Pediatr Surg Int (2016) 32:691–696
DOI 10.1007/s00383-016-3902-5

ORIGINAL ARTICLE

Quality improvement program reduces venous thromboembolism in infants and children with long-gap esophageal atresia (LGEA)

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Accepted: 31 May 2016 / Published online: 4 June 2016

Abstract
Purpose Patients with long-gap esophageal atresia (LGEA) treated with the Foker process are at increased risk of venous thromboembolism (VTE). An institutional quality improvement program to decrease VTE risk factor exposure and utilize prophylactic anticoagulation was implemented. We aim to evaluate the efficacy and safety of a VTE risk-reduction program in patients with LGEA.
Methods Implementation and evaluation of a VTE risk-reduction program in patients with LGEA from 2012 to 2015 was performed. Symptomatic VTE with radiographic confirmation were defined as events. Post-program characteristics were evaluated and compared to a historical cohort.
Results Sixty-seven patients were identified. Two developed VTE (7 %) post-program implementation; compared to 13/40 (33 %) VTE incidence in the historical cohort ($p = 0.018$). Baseline demographics were similar, including age, esophageal atresia type and gap length. Post-protocol patients had fewer paralysis episodes ($p = 0.004$), paralysis days ($p = 0.003$), central venous catheters ($p = 0.003$), thoracotomies ($p < 0.001$), ventilator hours ($p = 0.02$), and decreased hospital ($p < 0.001$) and ICU stay ($p < 0.001$). All patients in the VTE risk-reduction program were exposed to prophylactic anticoagulation. No bleeding complications and/or thrombosis-related mortality occurred.
Conclusion VTE risk-reduction program implementation decreased symptomatic VTE incidence with associated decreases in ICU and hospital length of stay. Prophylactic anticoagulation can be utilized safely in a complicated pediatric surgical population.

Keywords Safety · Thromboprophylaxis · Venous thromboembolism · Long gap esophageal atresia

Electronic supplementary material The online version of this article (doi:10.1007/s00383-016-3902-5) contains supplementary material, which is available to authorized users.

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Introduction

Pediatric patients with Long-Gap Esophageal Atresia (LGEA) treated with the Foker Process are at increased risk of venous thromboembolism (VTE) [1]. VTE risk in children ranges from 0.001 to 0.01 % in outpatients up to 0.5 % (58 cases per 10,000 hospital admissions) in pediatric tertiary care facilities, which is rising in recent years [2]. Amongst pediatric patients with VTE, 80–90 % have one or more risk factor, including congenital heart disease, malignancy, or presence of a central venous catheter (CVC) [3, 4]. This may, in turn, increase risk of mortality and long-term morbidity, including VTE recurrence and post thrombotic syndrome [5, 6].

Esophageal atresia is a rare congenital anomaly that occurs in 1.8–4 per 10,000 births [7, 8]. A subgroup of these patients have LGEA, defined as a distance between the upper and lower atretic esophageal segment of greater than three vertebral bodies [9]. Children with LGEA achieve oral-gastric continuity through various methods including the Foker process (FP). This surgical technique uses tension-induced natural growth to allow for re-anastomosis of atretic esophageal segments [9]. The FP often requires the use of adjunctive therapies including mechanical ventilation, CVC, parenteral nutrition, and prolonged immobilization facilitated by pharmacologic paralysis and sedation [9].

These adjunctive therapies, specifically CVC use and immobilization, are identified VTE risk factors that disrupt vascular and hemostatic health. Endothelial damage, chronic inflammation, and re-exposure to other pro-thrombotic factors enable the development of a thrombotic event [5, 9]. The incidence of VTE amongst LGEA patients undergoing FP was significantly higher (15/44, 34 %) [1] than the previously reported overall rate of 4.5 % of critically ill children with CVC-related VTE at our institution [10]. A previous retrospective analysis identified age at procedure, utilization of pharmacologic paralysis, CVC, and intensive care unit (ICU) length of stay as risk factors for VTE in patients with LGEA [1].

