmacy costs indicates that the price of IV APAP itself is not increasing the total costs of hospitalization.

\textit{Limitations}

Our study does not adjust for confounding factors that may have an impact on results. IV APAP may be more likely to be administered in more complex cases of EA/TEF, patients with other congenital anomalies, or cases with post-operative complications. In these instances, the longer LOS and days on TPN may be attributed to the disease severity rather than the administration of IV APAP. The significantly greater rate of infections and medical and surgical complications in the IV APAP group could contribute to the longer LOS.

Our dataset did not provide certain data that would be beneficial for further comparison of these cohorts. For example, we were unable to determine if the EA/TEF repair was completed by an open thoracotomy or a video-assisted thoracoscopic surgery. Thoracoscopy surgery has been shown to result in shorter LOS in addition to faster extubations and times to oral feeding.\textsuperscript{18} As another example, to determine each patient’s total days on TPN, we assumed TPN was administered every day between the first and last dose due to a lack of more granular information, thus excluding the possibility that some neonates were on and off TPN during their
stay. Pain scores, esophageal atresia gap length and the date of surgery could also impact outcomes but were not available in our dataset.

Another limitation is that our study is unable to account for the differences in long-term outcomes associated with the two pain management strategies. For example, morphine exposure has been associated with impaired cerebellar growth in the neonatal period and worse neurodevelopmental outcomes in early childhood. The study does not account for the costs associated with discharges to other facilities or varying health outcomes after discharge. Some patients from the study were discharged to intermediate care facilities, designated cancer centers, children’s hospitals, general hospitals for inpatient care, long-term care hospitals, and hospice facilities. Other patients were discharged home under the care of an organized home health service organization in anticipation of covered skilled care. Further costs associated with this continued care were not incorporated into the study due to the limitations of the database.

Conclusion

The findings of our analysis show that the use of IV APAP in addition to opioids in our cohort of neonates undergoing EA/TEF repair is correlated with prolonged LOS but substantially improved mortality, as well as decreased mean daily costs and opioid use. Given there is no association with increased pharmacy or total costs, IV APAP may be a cost-effective pain management adjunctive to opioids and provide a mortality benefit. Future research on the use of IV APAP in this population should incorporate more granular data on the surgery, potential comorbidities, long-term health outcomes, and associated costs.

Competing Interests: The authors declare no competing financial interests.
References


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Supplementary Files

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- Table1.pdf