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Original Article

Effect of timing of perioperative chemical thromboprophylaxis on thromboembolic, bleeding, and other complications during and after antireflux surgery: multicentre cohort study

PROTECTinG Investigators and VERITAS Collaborative

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Abstract

Background: Although guidelines recommend the use of perioperative chemical thromboprophylaxis for antireflux surgery, the optimal timing for its initiation is unknown. The aim of this study was to investigate whether perioperative timing of chemical thromboprophylaxis affects bleeding, symptomatic venous thromboembolism, and complication rates in patients undergoing antireflux surgery.

Methods: This study involved analysis of prospectively maintained databases and medical records of all elective antireflux surgeries in 36 hospitals across Australia over 10 years.

Results: Overall, chemical thromboprophylaxis was given early (before surgery or intraoperatively) in 1099 (25.6 per cent) patients, and after surgery in 3202 (74.4 per cent) patients, with comparable exposure doses between the two groups. Symptomatic venous thromboembolism risk was unrelated to chemical thromboprophylaxis timing (0.5 *versus* 0.6 per cent for early and postoperative chemical thromboprophylaxis respectively (odds ratio (OR) 0.97, 95 per cent c.i. 0.41 to 2.47, $P = 1.000$). Postoperative bleeding developed in 34 (0.8 per cent) patients, and 781 intraoperative adverse events were identified in 544 (12.6 per cent) patients. Both intraoperative bleeding and complications were associated with significantly higher postoperative morbidity affecting multiple organ systems. Importantly, compared with postoperative chemical thromboprophylaxis, early administration increased the risk of postoperative bleeding ((1.5 *versus* 0.5 per cent for early and postoperative chemical thromboprophylaxis respectively (OR 2.94, 95 per cent c.i. 1.48 to 5.84, $P = 0.002$)) and intraoperative adverse events ((16.1 *versus* 11.5 per cent for early and postoperative chemical thromboprophylaxis respectively (OR 1.48, 95 per cent c.i. 1.22 to 1.80, $P < 0.001$)), as well as independently predicted their occurrences.

Conclusion: Intraoperative adverse events and bleeding that occur during and after antireflux surgery are associated with significant morbidity. Compared with postoperative chemical thromboprophylaxis, early initiation of chemical thromboprophylaxis confers a significantly higher risk of intraoperative bleeding complications, without appreciable additional protection from symptomatic venous thromboembolism. Therefore, postoperative chemical thromboprophylaxis should be recommended for patients undergoing antireflux surgery.

Introduction

Antireflux surgery including hiatus hernia repairs are becoming increasingly common[1]. Patients undergoing these procedures are at risk of both venous thromboembolism (VTE) and bleeding[2–4]. Both complications can incur significant morbidity, mortality, and healthcare cost. Although strong evidence supports the use of prophylactic doses of anticoagulants in the perioperative interval[5], these agents may confer an increased risk of postoperative bleeding[6]. Fundamentally, the use of chemical thromboprophylaxis must balance the efficacy of thromboembolic deterrence against the risk of bleeding in order to optimize perioperative outcomes.

Recent studies by the PROTECTinG (Perioperative Timing of Elective Chemical Thromboprophylaxis in General surgery) Investigators from the VERITAS (Victorian collaborative for Education, Research, Innovation, Training and Audit by Surgical trainees) Collaborative have demonstrated that timing of chemical thromboprophylaxis in the perioperative interval is highly variable for patients undergoing antireflux surgery[4,7]. This may affect bleeding risk[8–10]. Currently, there are no data to guide optimal timing of chemical thromboprophylaxis for antireflux surgery. The authors hypothesized that poorly timed chemical thromboprophylaxis may increase patient morbidity through bleeding or VTE-related complications. Therefore, it is important to establish an evidence base that guides chemical thromboprophylaxis timing in patients undergoing antireflux surgery.

Dissection around the diaphragmatic hiatus can be challenging during antireflux surgery. This is in part due to the

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close proximity of key anatomical structures, and operating within a confined mediastinal space. Furthermore, revisional surgery, the presence of pre-existing mesh material, and a large hernial sac may render dissection even more difficult. Thus, clear definition of tissue planes is of utmost importance to facilitate safe surgery around the diaphragmatic hiatus. In this context, the authors have observed that patients who have received preoperative or intraoperative chemical thromboprophylaxis tend to develop oozy tissues obscuring anatomical planes. Whether this increases the risk of intraoperative complications remains undefined.

