Antifibrinolytic Use and Blood Transfusions in Pediatric Scoliosis Surgeries Performed at US Children's Hospitals

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Study Design: Retrospective cohort study using the Pediatric Health Information Systems database.

Objective: To determine the association between antifibrinolytic use and red cell transfusions in spinal fusion operations performed at 37 US Children's Hospitals.

Summary of Background Data: Evidence from randomized clinical trials and systematic reviews suggests that antifibrinolytic therapy can significantly reduce blood loss in children undergoing scoliosis surgery; however, the effectiveness of these agents as used in surgeries performed at US children's has not been studied.

Materials and Methods: We included children aged 0–18 years with diagnoses indicating adolescent idiopathic scoliosis (AIS) or neuromuscular scoliosis (NMS) for whom a spinal fusion procedure was performed between January 1, 2006 and September 30, 2009. Patients with malignancy, trauma, coagulation disorders, or for whom a cell salvage device was employed were excluded. Multilevel logistic regression was used to determine associations between ϵ-aminocaproic acid (EACA), tranexamic acid (TXA), and aprotinin (APR) use and blood transfusions, controlling for patient and surgery characteristics.

Results: Cohorts consisted of 2722 AIS and 1547 NMS procedures. Antifibrinolytic use varied across hospitals (AIS 3.3%, interquartile range, 0%–42%; NMS 12 interquartile range, 0%–46%), and was significantly associated with NMS, posterior fusion, number of vertebrae fused. Overall, 15% of children received EACA, 7% TXA, and 2% APR. The median hospital-specific rate of red cell transfusions was 24% for AIS and 43% for NMS. In AIS operations, EACA use, but not TXA use, was associated with significantly lower odds of transfusion (odds ratio, 0.42; $P < 0.001$ vs. odds ratio, 1.0; $P = 0.8$). In NMS operations, neither EACA nor TXA use was associated with a decrease in odds of red cell transfusions.

Conclusions: The effectiveness of antifibrinolytics as used outside of clinical trials is unclear and should continue to be explored. Future prospective research is needed to evaluate which administration protocols will most benefit patients, as well as to determine the comparative effectiveness of these drugs in the context of other blood conservation strategies.

Key Words: spinal fusion, adolescent idiopathic scoliosis, neuromuscular scoliosis, blood transfusion, blood conservation, antifibrinolytic therapy, practice variation

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Surgeries to correct moderate to severe scoliosis are often lengthy procedures, involving insertion of extensive devices and substantial blood loss. Massive hemorrhage (50%–100% of total blood volume) most commonly occurs in children with scoliosis secondary to neuromuscular disease; but even otherwise healthy children with idiopathic scoliosis can lose up to half of total blood volume during their operations.[1–3] Factors such as the number of vertebrae fused, surgical approach, patient body weight, neuromuscular disease, and even preoperative donation of autologous blood have all been associated with the risk of transfusion.[3] Despite common blood conservation strategies such as use of local fibrin sealants, patient positioning to lower intra-abdominal pressure, normovolemic hemodilution, and controlled hypotension,[4–6] greater than half of all patients require transfusion of allogenic or autologous red blood cells. Although intraoperative use of blood products can be lifesaving, transfusion of any blood product (donor directed, allogenic, or cell salvage) can lead to additional health care costs and greater risk of complications such as

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dilutional coagulopathy, pulmonary edema, and surgical site infection.[7–9]

Studies in the pediatric orthopedic literature, including several randomized controlled trials, suggest that the use of systemic fibrin inhibitors (antifibrinolytics) may be a safe and cost-effective method for reducing blood transfusions in pediatric scoliosis surgeries.[10–14] Lysine analogue drugs such as ϵ-aminocaproic acid (EACA), tranexamic acid (TXA), and the now Food and Drug Administration–restricted trypsin inhibitor, aprotinin (APR), have been shown to reduce blood loss volume and transfusion volumes for operations both in children with neuromuscular scoliosis (NMS) and in healthy children with adolescent idiopathic scoliosis (AIS).[15,16] Current practice for the use of these agents by orthopedic surgeons in US Children's Hospitals has not been investigated, and the effectiveness of systemic antifibrinolytics as used in nonstudy settings is unknown.

