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Pre-operative education improves patient compliance with extended venous thromboembolic prophylaxis

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ABSTRACT

Venous thromboembolism (VTE) is a medical condition which commonly manifests as deep venous thrombosis (DVT) and pulmonary embolism (PE). The incidence of VTE is low across the population, but potentially devastating those who develop this complication. Risk factors for patients developing VTE include surgical procedures, especially abdominal surgery for cancer. Prophylactic measures which are commonly utilised to prevent VTE include pharmacological prophylaxis using anticoagulant agents, and mechanical calf compression.

There is evidence to suggest that given the increased risk in patients undergoing major abdominal or pelvic surgery, administration of extended-duration VTE prophylaxis should be recommended in these patients. This practice is supported by national and international guidelines.

Compliance with extended-duration VTE prophylaxis and the effectiveness of dedicated pre-operative education on compliance has not been extensively described in the literature.

This thesis aims to evaluate compliance with extended VTE prophylaxis in a cohort of patients undergoing major abdominal surgery for malignancy, to assess factors which may contribute to compliance or non-compliance, and to measure the effect of formal pre-operative education on patient compliance.

Patients who had undergone major abdominal surgery for cancer were prescribed an extended course of daily low-molecular weight heparin (LMWH) injections and were recruited into two sequential cohorts. The first cohort received standard care without any pre-operative education about VTE and the treatment. The second cohort received formal verbal and written education prior to their surgery.

All patients were interviewed following the treatment and were asked about their degree of compliance with the treatment and questioned about their attitudes and beliefs regarding VTE and the treatment. The results demonstrated an improved compliance with extended-duration outpatient VTE prophylaxis, but minimal alteration in their beliefs regarding VTE. These results, while not statistically significant, suggest that pre-operative education has some merit. Additionally, patients who were educated believed that a longer duration of VTE prophylaxis was necessary to prevent VTE than those who were not educated, and this would be a potential area which could be the target of further studies with larger patient populations.

DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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1. INTRODUCTION

The term “venous thromboembolism” (VTE) refers to a range of conditions including deep venous thrombosis (DVT) and pulmonary embolism (PE). These conditions can range in severity from being subclinical, incidentally detected, to being potentially devastating and fatal.

While the incidence of VTE is relatively low, the clinical implications for the patient are significant. Additionally the financial burden on the Australian health system from patients developing VTE is estimated to be $1.72 billion annually[1].

Hospitalised patients, are at an increased risk of developing VTE. Several modalities are available to reduce or even prevent development of VTE. These include pharmacological prophylaxis in the form of oral or injectable anticoagulant agents, and various forms of mechanical calf compression ranging from simple compression stockings to pneumatic sequential calf compressors.

Many guidelines have been published nationally and internationally, all of which support this combination of modalities in order to prevent the development of VTE in hospitalised patients.

VTE risk can be stratified based on a variety of different factors, including type of surgery, presence of malignancy, and medical co-morbidities. The antithrombotic guidelines published by the American College of Chest Physicians [2] for non-orthopaedic surgical patients utilise a risk stratification model based on previously-validated risk factor point systems [3, 4].

Patients undergoing surgery are at an increased risk of VTE compared to the general hospital inpatient population and thus require careful, consistent implementation of VTE prophylaxis. Most surgical units administer inpatient thromboprophylaxis to their operative patients as injections of low-molecular weight heparin (LMWH) or unfractionated heparin as well as fitting them with compression stockings.

Certain surgical procedures have a substantially higher risk of VTE than the average. It is a well-established fact that patients undergoing orthopaedic procedures such as lower limb joint replacements are at an increased risk of VTE and the high-risk period extends beyond their inpatient stay due to their relative immobility after their operation. It is routine practice by many orthopaedic surgeons to administer an extended course of VTE prophylaxis for several weeks after the patient has been discharged from their acute hospital stay.

Major abdominal or pelvic surgery and malignancy are two factors which independently increase the risk of developing VTE, which is reflected in risk stratification scoring systems such as Caprini risk assessment model. [5] Both of these factors are present in patients who are undergoing major oncological resectional surgery.

The risk of developing **clinically** overt VTE has been shown to be 2.83% following general surgery for cancer, with 41% occurring later than 21 days after surgery. VTE is also the most common cause of death at 30 days after surgery.[6]

In patients hospitalised with medical illness, **asymptomatic** DVT detected by lower-limb compression ultrasonography was associated with a threefold increase in mortality.[7] Large autopsy series also indicate that fatal PE is uncommonly preceded by symptomatic DVT.[8]

The financial cost of VTE in Australia has been calculated to be $1.72 billion with an additional $20 billion taking into account loss of wellbeing.[9]

The rationale behind administration of extended-duration VTE prophylaxis is therefore two-fold:

- It has been shown to significantly reduce by more than half the risk of both sub-clinical/incidental VTE (which have the potential to cause subsequent morbidity and mortality down the track) and clinical VTE, which itself has a high risk of mortality.[10]
- A large proportion of VTE occurs at a delayed interval following the initial surgery, after the patient has already been discharged from hospital.

Compliance with extended-duration VTE prophylaxis has been studied in the orthopaedic population for both injectable and oral VTE chemoprophylaxis, but not in the general surgical population. The effectiveness of dedicated pre-operative education has not been reported in the available literature.

This study aims to evaluate compliance with extended VTE prophylaxis in a cohort of patients undergoing major abdominal surgery for malignancy, to assess factors which may contribute to compliance or non-compliance, and to measure the effect of pre-operative education on patient compliance.

1.1 Background of study

The dual aims of this project are:

- to demonstrate that formal preoperative education will improve patient compliance with extended VTE prophylaxis, in the context of the progressive rollout of a quality improvement program.
- to identify factors which may contribute to patient compliance with the prescribed treatment regimen.

1.2 Research Aims and questions

This project aims to examine the hypothesis that formal pre-operative education before surgery will positively influence patient compliance with an extended-duration course of prophylactic LMWH injections at home following discharge from hospital. These injections will be self-administered, or will be administered by a friend or family member.

The secondary aim is to identify factors and patient attitudes towards VTE complications which may lead to compliance/non-compliance. These factors could then be targeted with further studies to improve compliance.

Routine objective assessment and diagnosis of VTE in the patients (such as through direct venography/ultrasound) is not a part of this study. This has already been thoroughly addressed in other much larger studies and the benefit of extended VTE prophylaxis in preventing VTE events has already been established. If there is any clinical suspicion of VTE, the trial patients will be assessed along the usual diagnostic pathway.

2. LITERATURE REVIEW

2.1 Incidence of VTE after major abdominal cancer surgery

VTE is over 100 times more likely to occur in hospitalised patients than in the general community[11].

The overall incidence of ***clinical*** VTE has been quoted as occurring in less than 0.34 per cent of general medical inpatients[12]. This is in contrast to the estimated ***overall*** incidence of VTE quoted at 8%. Therefore the majority of VTE will be asymptomatic and subclinical. Nonetheless, given that a clinical VTE is still potentially life-threatening (with PE accounting for 10 per cent of in-hospital deaths[13]) appropriate risk-stratification and associated preventative measures should be considered.

Patients undergoing major abdominal and pelvic surgery, particularly those undergoing resection of malignancy, are at an increased risk of developing VTE complications. A hypercoagulable state persists in post-surgical patients and this is further heightened in patients with malignant disease[14]. The incidence of VTE in this subset of patients undergoing abdominal surgery is as high as 19-29% without adequate venous thromboprophylaxis [15].

The incidence of VTE also appears to be increasing. A large multicentre retrospective cohort study of 82 acute Australian centres, and including more than 4,000,000 post-operative elective surgical patients from 2002 – 2009 actually demonstrated an increase in the incidence of VTE by 30% over that study period. Mortality was 8% in this analysis and remained stable over the eight year time-frame.[16]

Laparoscopic surgery is becoming utilised more frequently, particularly in the realm of cancer resection surgery, and while there are benefits to patients such as shorter length of inpatient hospital stay, these patients are still at risk of VTE. In fact, a large meta-analysis of 11 randomised control trials showed no statistical difference in the incidence of post-operative VTE between open and laparoscopic colorectal cancer resectional surgery[17].