The aim of this multicentre cohort study was to investigate the timing of chemical thromboprophylaxis (initiated at any time before skin closure *versus* after surgery) in patients undergoing antireflux surgery, and the effect this has on the rates of bleeding, symptomatic VTE, and intraoperative and postoperative complications.

Methods

Study design

Analysis of prospectively maintained databases and patient medical records was performed for consecutive patients who underwent elective antireflux surgery from 1 January 2010 to 31 December 2020 at 36 hospitals across Australia (*Table S1*). Patients who received fundoplication with and without a concurrent hiatus hernia repair were included. All surgeries were performed by upper gastrointestinal surgeons or by trainees directly under their supervision. Exclusion criteria included patients under 18 years of age, emergency surgery, congenital and traumatic diaphragmatic hernias, bariatric procedures, and where antireflux surgery was not the primary procedure. This study received ethics approval from the Austin Health Human Research Ethics Committee (Audit 21/85).

This study was not preregistered with an institutional registry.

Venous thromboembolism prophylaxis

Mechanical thromboprophylaxis included graduated compression stockings and sequential compression devices, used together or separately. Chemical thromboprophylaxis involved subcutaneous injection of low molecular weight heparin (either enoxaparin or dalteparin, daily) or unfractionated heparin (twice daily), at doses adjusted to each patient's weight and creatinine clearance according to local institutional guidelines. Chemical thromboprophylaxis was not given post-discharge from hospital. The timing of chemical thromboprophylaxis was classified into two groups: administered before (early group—after anaesthesia induction or intraoperatively) or after (postoperative group, within 24 h) skin closure. The type and timing of thromboprophylaxis were at the treating team's discretion.

Data collection and quality assurance

Data were collated through an online REDCap database. This included patient demographics, co-morbidities, hernia characteristics, perioperative parameters, operative details, type and timing of thromboprophylaxis, postoperative bleeding, and VTE events, together with other intraoperative and postoperative complications. Quality assurance measures were applied to maximize data accuracy and minimize inter-observer variations. These included the use of a standardized data collection tool, training sessions for data collectors, in-program prompting, real-time data entry support, and exclusion of patients with more than 5 per cent missing data. After data entry, a random audit of 10 per cent of data fields, by cross-checking with patient medical records, demonstrated a mean(s.d.) accuracy rate of 98.4(2.2) per cent across all sites. In total, 90 (2.0 per cent) patients were excluded due to greater than 5 per cent missing data.

Study endpoints and definitions

The incidence of postoperative bleeding was the primary endpoint for this study. Secondary endpoints included rates of major and minor bleeding, the need for blood transfusion and haemostatic re-intervention, changes in haemoglobin after surgery, length of hospital stay, surgical duration, intraoperative complications, unplanned intensive care admission, clinical VTE, perioperative complications, and mortality, all within 30 days post-surgery. The authors defined postoperative bleeding as any bleeding identified clinically, endoscopically, and/or radiologically that occurred within the same admission interval. Major bleeding was defined as the need for blood transfusion, re-intervention (surgical, endoscopic, or radiological), or a greater than 20 g/L fall in haemoglobin from baseline[9]. Minor bleeding was defined as any bleeding event that failed to meet major bleeding criteria. Clinical VTE within 30 days post-surgery was defined as radiologically proven (CT pulmonary angiography, ventilation-perfusion scintigraphy, and/or venous duplex ultrasonography) symptomatic disease in the deep veins of the upper or lower limbs or within the pulmonary arterial circulation. Asymptomatic VTE was intentionally not captured as most patients did not routinely undergo postoperative vascular imaging. Each patient's VTE risk was quantified using the Caprini score (less than or equal to 2, low risk; 3–4, moderate risk; and greater than or equal to 5, high risk)[11]. Intraoperative complications included bleeding, inadvertent pleural breach, injuries to the liver, oesophagus, stomach, spleen, lung, heart, vena cava, and aorta, as well as unplanned oesophagogastric resection, and laparoscopic to laparotomy conversion. Postoperative complications were based on definitions used by the oesophagectomy complication consensus guidelines[12]. As per local hospital policies, oral antiplatelet and anticoagulant agents, excluding aspirin, were withheld 3–7 days pre-surgery. Patients who required ongoing therapeutic anticoagulation were given enoxaparin up to 24 h before surgery. All patients were followed up in the clinic between 4 and 6 weeks post-discharge.

Power calculation

Based on previous data[4], a 1.5 per cent risk of bleeding after elective antireflux surgery was used for power calculation. A greater than 50 per cent relative risk reduction between study groups was considered clinically significant. Given the approximate ratio of 1 : 3 for early *versus* postoperative chemical thromboprophylaxis usage in this study cohort, the total sample size required was 4000 patients (early, 1000; and postoperative, 3000) to attain 80 per cent statistical power (two-tailed α less than 0.05).