The objective of this study was to describe the use of EACA, TXA, and APR in children's hospitals and determine the association between antifibrinolytic use and noncell salvage blood transfusion procedures in a broad sample of children undergoing spinal surgery for NMS or AIS.

MATERIALS AND METHODS

Study Design and Setting

We performed a retrospective cohort study using the Pediatric Health Information Systems (PHIS) database. PHIS contains detailed hospital administrative and billing data from 43 freestanding children's hospitals affiliated with the Children's Hospital Association (CHA). Contributing hospitals are located in 17 of the 20 major metropolitan areas in the United States, and collectively perform an estimated 40% of all spinal surgeries in US children annually (hcupnet.ahrq.gov 2009 discharge report). PHIS data include: patient demographics; admission, surgery, and discharge date; insurance type; primary and secondary diagnoses and procedures; and line item charges, including daily pharmacy charge data. To make charge-level data comparable across hospitals, PHIS utilizes Clinical Transaction Codes (CTC) to map each hospital's charge codes (eg, Current Procedural Terminology codes) to a common classification system. The CTC system is owned and managed by Thomson Reuters Healthcare, the data processing partner. Oversight of PHIS data quality and accuracy is a joint effort between CHA, Thomson Reuters, and the participating hospitals.[17]

Subjects

We included all children aged 0–18 years discharged from one of 43 PHIS hospitals from January 1, 2006 to September 30, 2009 with an International Disease Classification Clinical Modification (ICD9-CM) procedure code for spinal fusion procedure and diagnostic code indicating scoliosis, kyphoscoliosis, or congenital curvature of the spine. We excluded patients with diagnoses indicating malignancy, trauma, or coagulation disorders, as well as patients with multiple concurrent procedures such as shunt placements or abdominal surgeries. For cases in which cell salvage equipment was used, it was not possible to differentiate transfusion of autotransufused blood only from transfusion of both autotransfused and allogenic blood. Therefore, we excluded all procedure records in which a billing CTC code for cell salvage equipment was identified.

We used a previously validated ICD9-CM algorithm to identify all patients with primary (spinal muscular atrophy, Duchene muscular dystrophy) or secondary (cerebral palsy) NMS.[18] Among children without NMS, we then selected a cohort of children with AIS by excluding all children with chronic comorbidities including genetic disorders, such a neurofibromatosis, dependence on medical technologies,[19] diagnoses indicating musculoskeletal anomalies (hemivertebrea, Klippel Fiel), or who were aged less than 10 years at the time of their initial surgery (indicating early progressive idiopathic disease as opposed to AIS).

Exposures

We examined the daily pharmacy records to identify CTC billing codes indicating the administration of EACA, TXA, and APR on the day of surgery. Because Current Procedural Terminology codes are not recorded in PHIS, we used ICD9-CM procedure codes to categorize each surgery as posterior (81.05, 81.07, 81.35, 81.37), anterior (81.04, 81.06, 81.34, 81.36), or posterior/anterior (81.08, 81.61, 81.38), and to identify the number of vertebrae that were fused during the operation (81.62: 2–3 vertebrae, 81.63: 4–8 vertebrae, 81.64: ≥ 9 vertebrae).

Outcomes

Blood transfusions were similarly identified using ICD9-CM procedure codes for red cell transfusions (99.0-99.04, 99.09), and were categorized as a binary (any transfusion vs. no transfusion) variable. As some hospital codes did not specify whether transfused blood was directed donor versus allogenic, all red cell transfusion codes were included.

ICD9-CM codes and billing CTC codes used for the cases, exposure, and outcomes definitions can be requested from the corresponding author.