Identification of this high-risk population prompted a multidisciplinary evaluation of pro-thrombotic risk factor exposure and development of a comprehensive quality improvement program aimed at VTE risk reduction. The quality improvement program focused on decreasing VTE risk exposure including decreased duration of immobility, limited CVC use, and utilized a risk-based approach to prophylactic anticoagulation. Programmatic enhancements were accompanied by educational activities provided to the physician, nursing, respiratory therapy and pharmacy staff in the neonatal and pediatric intensive care units. The purpose of this study is to evaluate the efficacy and safety of our VTE reduction program by comparing patients pre- and post-program implementation for thrombotic and bleeding complications.

Methods

Following institutional review board approval (IRB-P00005612), we prospectively evaluated all patients with LGEA treated at our institution from July 2012 to December 2015 as an interim analysis of a VTE risk reduction strategy. Patients with other forms of esophageal atresia were excluded. Arterial thrombotic events were also excluded.

Primary FP patients were those patients who had not undergone a prior esophageal operation [1, 11]. Patients who had prior surgical procedures to address esophageal atresia were considered secondary FP cases [11]. Variables assessed included estimated gestational age (EGA), birth weight (BW), gender, presence of congenital heart disease, and type of esophageal atresia (primary FP versus secondary FP cases). We also reviewed the distance (gap) between atretic esophageal segments, age and weight at time of FP initiation, number of surgeries and thoracotomies, number and location of CVCs, number of cumulative days and episodes of pharmacologic paralysis, duration of mechanical ventilation, and total ICU and hospital length of stay (LOS).

Paralysis episodes were defined as distinct periods of continuous pharmacologic paralysis, separated by at least a 24-h period in which the patient did not receive pharmacologic paralysis. Standard pharmacologic paralysis regimens included cisatracurium besylate and vecuronium bromide titrated per institutional ICU policy. Patients receiving pharmacologic paralysis received concomitant mechanical ventilation and pharmacologic sedation.

VTEs were defined as events only if clinically symptomatic (e.g., extremity swelling, skin color changes) and confirmed with ultrasonography and/or venography. Routine ultrasound screening to detect subclinical events was not performed. Patients who received pharmacologic thromboprophylaxis were compared to a historical cohort of patients meeting the above inclusion and exclusion criteria treated at our institution from January 1, 2005 to June 30, 2012, prior to implementation of the VTE risk-reduction program [1]. The historical cohort represents 13 VTE events in 40 patients (33 %) treated prior to program implementation; this comprises 13 of the 15 VTE events in 44 patients (34 %) reported previously from our institution [1].

Recommendations to decrease risk factor exposure were offered for all patients, including minimizing duration of immobility, reducing use and duration of CVCs, using mechanical thromboprophylaxis if age/weight appropriate, and consulting a physical therapist for active and/or passive range of motion. Patients with paralysis expected $\geq$7 days received pharmacologic thromboprophylaxis with enoxaparin in addition to targeted physical therapy (Supplemental Figure 1). Initial doses for enoxaparin followed American College of Chest Physicians (ACCP) guidelines with dosing recommendations for infants <2 months old of 0.75 mg/kg/dose every 12 h and for infants $\geq$2 months old of 0.5 mg/kg/dose every 12 h [12].

Enoxaparin began on post-operative day 1 if the patient was deemed to be physiologically stable based upon the mutual agreement of the surgeon and intensivist. Given evidence of variable pharmacokinetics of enoxaparin in neonates and infants, some clinicians chose to monitor anti-Xa levels to verify that prophylactic levels (0.1–0.4 units/

mL) were reached. If the level was lower than that range, the dose was increased by 10 % and a level was monitored per protocol (4–6 h following the second new dose). Pharmacologic thromboprophylaxis was held in the standard fashion (12 h) prior to any return to the operating room and resumed by consensus of the clinical team. We intended that patients with expected paralysis ≤7 days would not receive pharmacologic thromboprophylaxis.

Adherence to the risk reduction recommendations and use of prophylactic anticoagulation was evaluated. Bleeding events were defined as either major and/or minor. Those requiring blood transfusion and/or operative intervention were considered major complications; attribution to anticoagulation was determined by consensus of the LGEA clinical team. Overall thrombotic-related morbidities and death within the study period were also documented.

Statistical analysis

Continuous data such as days of paralysis or ICU stay and count data including number of paralytic episodes are presented as median and interquartile range and compared with the nonparametric Wilcoxon rank-sum test [13]. Proportions were compared by Fisher's exact test. Differences in catheter-associated VTEs and bleeding complications were compared by logistic regression using the likelihood ratio test to assess significance of the protocol on these events [14]. All p values are two-tailed using $p < 0.05$ as the criteria for statistical significance. Statistical analysis was conducted using the IBM SPSS software package (version 23.0, IBM, Armonk, NY).