Statistical analysis

Categorical and continuous variables were analysed using Fisher's exact test and Student's *t* test respectively. For non-parametric data, the Mann–Whitney *U* test was applied. To determine independent predictors of postoperative bleeding and intraoperative complications, whilst accounting for geographical differences in healthcare practices, a hierarchical multi-level multivariate logistic regression analysis was performed. In this

model, covariates were treated as fixed effects, whereas Australian states were treated as a random effect. The fixed-effect variables were selected for inclusion in the model based on a univariate *P* value of <0.200. Stepwise elimination of non-contributory variables was undertaken to arrive at the final model. A two-tailed $P < 0.050$ and 95 per cent c.i. around the OR that did not cross one was considered statistically significant. Statistical analyses were conducted using Prism v9 (GraphPad Software, San Diego, CA, USA) and R v4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the early and postoperative chemical thromboprophylaxis groups

In total, 4301 patients underwent elective antireflux surgery. Chemical thromboprophylaxis was administered early in 1099 (25.6 per cent) patients (before knife-to-skin, 556; and intraoperatively, 543), and after surgery in 3202 (74.4 per cent) patients. The number of chemical thromboprophylaxis exposure doses was similar between these two groups (median of 2 (interquartile range (i.q.r.) 2–4) and 2 (i.q.r. 2–3) for early and postoperative chemical thromboprophylaxis respectively, $P = 0.690$). The median time from skin closure to anticoagulant administration was 8.2 (i.q.r. 6.0–15.1) h in the postoperative chemical thromboprophylaxis group. Overall, both groups shared similar baseline characteristics, including patient demography, hiatus hernia size, operator experience, surgical approach, preoperative antiplatelet and anticoagulant use, VTE risk, and length of hospital stay (*Table 1*). The authors detected a small, but statistically significant, difference in age between the two groups (mean(s.d.) of 57.2(15.3) and 60.4(14.8) years for early and postoperative chemical thromboprophylaxis respectively, $P < 0.001$). All patients received perioperative mechanical thromboprophylaxis.

Clinical venous thromboembolism after antireflux surgery

Clinical VTE was identified in 24 (0.6 per cent) patients within 30 days post-surgery. Of these, 14 had pulmonary embolisms, six had deep-vein thromboses, and four had both pulmonary

Table 1 Baseline characteristics of the early and postoperative chemical thromboprophylaxis groups

Characteristics	Early chemical thromboprophylaxis, *n* = 1099	Postoperative chemical thromboprophylaxis, *n* = 3202	*P*
Demography			
Male	429 (39.0)	1171 (36.6)	0.148
Age (years), mean(s.d.)	57.2(15.3)	60.4(14.8)	<0.001
BMI (kg/m^2), mean(s.d.)	30.4(5.4)	29.8(4.9)	0.060
Caprini score, median (i.q.r.)	3 (2–4)	3 (2–4)	0.273
Operative details			
Hernia present	949 (86.4)	2732 (85.3)	0.426
Hernia size			0.233
Small–medium (<5 cm)	396 (41.7)	1252 (45.8)	
Large (>5 cm)	286 (30.1)	800 (29.3)	
Intrathoracic stomach	110 (11.6)	373 (13.7)	
Not documented	157 (16.5)	307 (11.2)	
Anaesthesia type			0.451
General only	1087 (98.9)	3156 (98.6)	
General and regional	12 (1.1)	46 (1.4)	
Surgeon level			0.237
Consultant	843 (76.7)	2512 (78.5)	
Trainee	256 (23.3)	690 (21.5)	
Approach			0.082
Open	13 (1.2)	90 (2.8)	
Laparoscopic	1067 (97.1)	3053 (95.3)	
Laparoscopic to open	19 (1.7)	59 (1.8)	
Fundoplication—yes	1099 (100.0)	3195 (99.8)	0.202
Fundoplication type			0.167
360°	166 (15.1)	497 (15.6)	
270°	339 (30.8)	868 (27.2)	
180°	570 (51.9)	1728 (54.1)	
90°	24 (2.2)	102 (3.2)	
Crural repair site			0.515
Anterior	47 (4.3)	113 (3.5)	
Posterior	746 (67.9)	2183 (68.2)	
Anterior and posterior	230 (20.9)	768 (24.0)	
Not documented	76 (6.9)	138 (4.3)	
Mesh use—yes	163 (14.8)	568 (17.7)	0.051
Revisional surgery—yes	62 (5.6)	230 (7.2)	0.083
Short gastric vessel divided—yes	170 (15.5)	529 (16.5)	0.458
Perioperative details			
Therapeutic anticoagulant use—yes	59 (5.4)	130 (4.1)	0.073
Antiplatelet agent use—yes	122 (11.1)	304 (9.5)	0.128
ASA score, median (i.q.r.)	2 (2–3)	2 (2–3)	0.578
Mechanical prophylaxis use—both	1099 (100.0)	3202 (100.0)	1.000
Hospital stays (days), mean(s.d.)	3.4(3.8)	3.4(5.3)	0.691