Not all VTE will occur during a surgical patient's inpatient hospital stay. Studies have shown that VTE can occur as a delayed phenomenon after discharge from hospital. In the literature, the incidence of post-operative DVT has been quoted to be as high as 25% and occurring up to six weeks after surgery[18]. A study which quoted an incidence of PE of 0.63%, also demonstrated that the median timeframe for occurrence of delayed, or out-of-hospital, PE in post-operative patients was six days after discharge, or 18 days after surgery[19].

2.2 Extended duration VTE prophylaxis

In our institution, as with the majority of medical centers nationally and worldwide, inpatient VTE prophylaxis is routinely administered for all surgical patients who do not have a specific contraindication such as increased bleeding risk.

There have been studies demonstrating significant reductions of DVT following prolonged VTE prophylaxis. The ENOXACAN II (enoxaparin and cancer) study, a large double-blinded randomised trial[20] evaluated patients undergoing elective open surgery for cancer. These patients received either enoxaparin or a placebo for 21 days post-operatively and it was shown that there was a reduction in U/S-detected lower limb DVT from 12% in the control group to 4.8% in the enoxaparin group within the 28 day double-blind period. This correlated to a risk-reduction (RR) of 60%. There was only one PE in the placebo group and none in the enoxaparin group. Even over the three month follow-up, the total VTE incidence was 13.8% in the placebo, and 5.5% in the intervention group, which still resulted in a RR of 60%.

A Cochrane review[10] was conducted in 2009 which analysed both randomised and non-randomised trials evaluating extended duration VTE prophylaxis, in the form of low molecular weight heparin, versus placebo or control in patients undergoing major abdominal and pelvic surgery. The outcome measures were VTE events and/or pulmonary embolism assessed by objective means such as routine imaging (ascending bilateral venography, ultrasonography, pulmonary ventilation/perfusion scintigraphy, spiral CT scan) or autopsy. Studies which only reported on clinical diagnosis, without objective measurements, were excluded.

In total there were 4 studies which met the criteria and were thus included in the meta-analysis. The participants in these studies had undergone general abdominal or pelvic surgery via either an open or laparoscopic approach. Three of the studies included a mix of benign and malignant conditions[20-22], while one of the studies[23] included surgery for malignant disease only. The surgical procedures included open and laparoscopic cases. There was a significant reduction of overall VTE events in the intervention group 6.1% vs the control group's 14.3% ($P<0.0005$). The number needed to treat (NNT) to avoid one case of VTE was thirteen patients. There were no significant differences between the two groups regarding the incidence of adverse bleeding events and mortality. The conclusion was that administration

of LMWH for 4 weeks compared to 5-7 days after major abdominal surgery significantly reduces incidence of VTE without jeopardising safety.

Subsequent to this Cochrane meta-analysis, there have been other large randomized studies supporting the use of extended-duration VTE prophylaxis in this setting. Vedovati et al[24] published a trial of 225 post-laparoscopic colorectal surgical patients who were randomized to short (one week) or extended (continued to four weeks) LMWH therapy. These patients were all investigated by lower limb Doppler at four weeks after surgery (or investigated for PE if they developed suspicious symptoms) – 9.7% of the control group vs 0% of the interventional group developed VTE (P=0.001).

Many published international and national guidelines provide evidence-based recommendations for post-surgical patients to be administered chemical prophylaxis for a period up to 28 days from the date of surgery, including the period of convalescence after being discharged from the acute hospital care. This is most commonly given in the form of daily subcutaneous injection of low molecular weight heparin (LMWH).

The "Prevention of Venous Thromboembolism" best practice guidelines[25] published by the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism recommend 5-10 days of VTE prophylaxis routinely following major abdominal surgery, but also make the statement that:

> *"Patient groups where the value of extended prophylaxis has been demonstrated and where prophylaxis should be continued for 28-35 days include patients following hip fracture or hip replacement surgery and possibly major curative surgery for cancer."*

The American College of Chest Physicians published evidence-based guidelines[2] in 2012 for a variety of scenarios, of which non-orthopedic surgical patients undergoing major abdominal or pelvic surgery had the following more definitive recommendation:

> *"For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis."*

From the United Kingdom, the NICE[26] (National Institute for Health Care and Excellence) evidence-based recommendations for patients undergoing major abdominal or pelvic cancer surgery also included a longer duration for VTE prophylaxis:

> *"If major cancer surgery in the abdomen or pelvis, continue pharmacological prophylaxis for 28 days after surgery."*

This practice is in place routinely at several large tertiary centres around the world. This was adopted as standard practice at our centre in 2014. All of the patients undergoing major abdominal or pelvic surgery for malignancy at our institution are prescribed a course of extended-duration VTE prophylaxis for 28 days following the day of surgery.

2.3 Factors affecting compliance with treatment

Compliance (which is often interchanged with the term 'adherence') can be defined as the 'extent to which patient's behaviours (including medication-taking) coincides with medical or healthcare advice'[27].

Patient compliance with any treatment regimen may be affected by a number of factors. Issues around poor understanding of the rationale behind the treatment, and/or anxiety regarding the treatment, could easily be addressed by providing formal patient education preoperatively.

Noncompliance with extended VTE prophylaxis specifically has been assessed before, most notably in an orthopaedic setting, where such programs are routinely implemented in many centres following major joint surgery. In fact, there has also been evidence supporting and a shift toward using direct-acting oral anticoagulants (DOACs) such as rivaroxaban in patients undergoing major lower limb orthopaedic surgery. Wilke [28] previously estimated that noncompliance with extended duration injectable VTE prophylaxis is in the range of 13-21%.

The importance of compliance to this treatment has been demonstrated in a study of outcomes of compliance to extended-duration VTE was assessed in 1214 elderly hip fracture patients who had extended pharmacological VTE prophylaxis[29]. These patients were stratified into three groups - 'Good compliant' (completing the full 28 days of treatment), 'Partial compliant' (completing 14-27 days), 'Poorly compliant'/'Non-compliant' (prophylaxis shorter than 14 days, or 0 days respectively). Of the three

groups, the overall VTE rate was lowest in the 'Good compliant' group (4.2% vs 5.4% vs 9.6% respectively, P=0.013).

Carrothers et al[30] investigated the compliance of patients to extended duration rivaroxaban (an direct-acting oral anticoagulant, rather than injectable) for VTE prophylaxis after major orthopaedic surgery. They identified female gender (68% vs 32%, p=0.003), older age (mean 70 vs 65 years, p<0.0001), and lower BMI (BMI 29 vs 31, p<0.0007) as significant risk factors leading to increased non-compliance. Even so, the non-compliance rate was only 4%, which compares favourably to other VTE prophylaxis modalities.

Studies have also addressed medication compliance in other areas. Kronish et al[31] examined the barriers to medication compliance in stroke patients. Patients overall self-reported non-compliance rate was 40%. They identified increased concerns about medications (OR 5.02, p<0.001) and perceived discrimination from the health system (OR 1.85, p=0.008) as significant factors contributing to non-compliance. Kronish also reviewed adherence to cardiovascular medications[32] quoting a prevalence of non-compliance of 43%. He proposed four key areas/issues that affect non-compliance:

1. Environmental – workplace, community resources, media
2. Provider Behaviours – communication skills, regimen complexity, monitoring and continuity
3. Health System – cost, formulary restrictions, insurance cover, access to care and system complexity
4. Patient attributes – disease and medication beliefs, self-efficacy, psychological disorders, memory and cognition, and social support

2.4 Measurements of compliance

Kronish et al[32], in the same paper, lists several methods of assessing compliance such as self-reporting, along with more objective measures including physiological/laboratory markers, pill count and electronic medication monitors.

Lam et al[33] also describes the different measures of compliance which can be grouped into direct and indirect methods.

Direct measures include:

- Laboratory assay of the drug or its metabolites
- Database analysis such as extracting data about patients' refilling of pharmacy scripts in the case of patients on long-term medications,
- Electronic medication monitoring with the use of a microprocessor embedded in the container which is an accurate method but can be costly and may also alert the patient that they are under surveillance

Indirect measures include:

- Pill counting involves counting the number of dosage units that have been taken between two dates in the formula (Number of dosage units dispensed − number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits). This is also accurate but also doesn't necessarily give information about the pattern of taking medication
- Subjective methods such as clinician assessments and patient self-reporting. These tend to be less reliable than the methods described above, but they are simple, low-cost and also may allow a more qualitative insight-oriented assessment of patient concerns and of barriers to compliance.