Results

Twenty-seven patients were identified following implementation of the VTE risk reduction program. Baseline demographics were similar for LGEA patients before and after initiation of the program (Table 1). Ages of the patients in the study (pre- and post-protocol cohorts) included 5 (8 %) neonates, 49 (73 %) infants, 9 (13 %) patients between 1 and 3 years of age, and 4 (6 %) that were greater than 3 years of age (ages 4, 9, 15, and 18 years old). Two patients in the post-protocol cohort developed symptomatic VTE (7 %), compared to 13 of 40 patients (33 %) in the historical cohort ($p = 0.018$) (Fig. 1).

All VTE events were CVC-associated. VTE incidence decreased from 48 to 9 % in secondary FP patients, compared to more modest improvement (12–6 %) in primary FP patients. Post-program patients had a significantly lower median number of paralysis episodes, total number of paralysis days, total ventilator hours, number of CVCs, number of thoracotomies, ICU LOS, and post-operative hospital LOS (Table 2). Post-operative hospital LOS was decreased by 52 % and ICU LOS decreased by more than 58 % (Fig. 2).

Ongoing education and structured review of VTE risk was incorporated into daily rounds with adherence monitored by members of the research team. All patients received enoxaparin prophylaxis as all required pharmacologic paralysis for greater than 7 days. Median postoperative day of enoxaparin initiation was postoperative day 1 (interquartile range 1–2 days). Median length of enoxaparin treatment was 16 days (interquartile range 14–21.5 days). Initial doses for enoxaparin followed ACCP age and weight based dosing guidelines as previously described [12]. One patient in the cohort qualified for and utilized serial compression devices (SCD) in accordance with institutional guidelines. None of the patients in the historical cohort utilized for comparison had received prophylactic pharmacologic anticoagulation.

Additional testing and monitoring of anti-Xa levels to verify that prophylactic levels were achieved was at the determination of the treating clinician. Of the 27 post-protocol patients, 17 ($n = 17/27$, 63 %) had monitoring of anti-Xa levels. Seven ($n = 7/17$, 40 %) patients had initial anti-Xa levels within appropriate prophylactic range (0.1–0.4 units/mL), four ($n = 4/17$, 24 %) patients required one increase of their enoxaparin dosing, and two ($n = 2/17$, 12 %) required more than one dose increase to achieve prophylactic anti-Xa range values. Four ($n = 4/17$, 24 %) patients never reached prophylactic anti-Xa levels. Of the two patients who developed a symptomatic VTE following program implementation, one infant and one 18 year old, both had anti-Xa levels less than 0.1 units/mL.

No minor bleeding complications were identified following the establishment of VTE risk reduction efforts. There were also no major bleeding complications among patients exposed to prophylactic anticoagulation. Two deaths occurred in the overall cohort prior to program implementation and occurred post hospital discharge following FP repair. The mortalities were unrelated to thrombotic or hemorrhagic complications.

Discussion

A multidisciplinary safety and educational program developed to target a 33 % incidence of catheter-related VTE in infants and children undergoing FP repair of LGEA resulted in a relative reduction in symptomatic VTE by 78 %. This current study highlights the safety and efficacy of a multidisciplinary approach to limiting risk factor exposure and the use of prophylactic anticoagulation.

Table 1 Patient characteristics before and after program implementation

Characteristic	Pre-program ($n = 40$)	Post-program ($n = 27$)	p value
EGA (weeks)	36 (34–39)	36 (34–38)	0.638
Birth weight (kg)	2.5 (1.9–3.1)	2.3 (1.9–2.8)	0.630
Gender			
Male	20 (50 %)	15 (56 %)	0.804
Female	20 (50 %)	12 (44 %)	
Congenital heart disease	16 (40 %)	8 (30 %)	0.444
Type of esophageal atresia			
Primary	17 (43 %)	16 (59 %)	0.218
Secondary	23 (57 %)	11 (41 %)	
Gap at admission (cm)	4.9 (4.0–5.5)	4.0 (3.2–4.8)	0.062
Age at Foker process (months)	4.0 (2.0–9.0)	4.0 (2.0–8.0)	0.923
Weight at Foker process (kg)	5.2 (4.2–8.3)	4.9 (3.8–7.1)	0.371