Statistical Analysis

We described the patient characteristics, surgery characteristics, and rates of antifibrinolytic use and blood transfusions using means and percents. We then determined relationships between patient and surgery characteristics and exposure and outcome variables using univariable linear and logistic regression models.

Multivariable Analysis

To determine the relationship between antifibrinolytic use and noncell salvage blood transfusion procedures, we performed multilevel logistic regression controlling for factors that were significantly associated with antifibrinolytic use or significantly associated with blood transfusions in univariable analyses. Other covariates were

retained in the models if: (1) they were associated with the outcome with a $P < 0.05$; (2) inclusion altered the estimated effects of other covariates by $\geq 10\%$; or (3) inclusion improved model fit based on likelihood ratio tests. All analyses were performed in the AIS and NMS cohorts separately.

Estimating Treatment Effects

Using logistic regression and accommodating the clustering of patients within hospitals, we estimated marginal probabilities of receiving a blood transfusion among the treated and untreated patients. The differences in these probabilities can be interpreted as the average treatment effect for antifibrinolytic use in patients with similar characteristics undergoing similar surgeries, and under the assumption that there is no residual confounding by unmeasured factors.[20]

Sample Size

Given a projected sample size of 1500 surgeries and baseline odds of transfusion of 0.4 from preliminary data, the minimum detectable change in odds with a $P < 0.05$ and β of 0.90 would be 0.3 [corresponding to an odds ratio (OR) of 0.7]. A change of this magnitude would be considered a clinically significant difference in rates of transfusion.

All data management and analyses were conducted using Stata12.0 (Stata Corp, College Station, TX).

Our study was considered not to constitute human subjects research by the Children's Hospital of Philadelphia Institutional Review Board according to 45 CFR 46.101(b4), as the participants in PHIS are not readily identifiable. Data use agreement between the CHA and Children's Hospital of Philadelphia addresses HIPAA and participant privacy requirements.

RESULTS

Patient and Surgery Characteristics

Of the initial 11,621 surgeries, 5922 (50%) were excluded because of the use of cell salvage equipment in the operating room. As compared with the noncell salvage cohort, those in the excluded cell salvage group were

TABLE 1. Patient and Surgery Characteristics of the Full Cohort, Antifibrinolytic Treated, and Untreated Groups After Exclusion of Surgeries That Used Cell Salvage Equipment in the Operating Room

Characteristic	Full Cohort	Treated	Untreated
AIS	2722	585 (22)	2121
Discharge year [n (%)]*			
2006	644 (24)	57 (10)	587 (27)
2007	733 (27)	118 (20)	615 (29)
2008	786 (29)	221 (38)	565 (26)
2009	559 (20)	190 (32)	369 (17)
Female [n (%)]	2134 (78)	446 (76)	1688 (79)
Age [mean (SD)]	15 (2)	15 (2)	15 (2)
Surgical approach*			
Posterior only	2258 (83)	468 (80)	1790 (84)
Any anterior	448 (17)	117 (20)	331 (16)
Vertebrae fused [n (%)]*			
2–3	208 (8)	60 (10)	148 (7)
4–8	636 (24)	129 (22)	507 (24)
≥ 9	1878 (69)	397 (68)	1481 (69)
NMS	1547	444 (29)	1103
Discharge year [n (%)]*			
2006	360 (23)	66 (15)	294 (27)
2007	407 (26)	88 (20)	319 (29)
2008	464 (30)	167 (38)	297 (27)
2009	316 (20)	123 (28)	193 (18)
Female [n (%)]	785 (51)	224 (50)	561 (51)
Age [mean (SD)]	12.7 (3.8)	13.1 (4.0)	12.5 (3.4)
Surgical approach [n (%)]			
Posterior only	1100 (72)	327 (74)	773 (72)
Any anterior	425 (28)	117 (26)	308 (28)
Vertebrae fused [n (%)]*			
2–3	191 (12)	42 (9)	149 (14)
4–8	234 (15)	54 (12)	180 (17)
≥ 9	1122 (73)	348 (78)	774 (70)
Cerebral palsy [n (%)]*	536 (35)	167 (38)	369 (33)
Spina bifida [n (%)]	196 (13)	46 (10)	150 (14)
Spinal muscular atrophy [n (%)]	60 (4)	18 (4)	42 (4)
Muscular dystrophy [n (%)]	122 (8)	40 (9)	82 (7)
Technology dependent† [n (%)]*	554 (36)	169 (38)	385 (35)