Values are *n* (%) unless otherwise stated. i.q.r., interquartile range.

embolisms and deep-vein thromboses. Twenty (83.3 per cent) of the events occurred in patients at moderate and high risk of VTE (based on Caprini score). The rate of clinical VTE was not significantly different between the early (six patients, 0.5 per cent) and postoperative (18 patients, 0.6 per cent) chemical thromboprophylaxis groups ($P = 1.000$) (*Table 2*), and timing of administration was not an independent predictor of VTE after antireflux surgery (*Table S2*).

Chemical thromboprophylaxis timing and bleeding risk after antireflux surgery

Overall, 34 (0.8 per cent) patients developed postoperative bleeding (*Table 2*). Of these events, 22 (64.7 per cent) were major events. Surgical haemostasis was required in seven (20.9 per cent) patients, and blood was transfused in 29 (85.3 per cent) patients. Intra-abdominal haemorrhage occurred most commonly (20 patients, 58.8 per cent), followed by bleeding in the abdominal wall (nine patients, 26.5 per cent), gastrointestinal tract (three patients, 8.8 per cent), and urinary tract (two patients, 5.9 per cent). Eight (early, two patients (0.2 per cent); and postoperative, six patients (0.2 per cent)) mortalities were recorded. One mortality was secondary to a saddle pulmonary embolism resulting in an out-of-hospital cardiac arrest. Another mortality was associated with major postoperative bleeding. All other deaths were not related to bleeding or VTE (myocardial infarction, three deaths; and respiratory failure, three deaths). Importantly, when compared with postoperative chemical thromboprophylaxis, early administration significantly increased the risk of bleeding (OR 2.94, 95 per cent c.i. 1.48 to 5.84, $P = 0.002$), particularly major bleeding (OR 2.93, 95 per cent c.i. 1.32 to 6.50, $P = 0.013$), after antireflux surgery (*Table 2*).

Critically, the authors found that postoperative morbidity was greatly increased in patients who bled after antireflux surgery (*Table S3*). Compared with non-bleeders, bleeding extended the length of hospital stay (mean(s.d.) 13.0(21.3) *versus* 3.3(4.5) days, $P = 0.012$). Bleeding was also significantly associated with higher rates of unplanned intensive care admissions, and mediastinal and abdominal sepsis, as well as increased respiratory, cardiac, neurological, and urological complications. A trend towards higher 30-day mortality was also observed in those who bled compared with non-bleeders (OR 18.4, 95 per cent c.i. 1.59 to 107.4, $P = 0.062$).

Early chemical thromboprophylaxis independently predicts bleeding after antireflux surgery

Factors that significantly correlated with postoperative bleeding on univariate analysis were included in a multivariate model (*Table 3*). An open surgical approach (OR 3.69, 95 per cent c.i. 1.39 to 9.82, $P = 0.009$), preoperative use of antiplatelet agents (OR 2.36, 95 per cent c.i. 1.04 to 5.36, $P = 0.040$), higher Caprini score (OR 1.19, 95 per cent c.i. 1.07 to 1.32, $P = 0.002$), and early chemical thromboprophylaxis (OR 3.25, 95 per cent c.i. 1.64 to 6.43, $P < 0.001$) were, on hierarchical multivariate analysis (accounting for regional differences in healthcare practices), independent predictors of bleeding after antireflux surgery.

