Risk of venous thromboembolism in children after general surgery

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Abstract

Background/Purpose

To determine absolute and relative rates of venous thromboembolism (VTE) following general surgical procedures in children compared to the general population.

Methods

We analysed data from all patients under the age of 18 years in the Clinical Practice Research Datalink, linked to Hospital Episode Statistics from England (2001-2011) undergoing a general surgical procedure and population controls. Crude rates of VTE and adjusted hazard ratios were calculated using Cox regression.

Results

We identified 15,637 children who had a surgical procedure with 161,594 controls. Six children undergoing surgery had a VTE diagnosed in the year after compared to five children in the population cohort. The overall rate of VTE following surgery was 0.4 per 1000 person years (pyrs) (95% confidence interval (CI) 0.15-0.88) compared to 0.04 per 1000 pyrs (95% CI 0.02-0.09) in the population cohort. This represented a 9 fold increase in risk compared to the population cohort (adjusted hazard ratio (HR) 8.80; 95% CI 2.59-29.94).

Conclusions

Children are at increased risk of VTE following general surgical procedures compared to the general population however the absolute risk is small and given this

the benefits of thromboprophylaxis need to be balanced against the risk of complications following its use.

Key words: deep vein thrombosis, pulmonary embolus, General Surgery

Abbreviations: CI - Confidence interval, CPRD – Clinical Practice Research Datalink, HES – Hospital Episode Statistics, HR – Hazard Ratio, IQR – interquartile range, OPCS - Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures, VTE – venous thromboembolism

1.0 Introduction

Venous thromboembolism (VTE) in children is becoming increasingly recognised[1]. The annual reported incidence of VTE in children has been reported as 0.07-0.14 per 10,000 children or 5-58 per 10,000 hospital pediatric admissions [2-6]. The rates of childhood VTE related hospitalisation have been reported to be increasing although this may reflect increased awareness, better diagnostic tools or increased use of indwelling catheters[5, 7]. Known risk factors for VTE in childhood include central venous lines, sepsis, malignancy, surgery, trauma and medical comorbidities[1, 8-13]. There are no population-based estimates of the risk of VTE following general surgery in childhood, which is considered to be a risk factor for VTE and is performed on over 40,000 children per year in England and 220,000 in the United States[6, 13, 14]. As a consequence of the lack of data on the risk of VTE following surgery there is currently a limited evidence base on which to make recommendations for prevention[1, 15]. The current British guidelines on the prevention of VTE in children suggest that further work is required to define the risk of VTE in these patients to inform decisions on prophylaxis[1]. We have therefore undertaken a large contemporary population-based study using linked healthcare data from both primary and secondary care in England to determine the risk of VTE following general surgery.

2.0 Patients and Methods

2.1 Clinical Practice Research Database (CPRD)

The CPRD contains diagnostic and prescription data for approximately 13 million people of the general population in the United Kingdom, with 3.4 million active patients contributing data. Originally developed in 1987, the database represents a prospectively collected source of continuous data on illness in General Practice in the UK where all patient care is coordinated by the general practitioners (GPs). The data collected are audited regularly and the participating General Practices are subjected to a number of quality checks to ensure they are “up to standard” for research purposes. The database consists of observations, and diagnoses made by, GPs, as well as information sent to them from hospitals such as pathology and radiology reports as well as discharge letters. Diseases are coded within the CPRD using Read codes[16].

2.2 Hospital Episode Statistics (HES)

HES is a data source containing details of all admissions to NHS hospitals in England including demographic data along with information about diagnoses and operations. Records are coded using a combination of International Statistical Classification of Disease and Related Health Problems (ICD-10) for diagnoses at discharge along with Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS-4) detailing procedures performed.