*Significant difference between treated and untreated groups with $P < 0.01$.
†Gastrostomy tube, intestinal ostomy, tracheostomy, or ventriculoperitoneal shunt.
AIS indicates adolescent idiopathic scoliosis; NMS, neuromuscular scoliosis.

significantly more likely to be older (OR, 1.1; $P < 0.001$), have surgeries involving a posterior approach (OR, 1.4; $P < 0.001$), and have at least 9 vertebral levels fused (OR, 1.3; $P < 0.001$). Cell salvage patients were also more likely to have diagnoses indicating cerebral palsy (OR, 1.2; $P = 0.02$) or muscular dystrophy (OR, 1.4; $P < 0.008$).

The final study cohort consisted of 2722 children with AIS and 1547 children with NMS. Characteristics of the full cohort, treated patients, and controls, are shown in Table 1. In both the AIS and NMS cohorts, the proportion of children in the treated group increased over time. Overall, children treated with antifibrinolytics were less likely to have a procedure with an anterior approach and more likely to be female, or have ≥ 9 vertebrae fused. For NMS operations, children in the treatment group were more likely to have a diagnosis of cerebral palsy and/or technology dependence.

Antifibrinolytic Use and Blood Transfusions Across Hospitals

Antifibrinolytics were used in a total of 586 (22%) AIS procedures and 444 (29%) NMS procedures. This rate varied broadly across hospitals (Fig. 1). EACA was the most frequently used drug (15%), followed by TXA (7%). APR use was relatively rare (2.2%) and not observed after 2007. The median hospital-specific red cell transfusion rate was 24% (interquartile range, 5%–44%) for children with AIS and 43% (interquartile range, 14%–63%) for children with NMS. Between 2006 and 2009, use of any antifibrinolytic drug increased from 8% to 35% for AIS procedures, and from 18% to 39% for NMS procedures, whereas the rate of blood transfusion procedures did not change significantly (Fig. 2).

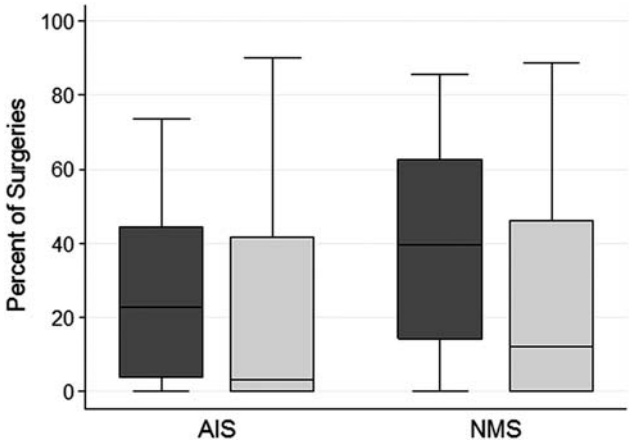

FIGURE 1. Distribution of hospital-specific rates of transfusion procedures (dark-gray boxes) and antifibrinolytic use (light-gray boxes) across 37 children's hospitals from 2006 to 2009. Boxes represent the 25th percentile (lower bound), median (line), and 75th percentile (upper bound) of hospital rates. Spikes and caps depict the 95% confidence intervals of the point estimates for median rates of transfusion and antifbrinolytic use. AIS indicates adolescent idiopathic scoliosis; NMS, neuromuscular scoliosis.