Sensitivity analysis for postoperative bleeding and clinical venous thromboembolism

Given that the use of antiplatelet agents and open antireflux surgery are independent predictors of bleeding, these factors, together with preoperative anticoagulant use, may confound the risk of postoperative bleeding and VTE. Therefore, a sensitivity analysis excluding patients with any of these three characteristics was performed. This resulted in 902 (25.1 per cent) and 2692 (74.9 per cent) patients who received early and postoperative chemical thromboprophylaxis respectively. Consistent with our parental analysis, there was no significant difference in clinical VTE rates between the two groups (five (0.6 per cent) and 12 (0.4 per cent)) for early and postoperative chemical thromboprophylaxis respectively (OR 1.25, 95 per cent c.i. 0.48 to 3.39, $P = 0.779$). Notably, early chemical thromboprophylaxis remained significantly associated with higher rates of postoperative bleeding (12 (1.3 per cent) and 12 (0.4 per cent)) for early and postoperative chemical thromboprophylaxis respectively (OR 3.01, 95 per cent c.i. 1.34 to 6.74, $P = 0.008$), including both major (seven (0.8 per cent) and eight (0.3 per cent)) for early and postoperative chemical thromboprophylaxis respectively (OR 2.62, 95 per cent c.i. 1.00 to 7.16, $P = 0.027$) and minor (five (0.6 per cent) and four (0.1 per cent)) for early and postoperative chemical thromboprophylaxis respectively (OR 3.75, 95 per cent c.i. 1.13 to 12.23, $P = 0.049$) bleeding (*Table S4*).

Table 2. Postoperative bleeding and venous thromboembolism outcomes

Postoperative outcomes	Early chemical thromboprophylaxis, $n = 1099$	Postoperative chemical thromboprophylaxis, $n = 3202$	OR (95% c.i.)	P
All bleeding	17 (1.5)	17 (0.5)	2.94 (1.48,5.84)	0.002
Major bleeding	11 (1.0)	11 (0.3)	2.93 (1.32,6.50)	0.013
Minor bleeding	6 (0.5)	6 (0.2)	2.92 (0.93,9.16)	0.089
Surgery for bleeding	1 (0.1)	6 (0.2)	0.49 (0.04,2.92)	0.686
Blood transfusion for bleeding	6 (0.5)	7 (0.2)	2.51 (0.84,6.82)	0.109
Blood transfusion overall	10 (0.9)	19 (0.6)	1.54 (0.75,3.26)	0.286
Blood transfusion (units), median (i.q.r.)	2.5 (2.0–3.0)	2.0 (2.0–4.0)	–	0.253
Haemoglobin drop (g/L), mean(s.d.)	−23.8(16.1)	−24.6(20.9)	–	0.911
Venous thromboembolism	6 (0.5)	18 (0.6)	0.97 (0.41,2.47)	1.000
Deep-vein thrombosis only	1 (0.1)	5 (0.2)	0.58 (0.05,4.18)	1.000
Pulmonary embolism only	3 (0.3)	11 (0.3)	0.79 (0.24,2.53)	1.000
Concurrent deep-vein thrombosis and pulmonary embolism	2 (0.2)	2 (0.1)	2.92 (0.46,18.65)	0.271

Values are *n* (%) unless otherwise stated. i.q.r., interquartile range.

Table 3 Predictors of postoperative bleeding

Characteristics	Postoperative bleed, *n* = 34	No postoperative bleed, *n* = 4267	Univariate *P*	Multivariate	
				OR (95% c.i.)	*P*
Demography					
Male	15 (44.1)	1585 (37.1)	0.477	–	–
Age (years), mean(s.d.)	64.3(15.0)	59.5(15.0)	0.072	–	–
BMI (kg/m^2), mean(s.d.)	28.1(4.8)	29.9(5.1)	0.300	–	–
Caprini score, median (i.q.r.)	3 (3–5)	3 (2–4)	0.047	1.19 (1.07,1.32)	0.002
Operative					
Anaesthesia type—general and regional	0 (0.0)	58 (1.4)	1.000	–	–
Surgeon level—consultant	31 (91.2)	3324 (77.9)	0.063	–	–
Operative time (min), mean(s.d.)	171.3(81.5)	129.6(66.6)	0.006	–	–
Hernia present	32 (94.1)	3649 (85.5)	0.219	–	–
Hernia size			0.016	–	–
Large (>5 cm)–intrathoracic stomach	17 (53.1)	1552 (42.5)			
Small–medium (<5 cm)	8 (25.0)	1640 (44.9)			
Not documented	7 (21.9)	457 (12.5)			
Approach—open	5 (14.7)	176 (4.1)	0.013	3.69 (1.39,9.82)	0.009
Fundoplication—yes	34 (100.0)	4260 (99.8)	1.000	–	–
Fundoplication type			0.689	–	–
360°	6 (17.6)	657 (15.4)			
270°	11 (32.4)	1196 (28.0)			
180°	17 (50.0)	2281 (53.5)			
90°	0 (0.0)	126 (3.0)			
Crural repair site			0.164	–	–
Anterior	1 (2.9)	159 (3.7)			
Posterior	19 (55.9)	2910 (68.2)			
Anterior and posterior	12 (33.3)	986 (23.1)			
Not documented	2 (5.9)	212 (5.0)			
Mesh use—yes	13 (38.2)	718 (16.8)	0.004	–	–
Revisional surgery—yes	4 (11.8)	288 (6.7)	0.287	–	–
Short gastric vessel divided—yes	5 (14.7)	694 (16.3)	1.000	–	–
Any intraoperative complication	7 (20.6)	537 (12.6)	0.188	–	–
Perioperative					
Therapeutic anticoagulant use—yes	2 (5.9)	187 (4.4)	0.660	–	–
Antiplatelet agent use—yes	8 (23.5)	418 (9.8)	0.016	2.36 (1.04,5.36)	0.040
ASA score, median (i.q.r.)	3 (2–3)	2 (2–3)	0.043	–	–
Mechanical prophylaxis use—both	34 (100.0)	4267 (100.0)	1.000	–	–
Chemical thromboprophylaxis type—UFH	11 (32.4)	760 (17.8)	0.040	–	–
Chemical thromboprophylaxis timing—early	17 (50.0)	1082 (25.4)	0.002	3.25 (1.64–6.43)	<0.001