2.5 Patient compliance with extended-duration VTE prophylaxis regimens

There are several studies which examine medical staff/health services compliance with local guidelines and institution of extended-duration prophylaxis [34-36]. They have also examined the beneficial effect of providing education to improve compliance with prescribing/administering extended VTE prophylaxis [34, 37].

Most of the research regarding compliance to medication involves measurements of long-term medications to treat chronic disease, not of a limited course of treatment. The literature contains very few studies specifically examining patient compliance with a prescribed course of extended-duration VTE prophylaxis.

The ETHOS study [38] of 2999 high-risk orthopaedic patients receiving extended-duration VTE prophylaxis found a compliance rate of 87.7% (although their definition of compliance was less strict than some other studies, specifying >80% of treatment and no more than two consecutive days without treatment). The majority (94%) received LMWH, with the rest receiving an oral vitamin-K antagonist (warfarin), fondaparinux (injection), or unfractionated heparin (injection). The most common reason for non-compliance was "drug not bought" (33.4%), with other factors affecting compliance being access to treatment, patient education, person responsible for administering the treatment, type of hospital ward at discharge. Interestingly, having injections (as opposed to oral anticoagulant medication) was not found to be a barrier to compliance.

Only one publication could be found which specifically examine patient compliance with extended VTE prophylaxis following major abdominal/pelvic surgery. Lemke et al [39] interviewed 100 patients receiving 28 days of post-operative LMWH following major hepatic or pancreatic surgery. 81.4% reported perfect compliance with the regimen. The most common reasons for not completing the treatment regimen were early cessation by the healthcare provider, or because of a poor experience with the injections. 78.4% of patients self-injected the LMWH, and 55.7% did not find the injections bothersome.

2.6 Conclusion

There is ample evidence to support the use of extended-duration VTE prophylaxis after major abdominal surgery and this is routine practice in many centres, as published in multiple national and international guidelines.

While there have been studies examining rates of compliance with extended-duration VTE prophylaxis, most of the evidence is in patients undergoing orthopaedic surgery, or those with chronic disease on long-term medications. There is a paucity of evidence looking specifically at compliance with this treatment following major abdominal surgery.

Multiple barriers to compliance for various treatment regimens have also been described, but again not in the post-major abdominal surgery setting.

3. METHODOLOGY

3.1 Study design

This was a prospective study of compliance with a prescribed regimen of outpatient post-operative VTE prophylaxis in patients undergoing major abdominal surgery for cancer. Two sequential patient cohorts were recruited, the first being a control group receiving standard practice of outpatient VTE prophylaxis, and the second group receiving the intervention of pre-operative education in the form of verbal and written information.

The patients were recruited sequentially, and not in a randomised fashion, as there was a concern about the patients, and more importantly the nursing staff who provided the patient education for technique of administering the injections, becoming aware that there were some patients who had received pre-operative education and some who had not. This had the potential to create an unwanted Hawthorne effect, which could affect the experience of the controls as more patients were recruited over the duration of the study. Also, by sequentially recruiting the two cohorts, there was generation of a Hawthorne effect in the second cohort of patients (pre-operative education) which was actually an intentional part of the study.

3.2 Ethics

This study was submitted for review by the Eastern Health Human Research Ethics Committee (HREC). Given that it was essentially a study investigating the behaviours of patients regarding an established best practice which we were introducing into our practice (ie. a prolonged course of injections of LMWH), rather than a drug trial at the injections themselves, it was assessed via the low risk pathway.

With approval from the HREC, patients were not formally consented prior to the commencement of the inpatient LMWH injections as they were having what could be considered best/standard practice and because the process of formally consenting the patients may have influenced the patients to seem more compliant than they would otherwise have been. A statement at the time of questionnaire informed patients that the answers they gave to the questionnaire would be stored for use in this research project.

3.3 Inclusion and Exclusion Criteria

Patients booked to undergo major elective abdominal surgery for malignancy were identified from the Box Hill Hospital Upper Gastrointestinal Surgery Unit's hospital waiting lists and were considered eligible candidates for inclusion in the study.

Exclusion criteria included the following exclusions:

- Patients with cognitive and/or physical impairment which may have prevent them from being able to successfully administer the LMWH injections
- Patients who were already on anticoagulant or anti-platelet medication for other indications prior to their surgery – they would be required to recommence their medication post-operatively making LMWH redundant
- Patients who only spoke a language other than English – this would be a barrier to receiving education, and also to completing the questionnaire without an interpreter (especially over the phone)

3.4 Standard of care

As part of the upper gastrointestinal surgery unit's standard practice, all patients undergoing major abdominal cancer surgery are advised post-operatively that they are at an increased risk for developing VTE and therefore recommended to have extended duration VTE prophylaxis for 28 days from the date of surgery. During the period of inpatient hospitalisation, patients are given prophylactic subcutaneous LMWH (in this institution the standard treatment is a once-daily dose of 5000 units Dalteparin injected subcutaneously).

Prior to the implementation of this study, patients would usually be discharged from hospital with the daily injections to be administered by an ambulatory nursing service such as Hospital in the Home. On the initiation of this study however, the patients were educated by the ward nursing staff in the technique of self-injecting the prior to their discharge from hospital, and then would be responsible for giving the injections to themselves for the duration of outpatient treatment. In some cases, the patient had someone else willing to administer the injections on their behalf such as a family member and this was also taken into account in the subsequent data collection.

3.5 Process of Preoperative Education

In this study there were two cohorts of patients: those who were prescribed the extended duration VTE prophylaxis without pre-operative education, and those who did receive formal pre-operative education. As stated previously, the two groups were recruited sequentially, rather than in a randomized manner.

Formal preoperative education consisted of a short verbal explanation detailing the risk of VTE in the post-surgical setting and the rationale for recommending extended VTE prophylaxis (see Appendix B). They were also given an English-language information sheet which explained these points.

The preoperative education was, given by the principle investigator in a pre-admission clinic where the patient came to be pre-operatively assessed by an anaesthetist and a surgical medical officer. This generally occurred several weeks prior to their surgery. On occasion where the patient did not attend the pre-admission clinic, or the principle investigator was unable to attend at the same time, then the education was given via a phone call and email.

3.6 Data collection

Patient demographics, information about the type of operation, duration of outpatient VTE prophylaxis and answers to the post-operative questionnaire were collected. In particular the primary outcome was the compliance with the outpatient VTE prophylaxis.

3.6.1 Demographic and operation information

Each patient's age and sex were recorded. The type of surgery, date of surgery and the date of discharge, as well as the number of days of outpatient VTE prophylaxis were also noted.

3.6.2 Post-operative questionnaire

At either a planned postoperative outpatient review appointment or phone call after the 28 days, they are asked to complete a structured questionnaire directed at their medication use and any problems they have encountered, as well as their views and attitudes towards VTE complications (see Appendix **A**).

The patients were not required to fill in a detailed diary of which days they administered or missed out on the treatment.

The questionnaire was designed to collect the following information:

- Questions about administration of the injections and compliance:
    - Whether the patient missed any doses of their prescribed outpatient treatment, and if so, how many
    - The reason for missing the dose
    - Who administered the injections (self or somebody else)
    - Any side-effects from the injections
- Questions assessing patient attitudes to VTE complications and the treatment:
    - Whether they were aware of the risk of VTE prior to their operation
    - How worried they were about developing VTE
    - To what extent they thought developing a VTE would impact them
    - How many days of treatment they thought is required to prevent VTE
    - Did they believe that medical therapy can prevent VTE

3.6.3 Assessing compliance

Compliance was defined as completion of the entire course of outpatient VTE prophylaxis. Patients who missed one or more daily injections were deemed non-compliant and were asked a follow-up question about what the reason was for the non-compliance.

3.6.4 Data not collected

Formal assessment for VTE in this patient population was not an aim of this study - the incidence of symptomatic VTE has already been quoted in much larger studies and is extremely low (<2%), meaning that this study would not be powered to detect a difference in VTE outcomes, even if there were a strong effect of the intervention in terms of better compliance in the study group. Routine imaging to assess for asymptomatic VTE was not performed as it would be costly and of low-yield. There were no patients in the study who had symptoms or signs suspicious for VTE.