Across hospitals, rates of antifibrinolytic use were not correlated with unadjusted mean transfusion rates. In univariable analyses for AIS, odds of transfusion was significantly associated with female sex (OR, 1.4; $P = 0.01$) and having ≥ 9 vertebrae fused (OR, 2.2; $P < 0.001$). For NMS, transfusions were associated with the number of vertebrae fused (OR, 2.5; $P < 0.001$), age (OR, 1.1; $P < 0.001$), and having diagnoses of cerebral palsy (OR, 1.4; $P = 0.01$) or muscular dystrophy (OR, 2.0; $P = 0.005$). Diagnoses of spina bifida or spinal muscular atrophy were not associated with greater odds of transfusion.

Antifibrinolytic Use and Transfusions

AIS

Given the small number of AIS patients who received APR, all AIS patients who received this drug were excluded from the final analyses. After controlling for sex, age, approach, vertebrae fused, and discharge year, EACA use was associated with a significant reduction in odds of transfusion (OR, 0.42; $P < 0.001$; Table 2). The associations between transfusions and female sex (OR, 1.4; $P = 0.01$), and fusion of ≥ 9 vertebrae (OR, 2.4; $P < 0.001$) also remained significant. The reduction in probability of transfusion for patients in the treated versus untreated groups was 13 percentage points (95% confidence interval, of 8–18 percentage point reduction), corresponding to a number needed to treat between 8 and 13 children (Fig. 3). We found no statistically significant associations between TXA use and transfusions (OR, 1.0; $P = 0.8$; Table 2).

NMS

After adjusting for patient and surgery characteristics, odds of transfusion were significantly greater in children having ≥ 9 vertebrae fused (OR, 2.2; $P < 0.001$), and in children with diagnoses of cerebral palsy (OR, 1.4;

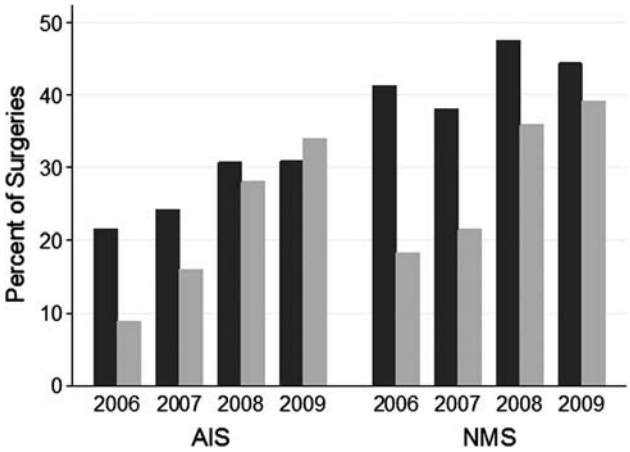

FIGURE 2. Proportion of surgeries performed at 37 children's hospitals in which red cells were transfused (dark-gray boxes) and/or antifibrinolytics were given (light-gray boxes) for years 2006, 2007, 2008, and 2009. AIS indicates adolescent idiopathic scoliosis; NMS, neuromuscular scoliosis.

TABLE 2. OR and 95% CI for the Association Between Red Cell Transfusion and EACA or TXA Use in AIS and NMS Procedures

	AIS Procedures n = 2722	NMS Procedures n = 1547
EACA, OR (95% CI)	0.42 (0.26–0.67)*	1.2 (0.73–1.9)
TXA, OR (95% CI)	1.0 (0.48–1.9)	1.3 (0.68–2.4)

*$P < 0.001$.

AIS indicates adolescent idiopathic scoliosis; CI, confidence intervals; EACA, ϵ-aminocaproic acid; NMS, neuromuscular scoliosis; OR, odds ratios; TXA, tranexamic acid.