The anonymised patient identifiers from CPRD and HES were linked by a trusted third party by using the National Health Service (NHS) number, date of birth, postcode, and sex. Most patients were matched exactly according to NHS number

(over 90% of patients are linked in this way), with the remaining patients linked probabilistically on the basis of postcode, date of birth, and sex. As HES covers only English hospitals, we excluded practices from Northern Ireland, Wales, and Scotland. Previously data from the linked portion of the CPRD have been shown to be similar in terms of age, sex, and geographical distribution to data from the UK population published by the Office for National Statistics (ONS) and the findings are generalisable[17]. The study had approval from the Independent Scientific Advisory Committee approval board (Protocol 11-051R).

2.3 Cohort Identification

We used all patients under the age of 18 years from the linked health registries described (such patients are hereby denoted “children”) from 2001-2011. The cohort was identified using OPCS-4 codes for general surgical procedures (Codes G-upper digestive tract, H-lower digestive tract, J-other abdominal organs-principally digestive and T-soft tissue from the HES data). We excluded endoscopic procedures and limited those in the T soft tissue to category to procedures relevant to gastrointestinal surgery (T 19-T48 and T97). Patients were followed up until they developed a VTE event, died, left a participating GP practice or 31st December 2011 or until 1 year after their operation, whichever was earliest. Patients were excluded if they were: not in a linked general practice, or had a VTE prior to first operative intervention given these patients are at an inherently increased risk of VTE following surgery.

2.4 Population Cohort

The general population cohort was identified from the CPRD and HES linked data. In order to maximize statistical power, all available controls without a diagnosis of surgery during their CPRD/HES linked record were eligible. Controls were frequency

matched in a ratio of 10:1 by 5-year-age bands. Controls then received a pseudo-diagnosis date generated at random within the registration period for each patient. Any control whose pseudo-diagnosis date was after they reached 18 years of age was then excluded.

2.5 Outcome Definition

Symptomatic VTE diagnosis was determined from medical codes for pulmonary embolism or deep vein thrombosis in the CPRD and HES. These were considered to be a valid VTE event if supported by either: a prescription for an anticoagulant or other evidence of treatment in an anticoagulation clinic (such as a medical code) between 15 days before and 90 days after the VTE diagnosis, or a date of death within 30 days of the event. Additionally, an underlying cause of death of VTE was included as evidence of VTE diagnosis. Only the first validated instance of VTE was included in the analysis. All cases with prior VTE in their CPRD record were excluded from the analysis. The definition using primary care data alone has been validated previously showing 84% of cases were valid [18]. The use of linked CPRD and HES data has been shown to allow better identification of the date of VTE when compared to using either dataset alone and more comprehensively identifies VTE cases from both primary and secondary care due to the use of prescription data[19]. The definition used in this study has been used to study VTE in pregnancy, cancer, paediatrics and surgery [10, 19-21].

2.6 Covariates

The timing of the admission was indicated as in-patient, day case or emergency based on the associated admission code from HES. Comorbidity was calculated prior to the admission using both primary and secondary care data to calculate the Charlson index[22].

2.7 Statistical Analysis

Person-time at risk commenced on the day before the day of operation for our overall analysis therefore VTE's recorded on the same day as the operation, were included within the analysis. We took the date of diagnosis of VTE's to be the episode start date for VTEs occurring within the same hospital spell as the index operation. First, we described the basic characteristics of our cohort. Absolute rates of VTE (per 1000 person years) were then calculated by dividing the number of people with VTE by the person-time at risk for the first 90 days and one year of follow up after the operation. This was done overall and then separately for each exposure of interest. A Cox proportional hazards model was then created to include all exposures to estimate hazard ratios (HR) and 95% confidence intervals (CI). All data management and analysis were performed using Stata 12 (Statacorp, Texas 77845 United States of America).