3.7 Statistical Analysis

An effect of size of a 35% increase in compliance was deemed to be a clinically useful effect. A sample size of 17 was calculated for power = 0.8 and desired $\alpha = 0.05$ using a two-sided calculation. This was rounded up to 20 patients in each of the two cohorts.

As the number of patients in the study was low, medians, rather than means were calculated as the average for the various categories. A two-tailed t-test was performed to calculate p-values in the comparisons between both cohorts, and between the compliant and non-compliant groups.

3.8 Recruitment of additional patients

Following assessment of the submitted thesis, it was recommended that a minimum of three extra patients be recruited into the intervention group in order to more closely comply with the power calculation – thus, a total of 18 patients in the intervention group were recruited (as seen in the results section)

4. RESULTS

During the initial study period, a total of 35 patients were recruited into the study. 20 patients were enrolled in cohort 1 (control group) and 15 patients enrolled in cohort 2 (pre-operative education group).

There were fewer patients in the second group due to time limitations – leading up to the deadline, many patients undergoing major abdominal surgery were fast-tracked to surgery and thus bypassed the pre-admission clinic – the study design had anticipated that this clinic would be the best opportunity to meet and recruit suitable patients.

Following assessment of the submitted thesis, it was recommended that extra patients be recruited into cohort 2, as the 15 patients was below the calculated sample size. Thus an extra 3 patients were recruited to bring the total of patients in the intervention group to 18.

4.1 Rate of compliance

Compliance was defined as completion of ≥80% the entire prescribed course of outpatient VTE prophylaxis. 13 of 20 patients (65%) in Cohort I were compliant, while 14 of 18 (78%) in Cohort II were compliant.

The median length of inpatient hospital stay was longer in the control group (11.5 vs 8.5 days). Conversely the duration of outpatient treatment was therefore longer in the education group (16.5 vs 19.5 days).

	COHORT 1	COHORT 2	P
LENGTH OF STAY	11.5 (8-25)	8.5 (2-20)	0.06
DURATION OF OP LMWH	16.5 (7-21)	19.5 (8-26)	0.18
RATE OF COMPLIANCE	13/20 (65%)	14/18 (78%)	0.39

Table 2. Rate of compliance

4.1.1 Number of doses missed

The 7 non-compliant patients in Cohort 1 missed a median of 10 doses (range 5 to 15 doses missed). The 4 non-compliant patients in Cohort 2 missed a median of 10.5 doses (range 5-17 doses missed).

4.1.2 Proportion of days missed

Of the *non-compliant* patients, the duration of planned outpatient VTE prophylaxis varied from 16 to 21 days in Cohort 1, and 18 to 26 days in Cohort 2. To express the compliance as a percentage the number of doses that were administered was divided by the number planned (see Table 3). Non-compliant patients in Cohort 1 had a median compliance of 44%, compared to those in Cohort 2 with a median compliance of 55%.

	PATIENT ID	DURATION OF OUTPATIENT FRAGMIN (DAYS)	HOW MANY DAILY DOSES MISSED?	PERCENTAGE COMPLIANCE
COHORT 1	4	18	12	33%
	5	19	7	63%
	7	21	15	29%
	11	16	9	44%
	12	16	5	69%
	14	21	15	29%
	19	20	10	50%
			Median	**44%**
COHORT 2	24	18	5	72%
	27	26	16	38%
	28	22	17	23%
	36	18	5	72%
			Median	**55%**

Table 3. Compliance expressed as percentage of total duration of outpatient VTE prophylaxis

4.1.3 Reason given for non-compliance

Of the seven non-compliant patients in Cohort 1, six stopped the course of VTE prophylaxis prematurely because they 'felt they didn't need it'. One patient stopped the injections early as they 'felt too unwell' from the surgery – this was a patient who had undergone a liver resection, and was self-administering the medication.

The four non-compliant patients in Cohort 2 also ceased the injections earlier than prescribed because they 'felt they didn't need it'.

	COHORT 1 (N=7)	COHORT 2 (N=2)
HOW MANY DOSES MISSED	Median 10 Range 5-15	Median 10.5 Range 5-17
REASON	Didn't need it - 6 Too unwell - 1	Didn't need it - 4

Table 5. Reasons for non-compliance

4.1.4 Adverse-effects or development of VTE

None of the patients in either cohort reported adverse-effects of the injections. During the follow-up period, no patients developed any objective clinical signs of DVT or PE.

4.2 Demographics

Table 1 shows the age range, gender breakdown, type of operation, length of stay and duration of outpatient treatment, grouped into Cohort I (no pre-operative education) and Cohort II (who did receive pre-operative education).

	COHORT 1 (NO PRE-OP EDUCATION) N=20		COHORT 2 (PRE-OP EDUCATION) N=18	
AGE (YEARS)	Med 61 (Range 34-78)		Med 60.5 (Range 51-80)	
FEMALE	6 (30%)		6 (33%)	
MALE	14 (70%)		12 (66%)	
TYPE OF OPERATION (* LAPAROSCOPIC)	Liver	9 (1)*	Liver	7 (6*)
	Whipple	6	Whipple	4
	Gastrectomy	3	Distal Pancreas	1
	Oesophagectomy	1	Gastrectomy	3
	Duodenal resection	1	Oesophagectomy	1
			Palliative bypass	1
			Laparoscopic lymph node excision	1*

Table 1. Demographics

Cohort 1 had a median age of 61 years (range 34-78), while Cohort 2 had a median age of 60.5 years (range 51-80). There was a predominance of males over females in both groups – 70% in Cohort 1, 66% in Cohort 2.

The most common type of surgery performed in the study patients was liver resection, followed by pancreatico-duodenectomy (Whipple's procedure), gastrectomy, and oesophagectomy.

One patient in Cohort 1 had a laparoscopic operation (a liver resection), whereas the rest of the patients in the cohort had open operations. This patient was non-compliant.

In Cohort 2, nine patients had laparoscopic operations (eight liver resections, one lymph node dissection), and three of these patients were non-compliant.

Two patients in Cohort 1 were insulin-dependent diabetics, and pre-operatively were already familiar with taking subcutaneous injections of insulin. Both were compliant. There were no diabetic patients in Cohort 2.

4.2.1 Incidence of self-administration of VTE prophylaxis

The compliant patients were more likely to have someone else administer the injections, and in each instance it was a family member living at home with the patient. There were no patients in the study who had nursing staff from the hospital coming to the home to give them injections.

Across the whole study, 26 of the 38 patients (68%) received the injections via self-administration. Of the 27 patients who were compliant across the study, 14 (52%) self-administered the injections, whereas 10 of the 11 patients (91%) who were non-compliant administered their own injections.

The effect was also seen within the two cohorts. In Cohort 1 the rate of self-administration was 69% in the compliant versus 86% in the non-compliant patients. In Cohort 2, the percentages were 50% and 100% (4 of 4) respectively.

	COHORT 1		**COHORT 2**	
	Compliant (n=13)	Non-Compliant (n=7)	Compliant (n=14)	Non-Compliant (n=4)
SELF-ADMINISTERED INJECTIONS	9/13 (69%)	6/7 (86%)	7/14 (50%)	4/4 (100%)
TOTAL	15/20 (75%)		11/18 (61%)	

Table 4. Self-administration

4.3 Patient attitudes and beliefs toward VTE

Table 6 summarises the patient responses to these questions in the post-operative survey:

a. Before your surgery, were you aware of the risk of VTE?
b. How concerned were you before your surgery about having a VTE complication?
c. To what extent do you think a VTE would affect you?
d. How many days of VTE prophylaxis is sufficient to prevent VTE?
e. Did the pre-operative education make you more comfortable with the extended VTE prophylaxis? (Only asked of the patients in Cohort II)

For questions b. and c., patients were given the following choices which were given a corresponding weighted score.

- Not at all – 1
- Not much – 2
- Moderately – 3
- Very – 4
- Extremely – 5

The median value of the scores given are shown in the tables below.

Question a: Before your surgery, were you aware of the risk of VTE?

Only 1 patient in Cohort 1 was unaware of what VTE was prior to their surgery. This patient was also non-compliant. The remainder of the patients in Cohort 1 and all of the patients in Cohort 2 stated that they were aware of what VTE was prior to their surgery.

Question b: How concerned were you before your surgery about having a VTE complication?