$P = 0.034$), spinal muscular atrophy (OR, 2.3; $P = 0.016$), or muscular dystrophy (OR, 2.2; $P = 0.002$). There was no association between red cell transfusions and the use of EACA (OR, 1.2; $P = 0.5$), TXA (OR, 1.3; $P = 0.4$), or APR (OR, 1.2; $P = 0.7$) (Table 2).

DISCUSSION

This is the first exploration of the overall effectiveness of antifibrinolyitics as used in real-world practice settings across a large sample of US Children's Hospitals. In this study of nearly 5000 children with surgically managed spinal deformities, we observed a significant decrease in odds of autologous or allogenic blood transfusions in AIS procedures for which EACA was administered and cell salvage equipment was not used. Conversely, use of TXA in the AIS population and use of any antifibrinolytic drug in the NMS population were not associated with significant differences in odds of transfusion. We also illustrated a gradual increase in the proportion of children receiving antifibrinolytics for spinal operations from 2007 to 2009, and marked variation in the use of these drugs across hospitals.

The role of antifibrinolytic drugs as one strategy for reducing perioperative transfusion requirements has been widely studied. Numerous randomized controlled trials and observational studies in pediatrics and adult surgery have demonstrated significant reductions in blood loss and transfusion volumes in the setting of antifibrinolytic use,[16,21] and—consistent with our findings—EACA use has also been associated with a 28%–30% reduction in the number of patients transfused.[15,22] However, with the exception of EACA in AIS procedures, our study demonstrates antifibrinolytics as they are being currently used in practice settings were not associated with the expected reductions in transfusions as reported in efficacy studies, indicating that blood protocols for antifibrinolytic use may not be optimizing the proven benefit of these drugs.

A few notable limitations to our study may have contributed to these null study findings. First, our study was not randomized, and there is a potential for misclassification of patients either by their likelihood to receive an antifibrinolytic or their baseline risk of transfusion. To minimize this type of confounding, we controlled for characteristics that were associated with use of antifibrinolytics or with bleeding risk. Despite this, residual confounding may exist and the population that received antifibrinolytics may have been sicker. Although this bias could explain our null findings, it would also add strength to the observed association for EACA in children with AIS.

Second, we did not have the ability to measure intermediate outcomes such as blood loss and transfusion

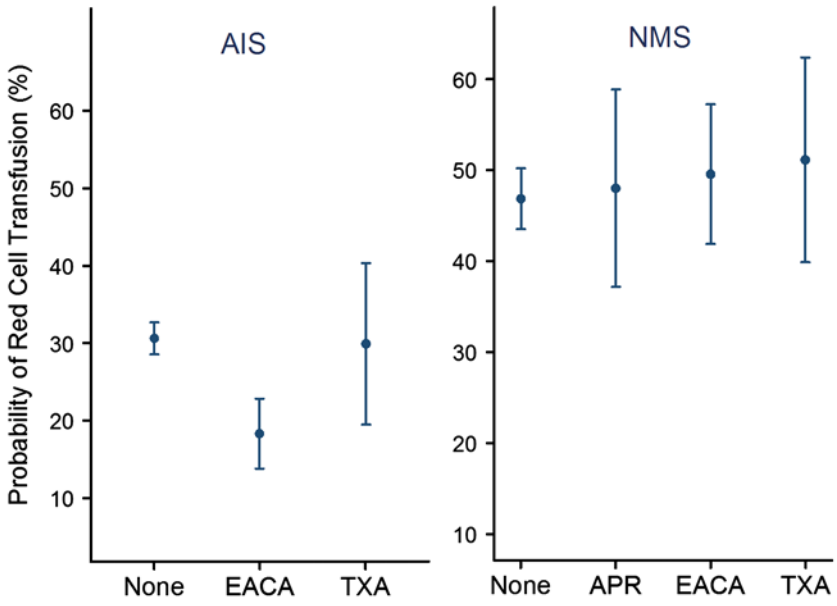

FIGURE 3. Standardized (adjusted) probabilities (point estimates with 95% confidence interval) for receiving a blood transfusion in adolescent idiopathic scoliosis (AIS) (left) and neuromuscular scoliosis (NMS) (right) procedures with and without use of antifibrinolytics, as estimated from multivariable analyses. APR indicates aprotinin; EACA, ϵ-aminocaproic acid; TXA, tranexamic acid.