3.0 Results

3.1 Demographics of cohort

In total we identified 15,637 patients who had a general surgical procedure recorded in the linked data with 161,594 controls. The median age at surgery was 9 (interquartile range (IQR) 3-14) years and 9 (IQR 2-13) years at pseudo-diagnosis date for the controls. In total 64.2% of those having surgery were male compared to 51.3% being male in the control cohort. Other demographic features are shown in Table 1. Those undergoing surgery were more likely to have significant comorbidity (3.4% vs. 0.9%, $p<0.001$). Of those having surgery the most commonly performed procedure was appendicectomy 6,437 (41.2%) followed by inguinal hernia repair 4,480 (28.7%). Of those patients having an inguinal hernia repair 3,840 (85.7%) were male. The median length of stay following an inpatient procedure was 2 days (IQR 2-4 days) with a median of 4 days following an emergency admission (IQR 3-5 days).

3.2 Risk of VTE following Surgery

In total six patients had a VTE diagnosed in the year following general surgery and five of the population cohort had a VTE in the year following their pseudo-diagnosis date. Of those having surgery five cases were of deep vein thrombosis and one of pulmonary embolism with four of the population cohort having a deep vein thrombosis and one a pulmonary embolus. In those undergoing surgery one VTE event occurred whilst an inpatient with the other five events occurring following discharge. Of those having a VTE following surgery none had an underlying diagnosis of malignancy. Four of the cases were male and the median age of the cases was 3 years (IQR 2-16 years). The majority of the cases had 1 or more

significant comorbidities as scored by the Charlson index. The overall rate of VTE in the first year following surgery was 0.4 per 1000 person years (95% CI 0.15-0.88) compared to 0.04 per 1000 person years (95% CI 0.02-0.09) in the population cohort. The highest rate occurred in the first three months following surgery with a rate of 0.78 per 1000 person years (95% CI 0.25-2.40). Adjusting for sex, age and comorbidity at surgery this represented a 9 fold increase in risk compared to the population cohort (HR 8.80 95% CI 2.59-29.94) in the year following surgery. There were no VTE events following inguinal hernia surgery in any setting (Table 2). There were no VTE events following day case surgery, which accounted for 32.4% of procedures performed. The rate of VTE following emergency surgery was 0.26 per 1000 person years (95% CI 0.07-1.05) with a one year rate following in-patient surgery of 1.64 per 1000 person years (95% CI 0.62-4.38).

4.0 Discussion

4.1 Summary of Findings

We have found that there is a 9 fold increase risk of VTE in children following general surgery compared to children from the general population. However the absolute rates of VTE are low (0.4 per 1000 person years) with the majority occurring following discharge. The majority (69.8% 10915/15637) of patients undergoing surgery during childhood for gastrointestinal disease are for conditions (hernia and appendicitis) associated with a low risk of VTE. The cases of VTE occurred in those patients who were young (median age 3 years) and in the majority of cases were male with no underlying diagnosis of malignancy. The majority of the cases had 1 or more significant comorbidities as scored by the Charlson index. Those undergoing planned in-patient surgery had the greatest rates of VTE.

4.2 Limitations of study

Our study used linked data to identify children undergoing general surgical procedures from population-based data, with identification of operative procedures from secondary care along with defining VTE in a validated manner from primary[23] and secondary care and in that sense it is uniquely placed to quantify symptomatic VTE risk accurately. Although we were unable in our analysis to identify those patients receiving thromboprophylaxis there were no specific recommendations following surgery in children at this time. Nevertheless we cannot exclude the possibility that rates of VTE might be higher in some groups than we observed precisely because they received prophylaxis. We also have no data on the use of central venous lines in these children which are known to increase the risk of VTE. However the children developing VTE had relatively short hospital stays and the

events mainly occurred following discharge suggesting they may not be related to indwelling central venous lines[7]. It may be that inaccuracies in coding of the data or misclassification of events by those coding records may result in missing cases however data entry within each practice in the CPRD is audited to ensure that 95% of entries are up to standard before data is used for research purposes from that practice. We have also exploited the link between primary and secondary care to confirm the diagnosis of VTE which has been previously validated[23]. The use of linked primary and secondary care data has also been shown to produce more reliable estimates of rates of VTE than either standalone primary or secondary care data[19].