Continuous data are median (interquartile range) with groups compared using the Wilcoxon rank-sum test. Proportions were compared by Fisher's exact test

EGA estimated gestational age

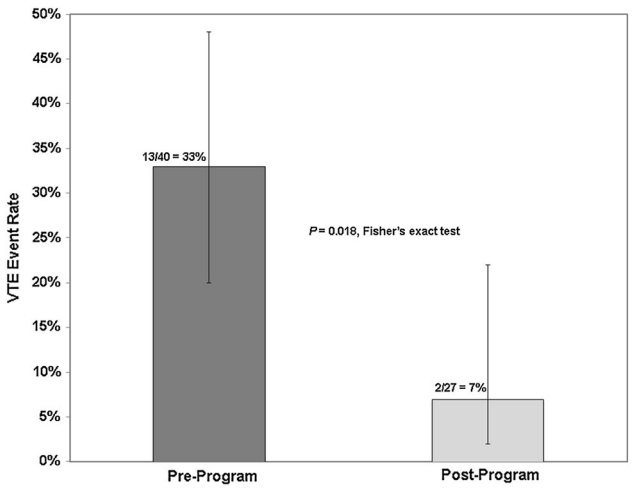

Fig. 1 Venous thromboembolism (VTE) rate decreased among patients with LGEA prior to quality improvement program implementation ($n = 13/40$, 33 %) and post-program implementation ($n = 2/27$, 7 %) ($p = 0.018$)

Evaluation of the initial patient cohort with elevated VTE risk identified immobility, measured as episodes of pharmacologic paralysis, as the primary exposure driving thrombotic risk. As the FP requires intermittent immobilization to allow for esophageal anastomosis, it posed a unique opportunity to minimize and mitigate other risk factor exposures.

In this study, the risk-reduction interventions were developed through consensus opinion among members of the pediatric surgery, hematology, critical care medicine, neonatology, and pharmacy divisions within the institution. The patient cohorts are similar between the initial and post-program development cohorts (Table 1), allowing comparison and conclusion that a comprehensive approach to limit risk exposure and utilize prophylactic anticoagulation significantly reduced symptomatic VTE burden without increased bleeding. While not statistically significant, the trend towards more primary FP repairs post-algorithm may indicate that a less complex patient population also contributed to the success of this algorithm; for example, primary FP patients required fewer thoracotomies, fewer CVCs, and decreased duration of paralysis. Decreased exposure to paralysis, CVCs, and mechanical ventilation resulted in significant reduction of symptomatic VTE with an associated reduction in ICU and hospital LOS.

While the overall efficacy of enoxaparin in this study is clouded by differences in paralysis, CVC exposure and number of thoracotomies, the absence of any significant bleeding following the program-wide use of prophylactic anticoagulation in a complex critical care, surgical pediatric population provides reassuring safety data. Surveys of thromboprophylaxis utilization for pediatric patients reveal heterogeneity among prescribers [15]. This may be due to relative rarity of VTE, limited evaluation of specific risk factors in pediatric patients, and limited evidence-based guidelines for VTE prophylaxis in patients less than 18 years [12, 16–18]. While this study targets a specific surgical cohort, the majority of patients were infants or young children; only three patients were older than 3 years of age. This study provides an informative experience regarding thromboprophylaxis in infancy and childhood, which is poorly studied to date.

Recent studies have called for an increase in the initial dose of therapeutic enoxaparin in neonates [19–22]. Based on these data and our experience with initial undetectable levels in this population, our current initial prophylaxis dosing strategy is 1 mg/kg/dose every 12 h for neonates <2 months and <37 weeks gestational age and

Table 2 Comparison of patient outcomes before and after initiation of program

Outcome	Pre-program ($n = 40$)	Post-program ($n = 27$)	p value
Catheter-associated VTEs	13 (33 %)	2 (7 %)	0.018*
Number of paralytic episodes	1 (1–4)	1 (1–1)	0.004*
Cumulative paralysis (days)	34 (16–47)	16 (10–21)	0.003*
Ventilator duration (hours)	876 (487–1817)	576 (288–741)	0.020*
Number of CVCs	3 (2–5)	2 (1–3)	0.003*
Number of thoracotomies	4 (2–6)	2 (2–3)	<0.001*
ICU stay (days)	110 (65–193)	46 (22–82)	<0.001*
Postoperative hospital stay (days)	139 (106–238)	73 (56–100)	<0.001*