Values are *n* (%) unless otherwise stated. i.q.r., interquartile range; UFH, unfractionated heparin.

Table 4 Intraoperative complications and timing of chemical thromboprophylaxis

Intraoperative complications	Early chemical thromboprophylaxis, *n* = 1099	Postoperative chemical thromboprophylaxis, *n* = 3202	OR (95% c.i.)	*P*
Total number of complications	260	521	–	–
Complication rate per patient	177 (16.1)	367 (11.5)	1.48 (1.22,1.80)	<0.001
Bleeding	55 (5.0)	113 (3.5)	1.44 (1.03,1.99)	0.038
Liver injury	47 (4.3)	88 (2.7)	1.58 (1.10,2.26)	0.016
Pleural breach	44 (4.0)	74 (2.3)	1.76 (1.21,2.58)	0.005
Oesophageal injury	13 (1.2)	17 (0.5)	2.24 (1.10,4.47)	0.034
Gastric injury	29 (2.6)	47 (1.5)	1.82 (1.15,2.90)	0.016
Gastric/oesophageal resection	7 (0.6)	13 (0.4)	1.57 (0.58,4.00)	0.314
Splenic injury	10 (0.9)	42 (1.3)	0.69 (0.33,1.35)	0.340
Lung injury	27 (2.5)	56 (1.7)	1.42 (0.89,2.22)	0.161
Cardiac injury	3 (0.3)	2 (0.1)	4.38 (0.89,24.71)	0.109
Major venous injury	3 (0.3)	4 (0.1)	2.19 (0.55,8.16)	0.382
Major arterial injury	3 (0.3)	6 (0.2)	1.46 (0.40,6.12)	0.702
Laparoscopic to open conversion	19 (1.7)	59 (1.8)	0.94 (0.54,1.55)	0.896
Surgery duration (min), mean(s.d.)	135.3(59.7)	128.1(69.0)	–	0.002

Values are *n* (%) unless otherwise stated.

Early chemical thromboprophylaxis and intraoperative complications during antireflux surgery

Overall, 781 (18.2 per cent) intraoperative complications occurred in 544 patients. Compared with postoperative chemical thromboprophylaxis, early administration was associated with a longer operative time (mean(s.d.) of 135.5(59.7) *versus* 128.1(69.0) min, $P = 0.002$), and an increased risk of intraoperative bleeding (OR 1.44, 95 per cent c.i. 1.03 to 1.99, $P = 0.038$), pleural breach (OR 1.76, 95 per cent c.i. 1.21 to 2.58, $P = 0.005$), liver injury (OR