volumes. Differences in these values in the setting of antifibrinolytic use may have been statistically significant. However, while several studies demonstrate a strong association between any blood transfusion and increased risk of surgical site infections, delayed wound healing, lengths of stay, and death,[7,23,24] the clinical significance of per milliliter changes in blood volumes in children is difficult to determine. Furthermore, use of estimated blood loss as an outcome may have introduced additional bias due to variation in the measurement of estimated blood loss among different providers.[25]

Third, although we excluded surgeries in which cell salvage equipment was used, our results could be confounded by the presence of other hospital-specific nonpharmacologic practices for blood conservation, such as protocols for transfusion thresholds or thrombin-containing sealants.[26–28] These processes could not be reliably measured in PHIS, and collection of such data will greatly inform future studies comparing the effectiveness of antifibrinolytics in pediatric spinal operations.

There are several other possibilities for our negative findings which need to be explored. For TXA in particular, several studies have shown that the efficacy is dose dependent[29–31]; and it is possible that concerns about the safety of high per kilogram doses in children may have led to variation in dosing regimens and dilution of the effect sizes observed in clinical trials. In addition, antifibrinolytic drugs may not be equally effective across all patient groups. Although many studies have reported that children with certain neuromuscular disorders are at greatest risk of massive bleeding,[1,2,32] there is little evidence to guide decisions about which NMS patients will benefit most from antifibrinolytic therapy, and risk-targeting practices may vary broadly. Finally, in anticipation of ongoing perioperative bleeding in children with NMS (sometimes losing up to 78% of blood volume during and after surgery), surgeons may differ in their criteria for transfusion in this fragile population.

Similar to what has been found for other perioperative processes of care including prophylactic antibiotic use, instrumentation, and surgical techniques, our findings indicate that there is no standard practice for antifibrinolytic use in spinal procedures.[33,34] Among the hospitals studied, 18 rarely used antifibrinolytics, 15 used primarily EACA, and 6 used primarily TXA. Baseline rates of transfusion were also highly variable. Exploring the impact of this variation on quality and outcomes will be crucial for establishing safe and effective protocols for antifibrinolytic use as well as for other perioperative processes of care.

Antifibrinolytics have proven efficacy in clinical trials, and may be an important intervention for minimizing blood loss and transfusions in spinal surgery; but they are costly and not without added risk to patients.[8,11] In a recent study by our research group, costs associated with administration of TXA, comprised 15%–23% of total pharmacy costs in the 6 hospitals that regularly used the drug (unpublished data). Antifibrinolytics such as TXA may also increase the risk of thrombosis—a risk that is heightened in the setting of oral contraceptive or isotretinoin use as may be common in the female adolescent population. Findings of this study along with existing evidence emphasize the need to monitor the administration and downstream impact of antifibrinolytics and blood transfusion procedures as they are currently used in pediatric spinal operations. Given the limitations of existing investigations, establishing best practice will require collection of prospective data on blood conservation protocols and patient risk, as well as development of reliable and clinically important outcomes metrics.

CONCLUSIONS

Among the 38 US Children's Hospitals included in this study, antifibrinolytic use in pediatric spinal operations involving children with AIS or NMS increased over time, but effectiveness of these drugs as used in practice may not be consistent. Generalized use of these drugs should be carefully monitored as one component of a hospital's blood conservation protocol; and benefits of their use in specific patient populations should be thoughtfully balanced with their high cost and potential risk of adverse events such as thrombosis.

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