Continuous data are shown as the median (interquartile range) with groups compared by the Wilcoxon rank-sum test. The incidence of symptomatic catheter-associated VTE was compared using the conservative Fisher's exact test

VTE venous thromboembolic event, *CVC* central venous catheter, *ICU* intensive care unit

* Statistically significant

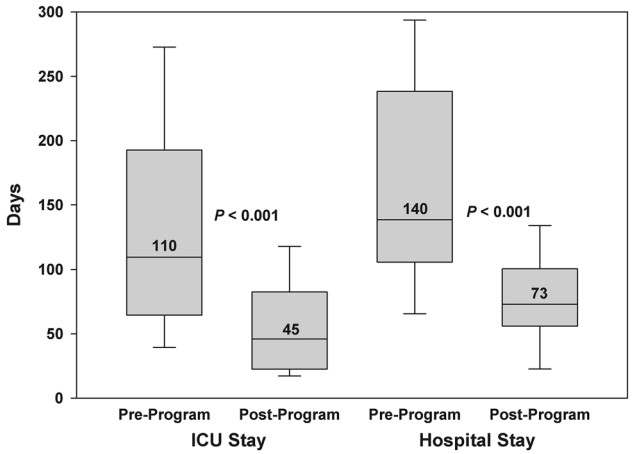

Fig. 2 ICU and post-operative hospital length of stay decreased among patients with LGEA following VTE risk reduction program implementation. Median ICU LOS decreased from 110 (interquartile range 65–193) to 46 (22–82) days ($p < 0.001$) and median post-operative hospital LOS decreased from 139 (106–238) to 73 (56–100) days ($p < 0.001$) among the pre- and post-program implementation patient cohorts

0.85 mg/kg/dose every 12 h for infants ≥2 months and ≥37 weeks gestational age. We hope this leads to shorter time to achieve prophylactic anti-Xa levels (0.1–0.4 units/mL) and fewer dose adjustments. Infants ≥2 months continue to receive enoxaparin 0.5 mg/kg/dose every 12 h. VTE treatment dosing for all age categories is double the prophylaxis dose.

This study demonstrates that focused efforts to identify and decrease VTE risk factor exposure supplemented with prophylactic anticoagulation can safely reduce VTE rates, decrease associated morbidity, ICU and hospital LOS without altering surgical efficacy. It also highlights that among non-traumatic, non-oncologic, complex surgical pediatric patients, prophylactic anticoagulation can be utilized safely and effectively. We report that in select patients, a multimodal VTE reduction program aimed at reduced risk factor exposure and standardized use of pharmacologic thromboprophylaxis reduces the risk of CVC-associated VTE in neonatal and pediatric patients.

Limitations

While presenting a significant reduction in CVC-associated VTE events and providing safety data in an at-risk population, our study is limited by comparing the efficacy of this multidisciplinary quality improvement program to a historical cohort at a single institution. We are not able to provide an assessment of VTE risk reduction and prophylactic anticoagulation use among a randomized sample as we were aware of the increased VTE rate and associated morbidities within a rare patient population. The multifactorial nature of VTE risk also limits the ability to detect which of the programmatic interventions (limiting immobility, decreasing CVC use, staff education and prophylactic anticoagulation) is the primary driver for VTE reduction. However, an effective program to minimize VTE will need to utilize a multifactorial approach for optimal outcomes.

Conclusions

After the implementation of a comprehensive safety and educational program aimed at VTE risk reduction, the incidence of symptomatic CVC-associated VTE decreased from 33 to 7 % with associated decreases in ICU and hospital LOS. The decrease in VTEs was achieved via limitation of risk factor exposure and standardized prophylactic anticoagulation without increased bleeding

complications or associated mortality. These efforts reduced morbidities and provide important safety data regarding prophylactic anticoagulation in a high-risk pediatric population.

Compliance with ethical standards

Conflict of interest All co-authors have seen and agree with the contents of the manuscript and there are no conflicts of interest or outside funding to report.

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