Table 5 Predictors of intraoperative-associated complications

Characteristics	Intraoperative-associated complications, $n = 433$	No intraoperative-associated complications, $n = 3868$	Univariate P	Multivariate	
				OR (95% c.i.)	P
Demography					
Male	151 (34.9)	1449 (37.5)	0.295	–	–
Age (years), mean(s.d.)	62.4(13.8)	59.3(15.1)	<0.001	–	–
BMI (kg/m^2), mean(s.d.)	30.0(5.3)	29.9(5.0)	0.270	–	–
Caprini score, median (i.q.r.)	3 (2–4)	3 (2–4)	<0.001	1.08 (1.02,1.14)	0.006
Operative					
Anaesthesia type—general and regional	12 (2.8)	46 (1.2)	0.013	–	–
Surgeon level—consultant	354 (81.8)	3001 (77.6)	0.050	–	–
Hernia present	394 (91.0)	3287 (85.0)	0.001	–	–
Hernia size			<0.001		
Large (>5 cm)–intrathoracic stomach	211 (53.6)	1358 (41.3)		1.81 (1.30,2.52)	<0.001
Small–medium (<5 cm)	117 (29.7)	1531 (46.6)			
Not documented	66 (16.8)	398 (12.1)			
Approach—open	47 (10.9)	134 (3.5)	<0.001	6.10 (4.16,8.96)	<0.001
Fundoplication—yes	432 (99.8)	3862 (99.8)	0.572	–	–
Fundoplication type			0.078	–	–
360°	83 (19.2)	580 (15.0)			
270°	126 (29.2)	1081 (28.0)			
180°	210 (48.6)	2088 (54.1)			
90°	13 (3.0)	113 (2.9)			
Crural repair site			0.109	–	–
Anterior	22 (5.1)	138 (3.6)			
Posterior	268 (61.9)	2661 (68.8)			
Anterior and posterior	117 (27.0)	881 (22.8)			
Not documented	26 (6.0)	188 (4.9)			
Mesh use—yes	109 (25.2)	622 (16.1)	<0.001	–	–
Revisional surgery—yes	58 (13.4)	234 (6.0)	<0.001	2.08 (1.47,2.93)	<0.001
Short gastric vessel divided—yes	99 (22.0)	600 (15.5)	<0.001	–	–
Perioperative					
Therapeutic anticoagulant use—yes	29 (6.7)	160 (4.1)	0.018	1.60 (1.03,2.48)	0.035
Antiplatelet agent use—yes	62 (14.3)	364 (9.4)	0.002	1.30 (0.96,1.75)	0.091
ASA score, median (i.q.r.)	2 (2–3)	2 (2–3)	0.054	–	–
Mechanical prophylaxis use—both	433 (100.0)	3868 (100.0)	1.000	–	–
Chemical thromboprophylaxis timing and type			<0.001		
Early, UFH	67 (15.5)	362 (9.4)	<0.001	1.46 (1.01,2.10)	0.044
Early, LMWH	85 (19.6)	585 (15.1)	0.017	–	–
Postoperative, UFH	53 (12.2)	289 (7.5)	0.001	–	–
Postoperative, LMWH	228 (52.7)	2632 (68.0)	<0.001	–	–

Values are n (%) unless otherwise stated. i.q.r., interquartile range; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

1.58, 95 per cent c.i. 1.10–2.26, $P = 0.016$), oesophageal injury (OR 2.24, 95 per cent c.i. 1.10 to 4.47, $P = 0.034$), and gastric injury (OR 1.82, 95 per cent c.i. 1.15 to 2.90, $P = 0.016$) (*Table 4*).

Early chemical thromboprophylaxis with unfractionated heparin independently predicts intraoperative complications

Factors that significantly correlated with intraoperative complications on univariate analysis were included in a multivariate model (*Table 5*). Of these, higher Caprini score (OR 1.08, 95 per cent c.i. 1.02 to 1.14, $P = 0.006$), large hernia size (OR 1.81, 95 per cent c.i. 1.30 to 2.52, $P < 0.001$), an open approach (OR 6.10, 95 per cent c.i. 4.16 to 8.96, $P < 0.001$), revisional surgery (OR 2.08, 95 per cent c.i. 1.47 to 2.93, $P < 0.001$), preoperative therapeutic anticoagulation (OR 1.60, 95 per cent c.i. 1.03 to 2.48, $P = 0.035$), and early use of unfractionated heparin (OR 1.46, 95 per cent c.i. 1.01 to 2.10, $P = 0.044$) were, on hierarchical multivariate analysis, independent predictors of intraoperative complications during antireflux surgery.

Discussion

In this national cohort study, the authors examined for the first time (to the best of their knowledge) the impact of chemical thromboprophylaxis timing on thromboembolic, bleeding, and other complications during and after antireflux surgery. The key findings were increased rates of bleeding, particularly major bleeding, when chemical thromboprophylaxis was initiated before skin closure. Moreover, it was demonstrated that, despite an overall low rate of postoperative bleeding, patients who bled experienced higher morbidity than those who did not bleed. Importantly, compared with those who received postoperative chemical thromboprophylaxis, initiation of chemical thromboprophylaxis before skin closure, particularly when unfractionated heparin was used, significantly increased the

risk of intraoperative complications. Notably, the incidence of symptomatic VTE after antireflux surgery was low, and early chemical thromboprophylaxis did not appear to confer significantly greater protection against clinical VTE. Therefore, postoperative chemical thromboprophylaxis is a safer approach for patients undergoing antireflux surgery compared with thromboprophylaxis given during anaesthesia.