The median scores given by compliant and non-compliant patients in Cohort 1 for question b. were both 3, while the difference between compliant and non-compliant patients in Cohort 2 was 3.5 vs 2.

	Compliant	Non-Compliant	
Cohort 1 n=20	3	3	
Cohort 2 n=18	3.5	2.5	

Table 6b. How concerned were you about getting a VTE? (Median)

Question c: To what extent do you think a VTE would affect you?

For question c, both Cohorts had median responses of 4 and 3 for compliant and non-compliant patient groups respectively.

	Compliant	Non-Compliant	
Cohort 1 n=20	4	3	
Cohort 2 n=18	4	3.5	

Table 6c. How much would a VTE affect you? (Median)

Looking at the responses across both cohorts:

- For question b, which dealt with pre-operative concerns about VTE, there were no responses of 1
- For question c, which dealt with the perceived effect of VTE on the patient, there were no responses of 1 or 2

Question d: How many days of VTE prophylaxis is sufficient to prevent VTE?

The compliant patients in Cohort 2 had much higher median than those in Cohort 1. In both Cohort 1 and Cohort 2 the compliant patients had a higher number of days compared to the non-compliant patients (14 to 7, and 21 to 7 respectively).

	Compliant	Non-Compliant
Cohort 1 n=20	14	7
Cohort 2 n=18	21	7

Table 6d. How many days of prophylaxis is required to prevent a VTE? (Median)

Question e: Did the pre-operative education make you more comfortable with the extended VTE prophylaxis?

All of the patients who received education said that they felt more comfortable with the treatment than they would have otherwise had they not received education.

	Compliant	Non-Compliant	
Cohort 2 n=15	14	4	18 (100%)

Table 6e. Did the pre-operative education make you more comfortable with the treatment?

4.4 Sub-analysis by compliant and non-compliant status

The data was re-organised and grouped by compliant and non-compliant patients across the two patient groups.

4.4.1 Compliant patients

There were 25 patients in total who were compliant with the extended VTE prophylaxis. 13 of these did not receive pre-operative education, 12 did receive education. (See Table 7)

- A similar mean age was seen between both compliant and non-compliant groups.
- The duration of outpatient VTE prophylaxis was longer in the education group (16 vs 18 days).
- Fewer patients in the education group administered the injections themselves.

All of the compliant patients in both cohorts were aware of VTE prior to their surgery. They also had almost equivalent mean scores for how concerned they were about getting VTE, and how much they thought a VTE would affect them (3 vs 3.5, and 4 vs 4). The number of days of treatment which they thought was sufficient to prevent VTE differed between groups (14 vs 21 days).

	No Education (n=13)	Education (n=14)	p-value
Age (median)	58 yrs (range 34 – 78)	62 yrs (range 51 -76)	0.59
Self-administered (vs someone else administering for them)	9 (69%)	8 (57%)	
Duration of OP VTE prophylaxis (median)	16 (range 7 - 28)	19.5 (range 8 - 23)	0.22
Awareness of VTE before surgery	100%	100%	
How concerned about getting a VTE complication	3	3.5	0.91
How much they think getting a VTE would affect them	4	4	0.96
How many days of VTE prophylaxis do they think is sufficient? (median)	14 (range 7 - 28)	21 (range 14-28)	0.44

Table 7. Compliant subgroup

4.4.2 Non-compliant patients

10 patients were non-compliant in this study, seven who did not receive pre-operative education and three who did (see table 8). The education group were older and had a higher proportion of self-administration.

The no-education group's patients also had a marginally lower duration of outpatient VTE prophylaxis (19 vs 22 days) and they missed a lower number of doses than the education group (10 vs 16 doses), but the proportion of doses missed was almost the same (44% vs 38%).

Only one patient in the no-education group was not aware of VTE prior to surgery. The two groups had similar mean values for the questions regarding concern about getting a VTE, and how much they thought developing a VTE would affect them. They also thought a lower number of days would be sufficient to prevent VTE in comparison to the compliant patients.

	No Education (n=7)	Education (n=4)	p-value
Age (median)	61 yrs (53 - 76)	74 yrs (63 - 80)	0.18
Self-administered (vs someone else administering for them)	9/13 (69%)	7/8 (86%)	
Duration of OP VTE prophylaxis (median)	19 days (16 - 21)	20 days (18 – 26)	0.33
How many doses missed (mean)	10	10.5	
% compliance	44%	38%	0.97
Reason	Didn't need it - 6 Felt unwell - 1	Didn't need it - 4	
Awareness of VTE before surgery	6/7 (86%)	4/4 (100%)	
How concerned about getting a VTE complication	3	2.5	0.85
How much they think getting a VTE would affect them	3	3.5	0.82
How many days of VTE prophylaxis do they think is sufficient? (median)	7 days (7 - 14)	7 days (7-21)	0.08

Table 8. Non-compliant subgroup

5. DISCUSSION

This chapter's discussion is directed toward the main research question as well as the secondary questions:

i. What is the degree of patient compliance with post-operative extended VTE prophylaxis, and to what extent is this influenced by formal pre-operative education?
ii. What, if any, other factors can be identified which influence patient compliance?
iii. How does pre-operative education affect patient's beliefs about, and attitudes towards VTE?

5.1 Compliance with extended VTE prophylaxis

The definition of compliance, or adherence, in the literature varies from study to study. In this study, compliance was defined as completion of the entire course of outpatient VTE prophylaxis.

This definition was used in the study by Lemke et al[39], whose paper described a study population that was most comparable to this study – patients post-abdominal hepatobiliary surgery who were prescribed extended VTE prophylaxis. Patients were surveyed about their compliance, using a definition of compliance meaning that no doses were missed, and it revealed a compliance rate of 81.4%. This was an observational study and did not implement any specific interventions to improve compliance.

In comparison, the current study, the educated patients in Cohort 2 in had a 78% compliance rate which is almost equivalent to that of Lemke's study. The patients in Cohort 1, however, had a compliance rate of 65% which fell well short of this.

The ETHOS study [38] of post-orthopaedic surgical patients defined compliance as a patient taking >80% of treatment with no more than two consecutive days without treatment, and had a compliance rate of 87.7%. This study also did not have an intervention targeting compliance. It should be noted that the extended VTE prophylaxis included a variety of treatments including oral and injectable anticoagulants. If the patients in the current study were assessed using this looser criteria for being compliant, the number of non-compliant patient's would still be the same – all of the non-compliant patients took less than 80% of their doses.

Even if each of the patients in the non-compliant group had missed one less dose, the highest compliance is 78%, which is still less than a 80% cutoff. If they were to miss two fewer doses, then one in Cohort 1, and two in Cohort 2 would then become compliant with a 80% cut-off (Table 9).

	PATIENT ID	DURATION OF OUTPATIENT FRAGMIN (DAYS)	HOW MANY DAILY DOSES MISSED? (ORIGINAL IN BOLD)	PERCENTAGE COMPLIANCE (%)
COHORT 1	4	18	**12**/11/10	33/39/44
	5	19	**7**/6/5	63/68/74
	7	21	**15**/14/13	29/33/38
	11	16	**9**/8/7	44/50/56
	12	16	**5**/4/3	69/75/**81***
	14	21	**15**/14/13	29/33/38
	19	20	**10**/9/8	50/55/60
COHORT 2	24	18	**5**/4/3	72/78/**83***
	27	26	**16**/15/14	38/42/46
	28	22	**17**/16/15	23/27/32
	36	18	**5**/4/3	72/78/**83***
			*If two fewer doses are missed, then three patients become compliant using a 80% cut-off	

Table 9. Altering number of doses missed

If we change the definition of compliance to ≥70% of doses taken, the number of compliant patients in Cohort 1 would remain the same, but two of the four non-compliant patients in Cohort 2 would then be considered compliant, which would lead to an overall rate of 89% compliance in Cohort 2 ($p = 0.08$).

The “degree of compliance” was quantified in the present study as a percentage of doses which were taken of the total number of days of outpatient VTE prophylaxis which were prescribed. When the non-compliant patients in both cohorts were compared, the average rate of compliance was 44% in Cohort 1 and 55% in Cohort 2 (p=0.97) [see Table 3]. This means non-compliant patients ended up taking around half of the prescribed doses, regardless of which cohort they were in.