4.3 Other literature

There are no other studies to our knowledge that report the risk of VTE in children just undergoing general surgery. Our estimates from the general population are greater than previously published studies at 0.37 per 10,000 person years compared to 0.07-0.14 per 10,000 children[2, 3] however they are comparable to previously published data from the CPRD[10]. These differences may be due to under reporting or different diagnostic criteria used for VTE between the studies. It has previously been suggested that these prior studies may have under estimated rates due to a failure to capture all events within registries[13]. Andrews et al reported a rate of DVT/PE of 5.3 per 10,000 hospital admissions across 13 tertiary referral centres in Canada[2]. They had 8 VTE events following surgery. A further study from a Tertiary pediatric centre in Australia reported an overall rate of VTE of 8 per 10,000 hospital admissions with 64 of 95 VTE events occurring in surgical patients who predominantly underwent cardiac surgery[4]. Neither of these studies reported rates following general surgery. Both studies identified a higher proportion of VTE in

children under the age of one-year. We did not identify any cases under the age of one-year following surgery and this may reflect the different populations under study with those patients in the first study drawn only from tertiary referral centres and those in the second study being in a tertiary centre for cardiac surgery[2, 4]. Takemoto et al reported a rate of VTE to a large tertiary centre of 30 per 10,000 admissions however this study included patients up to the age of 21 years and those between the age of 18-21 years had the highest rates of VTE which may have increased their overall rate. The also included recurrent VTE events which will have overestimated the occurrence of VTE in hospitalised patients as prior VTE is a known risk factor for subsequent VTE[6]. Interestingly they did report that fifty of their cases had undergone either trauma surgery or general surgery in the three months prior to VTE but did not give rates specific to general surgery. A further study of tertiary centres in the United States reported an increase in the rate of VTE during an in-patient hospital admission from 34 to 58 per 10,000 hospital admissions however this study did not publish rates following general surgery and included patients with recurrent VTE which may have overestimated the true incidence[5]. Our current study had a high number of male patients undergoing surgery due to the large proportion of patients undergoing inguinal hernia surgery of which 85% were male. Our population cohort also had less comorbidity than the patients undergoing surgery. It may be that this difference contributes to the increased risk of VTE associated with surgery however we have accounted for this in our models but there is the possibility of residual confounding.

Previous studies reporting the occurrence of VTE in the children have concentrated on the overall occurrence during hospitalisation and have not reported how the risk of VTE alters with time following hospitalisation with the majority of studies reporting

in-patient data only [5-7, 24]. A single centre retrospective study of hospital associated VTE reported that 18% of patients with an admission for VTE had undergone a general surgical or trauma related surgical procedure in the three months prior to admission with VTE[6]. This is in keeping with our finding of the majority of VTE events occurring post discharge with the highest rates in the first three months following discharge. This information regarding timing is essential for the direction of thromboprophylaxis use.

4.4 Conclusion

Of interest those undergoing hernia surgery and day case surgery had no episodes of VTE following their operation. Our results do suggest children are at increased risk of VTE following surgery for gastrointestinal disease compared to the general population however the absolute risk of VTE is small and these events principally occur following hospital discharge. As the risk-benefits of thromboprophylaxis in this patient group are unclear further studies will be required before broad implementation of prophylaxis in pediatric surgical patients given the low incidence of VTE we have found.

Table 1. Demographics of cohort of surgical patients and general population.

	Surgery patients	%	Population controls	%
Total	15637		161594	
Gender				
Male	10031	64.2	82892	51.3
Female	5606	35.8	78702	48.70
Age (years)				
0-4	4913	31.4	53244	32.9
5-9	3243	20.7	32870	20.3

10-14	4290	27.4	43245	26.8
>15	3191	20.4	32235	20.0
Comorbidity (Charlson index)				
0	12341	78.9	136388	84.4
1	2764	17.7	23691	14.7
≥2	532	3.4	1515	0.9

Table 2. Rates of VTE following gastrointestinal surgery by procedure type.