Overall, these rates of clinical VTE, postoperative bleeding, and non-bleeding complications are comparable to contemporary international literature[13–16]. The observation that postoperative chemical thromboprophylaxis is associated with a lower risk of bleeding than early usage in antireflux surgery is consistent with studies in gallbladder[9], liver[17], ventral hernia[10], bariatric[18], breast[19], hip[20], and abdominal visceral surgery[8]. Additionally, within major abdominal surgery, subgroup analysis of patients with an inherently high thromboembolic risk also favours postoperative chemical thromboprophylaxis over early usage[21]. These reports, along with findings from two recent meta-analyses, one of randomized trials involving different surgical disciplines[22], and the other of randomized trials and cohort studies involving major abdominal surgery[23], demonstrated that postoperative chemical thromboprophylaxis did not diminish protection against VTE. Therefore, in the context of significant global variations in practice[4,24], this study contributes to a growing body of evidence, spanning multiple specialties and procedural types, that postoperative chemical thromboprophylaxis is a safer approach for patients, resulting in a similar risk of VTE, but lower rates of bleeding.

Despite the anti-thromboembolic benefits of chemical thromboprophylaxis, there is now high-level evidence demonstrating that prophylactic doses of anticoagulants carry a clinically significant risk of postoperative bleeding[6]. Here, it was shown for the first time (to the best of the authors' knowledge) that, in antireflux surgery, this increased risk of bleeding manifests intraoperatively, and is associated with a higher rate of other adverse events. This validates the authors' own anecdotal experience that patients who received early chemical thromboprophylaxis tended to develop oozy tissue planes more readily than when chemical thromboprophylaxis was started after surgery. This observation is further supported by the finding that early use of unfractionated heparin, but not low molecular weight heparin, independently predicts the occurrence of intraoperative complications. The fact that the onset of action of unfractionated heparin is significantly quicker than that of low molecular weight heparin when delivered subcutaneously (20–60 *versus* 60–120 min) lends biological plausibility to this analysis[25]. The authors hypothesize that chemical thromboprophylaxis given before skin closure leads to oozy tissues planes, obscuring vision around the hiatus, and thus potentiating injury to regional structures, particularly the oesophagus, stomach, pleura, and liver, located in close proximity to each other.

These findings are clinically important, especially because both bleeding and intraoperative complications are associated with significantly higher postoperative morbidity, and potential mortality. Furthermore, most of the independent risk factors for bleeding and intraoperative complications that were identified, such as patient co-morbidities (Caprini score), hernia size, open surgery, and revisional surgery, are not modifiable. In contrast, however, chemical thromboprophylaxis timing is an easily modifiable risk factor for reducing patient morbidity.

It is important to highlight that, even in high-volume centres, most surgeons will perform less than 30 fundoplications per year[1,14]. Therefore, the relationship between chemical thromboprophylaxis timing and bleeding may not be easily appreciable at an institutional level, let alone by individual surgeons. However, based on the current data, the number needed to treat to prevent one additional event of clinical VTE is 1000 when chemical thromboprophylaxis is given early. By comparison, the number needed to harm is 100 for postoperative bleeding, and 21 for intraoperative complications. Translating this to a population level, with over 20 000 antireflux surgeries performed annually in the USA[14], a 1.0 per cent absolute risk reduction in postoperative bleeding and a 4.6 per cent absolute risk reduction in intraoperative complications potentially save over 1100 patients from bleeding-related morbidity and mortality per year.

The authors acknowledge that this study included only clinical VTE, and asymptomatic events were not routinely screened by radiological tests. Additionally, as patients may present to other health services for care, the true total (clinical and asymptomatic) incidence of VTE in our cohort is unknown. Despite this, all patients were followed up, and the reported rate of symptomatic VTE is similar to that in contemporary series. Moreover, given the low rate of VTE seen in this cohort, this study was not powered to detect a true difference in clinical VTE. It is recognized that there is potentially an optimal window within the postoperative interval to start chemical thromboprophylaxis. Although this is beyond the scope of this study, the authors have examined this aspect in another publication[26]. They considered performing propensity score matching to address minor imbalances between the groups. However, given the relatively low proportion of bleeding and VTE events, this would not have produced meaningful conclusions.

Collaborators

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Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data contained within this article can be made available on a collaborative basis.

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