There may be some clinical relevance of “degree of compliance” in the post-abdominal surgery patient undertaking a course of extended VTE prophylaxis, with regards to lesser compliance correlating to an increased risk of increased VTE events. Gao et al[29] showed a small but significant increase in VTE events for 2099 non-compliant orthopaedic patients. By stratifying these higher-risk patients according to their degree of compliance, the study showed a difference in VTE between fully compliant and partially compliant patients. Vedovati et al[24] also showed a significant increase in VTE for colorectal cancer surgery patients who received 1 week instead of 4 weeks of treatment.

Patients in the present study were not stratified by degree of non-compliance, given the extremely small numbers recruited and the low likelihood of developing VTE (none of the patients in this study developed clinical evidence of VTE). Such stratification would have been purely arbitrary and a meaningful clinical correlation would not be able to be obtained, besides being outside of the scope of this study.

While injectable anticoagulants have been widely used as extended VTE prophylaxis, a newer development is the use of a direct-acting oral anticoagulant (DOAC) such as rivaroxaban for this same purpose. DOACs may be more acceptable to the patient than having injections and this may affect compliance. This has been extensively researched in orthopaedic patients and is even used routinely in many centres. The study by Carrothers at al [30] showed 83% compliance, with 4% non-compliance and 13% having incomplete data, indicating that compliance is not necessarily better with (oral) DOACs than with injectable modalities. The barrier to the use of DOACs in abdominal surgery generally, and gastro-intestinal surgery in particular, is the likelihood of unreliable and incomplete absorption due to either altered anatomy or functional post-operative ileus – further research into efficacy is necessary before DOACs would be able to replace injectable agents in this population.

With regards to the influence of the pre-operative education, there did seem to be a difference between the two cohorts – 65% in the no-education cohort compared to 78% in the patients who received pre-operative education, a difference of 13%. In order to generate a significant difference in compliance of 15%, for an α of 0.05, a sample size of 276 patients would need to be recruited.

As we have seen, compliance as a percentage of total prescribed doses was greater in the non-compliant patients who received education than in those who did not (55% vs 44%) but the difference was not significant, although the numbers were small.

Education can take many forms. In this study, education consisted of a short verbal presentation, as well as the same information provided as an information sheet. Additional education material could be provided in the form of a video or slideshow. The education could also be provided by different people – in this study it was provided by a medical professional, but nursing staff or pharmacists could also be involved in this process. It may be given on a single occasion, or multiple times, in and out of the hospital setting.

The effect of an intervention of education on compliance with extended VTE prophylaxis has not been specifically investigated in the literature, although there are studies examining the effect of interventions on compliance of treatments of chronic diseases. A Cochrane review [40] evaluated education for patients receiving long-term medical treatment for chronic diseases, albeit as only one in a wide heterogeneous mix of interventions. The main conclusion from this large meta-analysis was that current interventions for medication adherence in chronic health problems are mostly complex and not very effective, pointing toward the need for design of feasible long-term interventions, objective adherence measures and sufficient study power to detect improvements.

Patients with chronic disease in which the patient relies on long-term treatment differs greatly from the population of patients in this study, with short defined duration of treatment with a set end-point, in which compliance would be expected to be better, and targeted education interventions can be implemented.

5.2 Factors which affect compliance

5.2.1 Demographics

There were more males than females in both cohorts. Female patients were more compliant than males with a compliance of 83% (10/12) versus 62% (16/26).

The median age of the compliant patients was 61 years, compared to 66 years in the non-compliant patients, which was not a significant difference (p=0.24).

Based on these results a definite link between sex, age and compliance could not be established.

5.2.2 Type of surgery

The two most common operations were liver resections (16) and pancreatico-duodenectomy (10). The compliance for these operations was 75% and 80% respectively. One of the three non-compliant liver resection patients and the two non-compliant Whipple patients did not receive education. A relationship between the type of surgery and the compliance couldn't be ascertained due to the small numbers, but apart from laparoscopic surgical procedures, the experience of patients undergoing the range of different operations is similar – for example, they all have large abdominal incisions, drain tubes in-situ, similar pain management with wound-infusion catheters and patient-controlled analgesia.

5.2.3 Self-administration of injections

The VTE prophylaxis was self-administered in 26 (68%) patients. Overall compliance rates were 83% (10/12) in those who had someone else administer the injections, and 58% (15/26) in those who self-administered. In Lemke et al's study [39] the majority (78.4%) self-administered their injections, however the study did not comment on whether this had an impact on compliance.

The higher compliance in the patients who had somebody else administering the medication (who in all cases was a family member living with the patient) was likely due to the fact that somebody else is having a motivation to keep the patient compliant, and therefore reduce the risk of an adverse event, even if the patients themselves don't feel like taking it. It may also mitigate the sense of distaste which patients experience with having to self-inject.

5.2.4 Barriers to compliance

In other studies, various barriers to compliance were found. In the Bergqvist[38] study most of the patients gave the reason - 'the drug was not bought', although patient education and prescribing practices at time of discharge also played a role. Lemke found that the healthcare provider stopping the regimen, or poor experience with injections (such as adverse effects) were the main causes for non-compliance.

In this study, the most common reason for patients' non-compliance given, in both the no-education and the education cohorts, was that they 'felt they didn't need it'. The drug was supplied on discharge by the

hospital pharmacy, so the reason 'the drug was not bought' was not given. Only one non-compliant patient claimed to be 'feeling too unwell' to continue. So, despite having pre-operative education, these three non-compliant patients still believed that they didn't need to take the full 28 day course. In fact, when asked how many days of VTE prophylaxis were required to prevent a VTE complication, the non-compliant patients answered with a median of only 14 days. Even the compliant patients gave a median of 21 days, which is seven days short of the recommended 28 days.

The patients' erroneous beliefs could be due to a failure of the education technique, or the patient's comprehension of the education, and this is a specific area which could be targeted more closely on further expansions of this study.

5.3 Attitudes to VTE and prophylaxis

Patients were asked a range of questions about the patient's understanding of and beliefs surrounding VTE.

- *Awareness of VTE prior to surgery*

Only 1 of the 38 patients in this study did not know what VTE was prior to their surgery. This included the majority of the patients in Cohort 2. The public awareness of thrombosis, DVT and PE internationally has been shown to be 68%, 44% and 54%, respectively [41]. In comparison, the patients in this study have an extremely high awareness of VTE of 97%.

The patients were asked how worried they were about getting a VTE following their operation, and also how much they thought developing a VTE would affect them. These responses were weighted to a score of between 1 to 5.

- *How worried are you about getting a VTE?*

Compliant and non-compliant patients in Cohort 1 gave a median response of 3 to this question. The compliant patients in Cohort 2 had a median response of 3.5, which was higher and also what you might expect after receiving education on the topic. The non-compliant patients had a response of 2.5 which was lower than those in Cohort 1– it is unclear why this might be the case, although it must be noted that there were only four patients in this category.

- *How much does VTE affect you?*

The compliant patients in both cohorts gave median scores of 4, compared to non-compliant patients giving median scores of 3/3.5. It would make sense for compliant patients to think that VTEs would affect them to a greater extent than the non-compliant patients would, and this may contribute to their compliance.

For both of the questions above, the only improvement in scores when comparing education and no-education was in the compliant patients answers to the first question – how worried were they about getting a VTE – meaning that, based on this study, education had very little to no effect on patient beliefs in these areas.

- *How many doses of VTE prophylaxis are required to prevent a VTE?*

Patients were also asked how many doses they thought would be necessary to prevent a VTE. The compliant patients in both cohorts gave higher numbers than the non-compliant patients who both gave median answers of 7 days. This result suggests that better compliance is associated with seeing the VTE and its prevention as a larger problem.

The compliant patients' median answers were also higher in the educated group (21 days) when compared to the non-educated group (14 days). This suggests that assimilation of the educational material provided did improve the patients' understanding of VTE and its prevention. However, non-compliant patients seem not to have understood or assimilated the educational material provided, with both the educated and non-educated groups suggesting a median of 7 days.

It should again be noted that there were only four non-compliant patients in Cohort 2, so with greater numbers of patients a difference may have been demonstrated.

Overall, the effect of education on patients' answers to this set of questions seems to be fairly limited, with only the belief regarding number of doses necessary to prevent VTE in the compliant patient group seeming to have an appreciable difference. The small sample of patients in the non-compliant group of Cohort 2 may have limited the differences, and recruiting a larger number of patients might demonstrate a greater effect of pre-operative education.