Indication	Number of children	Rate per 1000 pyrs*	95% CI
Appendicectomy	6435	0.32	0.08-1.30
Inguinal Hernia Repair	4480	0	0
Other indication	4716	0.9	0.34-2.41

*pyrs = person years

References

[1] Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D, et al: Guideline on the investigation, management and prevention of venous thrombosis in children. Br J Haematol 2011;154:196-207

[2] Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, et al: Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994;83:1251-7

[3] van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M: Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 2001;139:676-81

[4] Newall F, Wallace T, Crock C, Campbell J, Savoia H, Barnes C, et al: Venous thromboembolic disease: a single-centre case series study. J Paediatr Child Health 2006;42:803-7

[5] Raffini L, Huang YS, Witmer C, Feudtner C: Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 2009;124:1001-8

[6] Takemoto CM, Sohi S, Desai K, Bharaj R, Khanna A, McFarland S, et al: Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. J Pediatr 2014;164:332-8

[7] Boulet SL, Grosse SD, Thornburg CD, Yusuf H, Tsai J, Hooper WC: Trends in venous thromboembolism-related hospitalizations, 1994-2009. Pediatrics 2012;130:812-20

[8] Hanson SJ, Punzalan RC, Greenup RA, Liu H, Sato TT, Havens PL: Incidence and risk factors for venous thromboembolism in critically ill children after trauma. J Trauma 2010;68:52-6

[9] Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, et al: Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011;60:937-43

[10] Walker AJ, Grainge MJ, Card TR, West J, Ranta S, Ludvigsson JF: Venous thromboembolism in children with cancer - a population-based cohort study. Thromb Res 2014;133:340-4

[11] Hanson SJ, Punzalan RC, Christensen MA, Ghanayem NS, Kuhn EM, Havens PL: Incidence and risk factors for venous thromboembolism in critically ill children with cardiac disease. Pediatr Cardiol 2012;33:103-8

[12] Polikoff LA, Faustino EV: Venous thromboembolism in critically ill children. Curr Opin Pediatr 2014;26:286-91

[13] Chalmers EA: Epidemiology of venous thromboembolism in neonates and children. Thromb Res 2006;118:3-12

[14] National Hospital Discharge Survey: 2010 table, Procedures by selected patient characteristics - Number by procedure category and age. http://wwwcdcgov/nchs/fastats/inpatient-surgeryhtm June 2014;

[15] Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al: Antithrombotic therapy in neonates and children: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. CHEST Journal 2012;141:737-801

[16] Benson T: The history of the Read Codes: the inaugural James Read Memorial Lecture 2011. Inform Prim Care 2011;19:173-82

[17] Crooks C: Epidemiology of upper gastrointestinal bleeding studying its causes and outcomes using case control studies and survival analyses. [PHD Thesis]. University of Nottingham 2013;

[18] Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD: Validation of the diagnosis of venous thromboembolism in general practice database studies. Br J Clin Pharmacol 2000;49:591-6

[19] Abdul Sultan A, Tata LJ, Grainge MJ, West J: The incidence of first venous thromboembolism in and around pregnancy using linked primary and secondary care data: a population based cohort study from England and comparative meta-analysis. PLoS One 2013;8:e70310

[20] Walker AJ, Card TR, West J, Crooks C, Grainge MJ: Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. Eur J Cancer 2013;49:1404-13

[21] Walker AJ, West J, Card TR, Humes DJ, Grainge MJ: Variation in the risk of venous thromboembolism in people with colorectal cancer: a population-based cohort study from England. J Thromb Haemost 2014;12:641-9

[22] Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83

[23] Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RDT: Validation of the diagnosis of venous thromboembolism in general practice database studies. British Journal of Clinical Pharmacology 2000;49:591-6

[24] Branchford BR, Mourani P, Bajaj L, Manco-Johnson M, Wang M, Goldenberg NA: Risk factors for in-hospital venous thromboembolism in children: a case-control study employing diagnostic validation. Haematologica 2012;97:509-15