5.4 Limitations

5.4.1 Small numbers

There were only a small number of patients enrolled into the study. Only patients undergoing abdominal cancer surgery were included, and even then, only those of one surgical unit. This was done in order to maintain some "quality control" and consistency over the patient education and also what was told to the patient in the post-operative period. Patients undergoing abdominal surgery for other conditions were also not included, because a) they may not have necessarily benefited from extended-duration thromboprophylaxis according to what we have gleaned from the literature, and b) there may also have been a difference in the motivations of someone having surgery for cancer vs surgery for uncomplicated appendicitis, for example (i.e. the patient with the greater emotional investment in their outcome would be more motivated to be compliant).

5.4.2 Type of surgery

All of the patients recruited into the study were under the care of a single surgical unit in this tertiary hospital institution whose specialty is upper gastrointestinal and hepatobiliary surgery. Therefore the types of operations performed on these patients were limited in scope. Patients undergoing colorectal cancer operations, which comprise a large proportion of abdominal cancer surgery, were not included in this study. This was to maintain consistency with the patient education and ward care being carried out by a single team, rather than involving multiple teams. Inclusion of other types of abdominal cancer surgery may or may not have made a difference with compliance to extended duration VTE-prophylaxis, and further studies should incorporate a breadth of types of surgery in order to accurately reflect the patient population being treated.

5.4.3 Sequential recruitment

As explained in Chapter 3, patients were sequentially recruited into the no-education and education cohorts due to concern about the patients and nursing staff being aware that there were some patients who had received pre-operative education and some who had not, potentially creating an unwanted Hawthorne effect.

5.4.4 Using a questionnaire instead of objective measurements

The patients were interviewed following the end of their treatment. The effectiveness of this relies on patients being truthful with their answers. Some of the questions also related to their knowledge of VTE prior to the surgery – the answers given may not have been entirely accurate and subject to memory bias.

Rather than relying on the patient to tell the interviewer whether they were compliant or not, and how many doses were missed, an objective assessment such as medication counting or electronic medication monitoring are options which could have been employed. The downsides to this were again creating a potential Hawthorne effect, plus it would be costly to use these other methods.

5.4.5 Not recording pattern of missed doses

There are many methods for recording compliance. In this instance a questionnaire was used to ascertain whether a patient was compliant or not, and also the proportion of doses missed. A more detailed patient medication diary could have been incorporated in the assessment of compliance, and would allow any patterns in missed doses for individual patients to be detected. It was decided that for such a relatively short duration of treatment this would not be necessary. It may also have led to the patient being reminded that they were being studied and thus potentially influence them to be compliant. In fact, all of the non-compliant patients, once prematurely ceasing the medications, did not resume any doses.

5.4.6 Strict definition of compliance

In some studies, compliance has been sub-stratified in a more nuanced fashion[29] (e.g. partially compliant, poorly compliant, non-compliant, etc.). A strict definition of compliance was used in this study – a compliant patient was one who did not miss a single dose of the prescribed course of outpatient thromboprophylaxis. It could be argued that a patient who missed a single dose is not the same as a patient who only took one dose yet they were both categorised as non-compliant, and potentially this may have a clinical impact in the risk of developing VTE. The strict definition of compliance was used in this study as the numbers were going to be small and further sub-stratifying compliance would create much smaller subgroups. No patients in the study were completely non-compliant (i.e. missing 100% of their doses).

5.5 Areas for further research

Oral VTE prophylaxis

The use of oral anticoagulants as VTE chemoprophylaxis (such as the direct factor Xa inhibitor, rivaroxaban) in the post-major joint surgery setting is now widely accepted internationally, with rivaroxaban even being available on the Pharmaceutical Benefit Scheme for patients undergoing total hip and knee replacements. An oral agent taken once a day may be better tolerated than an injection, and this may improve compliance. There may be an issue applying this strategy in patients undergoing major abdominal surgery, in terms of potential malabsorption of the medication.

Reminder systems

Another intervention which has been proposed is a patient-alert or reminder system. Granger[42] reviewed technology such as cellular phone reminders and in-home electronic technology to communicate reminders to patients taking cardiovascular medications showed only mixed results with regards to compliance and clinical outcomes. This is in contrast to other studies which showed increased compliance associated with reminder systems such as automated text messaging[43, 44], albeit in patients on long-term treatment for chronic diseases such as asthma.

None of the non-compliant patients in the present study cited forgetfulness as a reason for missing doses, so based on those findings, implementing a reminder system may not have any appreciable effect on compliance.

6. CONCLUSION

Venous thromboembolism is a significant, potentially life-threatening event which affects patients. While many published guidelines throughout the world recommend an extended course of VTE prophylaxis, and evidence exists to justify its use, there hasn't been an in-depth attempt to ascertain effect of education on the compliance rate of patients to this regimen following major abdominal surgery for cancer. This study therefore aimed to assess the effect of pre-operative education on patient compliance with a prescribed course of injectable VTE prophylaxis.

The majority of patients in the study were aware of VTE prior to their surgery, and they also had reasonable compliance to the treatment. There was a non-significant improvement in compliance after the introduction of pre-operative education in the second cohort of patients. Age and sex of the patients did not directly affect compliance within the limits of this study, nor did the type of operation.

A difference in patient attitudes and beliefs towards the VTE prophylaxis treatment following the education intervention was not readily demonstrated. The educated group did, however, believe that a higher number of doses of the treatment were necessary to prevent VTE than the non-educated group did, but it was still short of the recommended 28 days course of treatment. And although it was not a significant difference, this would be a potential target for future studies examining education and its impact on compliance.

Other related areas which could be analysed include the use of oral instead of injectable anti-VTE drugs, different measures of compliance including the use of technology (such as electronic medication monitoring), different modalities of education, and effect of reminder alerts. Future studies also need to include other types of surgery, in particular colorectal cancer surgery, in order to more accurately represent the patient population.

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APPENDIX A – Post-treatment questionnaire

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Post-Extended DVT prophylaxis Questionnaire

Name:
UR:
DOB: Age:
Operation:
Date of Operation:
Date of discharge: Days of IP stay:

☐ Participant filling out questionnaire at follow-up visit
☐ Participant interviewed by researcher over the phone

Disclaimer: All information collected is confidential and will in no way affect your ongoing treatment, please answer truthfully

1. When were you discharged from hospital?	
2. Did you experience complications following the surgery?	
3. How many different medications were you discharged on per day?	
4. Which of these were commenced while you were in hospital?	
5. How often and when were you given these medications?	
6. Were there any medications where you had problems taking them?	
7. Did you sometimes forget to take medications?	
8. Did you sometimes decide against taking the medications because you felt like you didn't need them?	
9. Did you sometimes decide against taking the medications if you weren't not feeling well?	
10. Were you worried about taking the injections before starting them?	Extremely / very / moderately / not much / not at all
11. How did you feel after having finished the course of injections compared to before?	Better/ Same / Worse
12. Did you have any side-effects or adverse reactions	

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related to the injections?	
13. How many unused injections do you still have at home?	
14. Did you also have anti-clotting injections whilst inpatient, if so who gave them to you?	
15. What risks of the operation were you aware of prior to your surgery?	
16. Following your operation were you afraid of suffering from thickening of the blood or developing blood clots?	Extremely / very / moderately / not much / not at all
17. In your opinion, how much does having blood clots restrict a person in daily life?	Extremely / very / moderately / not much / not at all
18. In your opinion, how many days or weeks do you need to take the injections to prevent blood clots?	
19. Do you believe a person can avoid blood clots by drinking lots of liquids and moving a lot?	
20. Do you believe that medications against thrombosis give you good protection?	
21. Did somebody else give you injections at home, if so, how many?	
22. Who lives at home with you?	
23. What education have you had about preventing blood clots?	

Answering this questionnaire implies consent to participation in this project.

APPENDIX B – Patient education leaflet

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Pre-operative Patient Information Sheet: Prevention of deep venous thrombosis and pulmonary embolus after major abdominal surgery

You will be undergoing major surgery in the near future. There are significant risks associated with this surgery including developing a clot in the deep veins in the legs (deep venous thrombosis, or DVT), which can also travel to the lungs (called a pulmonary embolus or PE).

This is associated with significant implications for your health, including pain and swelling in the legs, and in the case of PE, shortness of breath or even death. The risk of death in patients who develop a PE is 5 to 10% - which is higher than the risk of death from the surgery itself.

There are a few methods we use to reduce the risk of these complications. One is to put compression stockings on your legs, which helps to increase the blood flow in the veins. The other method is to administer anti-clotting injections to you once or twice a day. These injections are very fine needles which are usually given in the skin/fat fold of the tummy or in the thigh. This is routine for ALL patients in our hospital after surgery.

Studies have shown that patients undergoing major abdominal surgery are at risk of developing blood clots. The risk of developing a DVT or PE following major abdominal surgery continues even up to a month after your operation, by which time you will most likely be at home. This risk is reduced by more than half by patients having a course of anti-clotting injections after going home from hospital, rather than only having them while in hospital.

We will therefore recommend that you go home with a course of these injections. You will be taught to administer these during your hospital stay by the ward nursing staff, and you will be given a supply of the injections to take home with you, in addition to all of your other discharge medications.

In order to assess the effectiveness of this treatment, we will conduct a brief 5-10 minute questionnaire at up to 4 weeks after the course of injections has finished. This may either be at the outpatient clinic review, or via telephone. By agreeing to complete or answer this questionnaire, you consent to your answers being recorded for study purposes.

Version 2.2 24/04/15

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This project has been approved by the Eastern Health Human Research Ethics Committee.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name Eastern Health Human Research Ethics Committee
Position Chairperson
Telephone 03 9895 3398
Email ethics@easternhealth.org.au

For any problems or complaints, please contact:

Dr Benjamin Keong
Consultant Surgeon
benkeong@easternhealth.org.au
Phone: 0411151173
or via Box Hill Hospital switchboard

Version 2.2 **24/04/15**

APPENDIX C – Results Cohort 1

Patient ID	Initials	Age	Operation	Inpatient Stay (days)	Duration of outpatient fragmin (days)	Missed a dose?	How many?	Reason for not taking	Who gave the injections?
01	JM	52	Liver resection	9	28	No			Self
02	GM	55	Oesophagectomy	12	16	Yes	5	Felt like didn't need it	Self
03	AC	51	Liver resection	12	16	No			Family member
04	RR	73	Gastrectomy	10	18	Yes	12	Felt like didn't need it	Self
05	RR	54	Whipple	9	19	Yes			Family member
06	SL	44	Liver resection	12	16	No			Self
07	JU	61	Liver Resection	7	21	Yes	15	Felt like didn't need it	Self
08	LE	61	Liver Resection	11	17	No			Self
09	ZL	34	Duodenal resection	10	18	No			Self
10	PS	48	Whipple	8	20	No			Self
11	RM	76	Whipple	12	16	Yes	9	Felt like didn't need it	Self
12	DW	70	Whipple	14	14	No			Self
13	LS	71	Gastrectomy	13	15	No			Self
14	MF	66	Liver Resection	9	21	Yes	15	Felt too unwell	Self
15	PC	78	Whipple	25	7	No			Family member
16	JM	62	Liver resection	18	10	No			Self
17	RI	61	Liver resection	9	20	No			Family member
18	JO	63	Whipple	19	9	No			Self
19	SP	53	Gastrectomy	8	20	Yes	10	Felt like didn't need it	Self
20	DA	64	Liver resection	13	15	No			Family member

APPENDIX C – Results Cohort 1

Patient ID	Initials	Were you aware of the risk of VTE prior to your operation	Following your operation were you afraid of suffering from VTE?	How much does VTE affect you	How many days do you need to prevent VTE	Do you believe you can avoid VTE by drinking lots of liquids and moving	Do you believe that medications against blood clots give you good protection?
01	JM	Yes	Very	Extremely	14	Yes	Yes
02	GM	Yes	Moderately	Very	14	Yes	Yes
03	AC	Yes	Very	Very	28	Yes	Yes
04	RR	Yes	Moderately	Very	14	Yes	Yes
05	RR	Yes	Moderately	Very	14	Yes	Yes
06	SL	Yes	Very	Extremely	28	Yes	Yes
07	JU	Yes	Moderately	Moderately	7	Yes	Yes
08	LE	Yes	Extremely	Very	28	Yes	Yes
09	ZL	Yes	Moderately	Very	21	Yes	Yes
10	PS	Yes	Not much	Very	14	Yes	Yes
11	RM	Yes	Moderately	Moderately	7	Yes	Yes
12	DW	Yes	Very	Extremely	28	Yes	Yes
13	LS	Yes	Moderately	Moderately	14	Yes	Yes
14	MF	Yes	Not much	Moderately	7	Yes	Yes
15	PC	Yes	Moderately	Very	14	Yes	Yes
16	JM	Yes	Very	Very	7	Yes	Yes
17	RI	Yes	Moderately	Very	14	Yes	Yes
18	JO	Yes	Moderately	Moderately	7	Yes	Yes
19	SP	No	Moderately	Moderately	7	Yes	Yes
20	DA	Yes	Moderately	Extremely	14	Yes	Yes

APPENDIX C – Results Cohort 2

Patient ID	Initials	Age	Operation	Inpatient Stay (days)	Duration of outpatient fragmin (days)	Missed a dose?	How many?	Reason for not taking	Who gave the injections?
21	LV	56	Whipple	10	18	No		Forgot	Self
22	CM	71	Whipple	14	14	No			Self
23	CM	76	Whipple	10	18	No			Family member
24	AM	74	Subtotal Gastrectomy	10	18	Yes	5	Felt like didn't need it	Self
25	DC	52	Palliative bypass (pancreatic ca)	7	21	No			Self
26	JC	58	Subtotal Gastrectomy	7	21	No			Self
27	DM	65	Laparoscopic node resection	2	26	Yes	16	Felt like didn't need it	Self
28	JB	80	Liver resection	6	22	Yes	17	Felt like didn't need it	Self
29	IC	67	Liver resection	6	22	No			Family member
30	PR	58	Liver Resection	5	23	No			Self
31	CD	51	Lap liver resection	5	23	No			Self
32	AK	73	Whipple	20	8	No			Family member
33	WR	65	Distal pancreatectomy/splenectomy	13	15	No			Family member
34	RW	57	Liver resection	16	12	No		N/A	Family member
35	IF	54	Oesophagectomy	11	17	No			Family member
36	JA	63	Liver resection	10	18	Yes	5	Felt like didn't need it	Self
37	MO	58	Subtotal Gastrectomy	7	21	No			Self
38	PT	52	Liver resection	6	22	No			Family member

APPENDIX C – Results Cohort 2

Patient ID	Initials	Were you aware of the risk of VTE prior to your operation	Following your operation were you afraid of suffering from VTE?	How much does VTE affect you	How many days do you need to prevent VTE	Do you believe you can avoid VTE by drinking lots of liquids and moving	Do you believe that medications against blood clots give you good protection?	Did you find the education made you more comfortable with the treatment?
21	LV	Yes	Not much	Very	14	Yes	Yes	Yes
22	CM	Yes	Very	Extremely	10	Yes	Yes	Yes
23	CM	Yes	Very	Very	14	Yes	Yes	Yes
24	AM	Yes	Moderately	Moderately	7	Yes	Yes	Yes
25	DC	Yes	Extremely	Very	21	Yes	Yes	Yes
26	JC	Yes	Moderately	Extremely	10	Yes	Yes	Yes
27	DM	Yes	Not much	Very	7	Yes	Yes	Yes
28	JB	Yes	Not much	Moderately	7	Yes	Yes	Yes
29	IC	Yes	Not much	Very	14	No	Yes	Yes
30	PR	Yes	Moderately	Moderately	12	Yes	Yes	Yes
31	CD	Yes	Not much	Extremely	14	Yes	Yes	Yes
32	AK	Yes	Extremely	Very	14	Yes	Yes	Yes
33	WR	Yes	Very	Very	28	Yes	Yes	Yes
34	RW	Yes	Moderately	Very	21	Yes	Yes	Yes
35	IF	Yes	Very	Very	28	Yes	Yes	Yes
36	JA	Yes	Very	Very	21	Yes	Yes	Yes
37	MO	Yes	Extremely	Extremely	28	Yes	Yes	Yes
38	PT	Yes	Moderately	Moderately	28	Yes	Yes	Yes