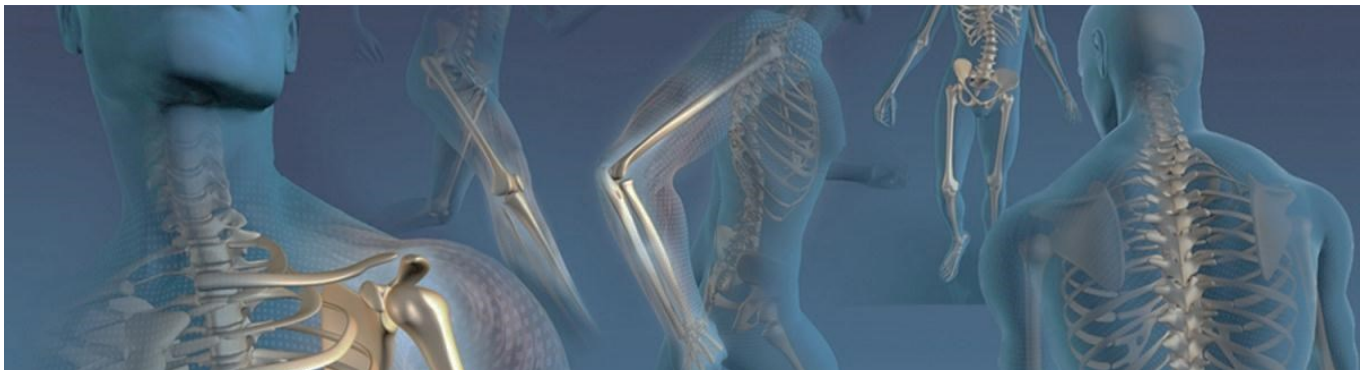
Is Blood loss reduced by delaying the first administration of a Direct Thrombin Inhibitor for Thromboprophylaxis in elective total knee replacement? - Original Study.



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ABSTRACT

The primary aim of this study was to examine the correlation between the dabigatran administration initiation time (0-4 h vs. > 4 h post-surgery) and the respective blood loss in patients undergoing elective total knee replacement.

Patients facing major orthopaedic operations, including total knee and total hip replacement, are at risk of venous thromboembolism. Dabigatranetexilate is a new oral, direct thrombin inhibitor, clinically approved for prophylaxis of thromboembolism in patients undergoing elective orthopaedic joint replacements.

Patients selected for the study were split into two groups differing in the time of DE administration initiation (0-4 h vs. > 4post-surgery). The formula of Nadler was used for the quantitative determination of the peri-operative blood loss in these patients.

There was no significant difference in the calculated mean blood loss between the two groups. The calculated mean blood loss for the 1-4 h group was 331ml, compared with 331 ml in the > 4 h group ($p > 0.05$). This showed no reduction in bleeding even with a delayed DE administration. Investigation of the delayed initiation ofdabigatran administration suggested that the late dabigatran administration have been due surgeon's decision based on increased risk of bleeding.

The efficacy and safety of DE administration was comparable at both times (0-4 h vs. > 4post-surgery) and no clinically significant disadvantage concerningperi-operative blood loss could be observed when performing an early administration initiation of DE.

Keyword: Dabigatran etexilate, Total knee replacement, Blood loss, Venous thromboembolism, DE administration initiation

I. INTRODUCTION

The introduction of the paper should explain the nature of the problem, previous work, purpose, and the contribution of the paper. The contents of each section may be provided to understand easily about the paper. Patients facing major orthopaedic operations, including total knee (TKR) or total hip replacement (THR), are at risk of venous thromboembolism (VTE).[1-3] Treatment with low molecular weight heparins (LMWH) is efficient and safe 4 but has its own drawbacks, including indirect mechanism of action, administration through injection (and regular monitoring and adjustment of dose to ensure that optimum anticoagulant effects have been achieved 5, 6. Latest oral anticoagulants, such as Dabigatran etexilate, present great potential in preventing and managing thromboembolic events without such limitations.[7-11] Dabigatran etexilate (DE) is a new oral, direct thrombin inhibitor, clinically approved for prophylaxis of thromboembolism in patients undergoing orthopaedic surgeries and prevention of stroke in patients with atrial fibrillation, without specific drug monitoring requirements. [12-15] Data from the literature suggests the optimum dosage amount of 100-300 mg DE post-operatively for preventing VTE after total knee or total hip replacement. [16, 17] It is advised to monitor patients receiving dabigatran who are either older than 75 years or have known renal impairments. [18, 19] These patients are usually prescribed a reduced dose of 75 mg initially and 150 mg from post operative day 1 onwards. Patients with no impairment or under the age of 75 received 110 mg initially and 220 mg from post operative day 1 onwards.

In addition to the increasing scientific evidence showing the safety and efficiency of DE. [20, 21] investigations for the same have also been made using phase III trials such as RE-MODEL and RE-MOBILIZE randomized trials. [8, 10] These two trials compared DE to a low molecular-weight heparin, enoxaparin, in preventing VTE after TKR surgeries. The results proved DE to be as effective as enoxaparin with a similar safety profile. The RE-MODEL and RE-MOBILIZE trials differed from each other in three important aspects, namely, the timing of first DE administration, the duration of treatment and the quantity of dose. In the RE-MODEL trial, DE was first administered 1-4 h post-surgery with 6-10 days of prophylaxis in TKR patients, compared to the RE-MOBILIZE trial where the administration of DE was delayed to between 6-12 h after surgery with 12-15 days of prophylaxis. In both the trials, DE was tested at two doses: 150 mg and 220 mg starting with half the dose on the first day of surgery. In the RE-MODEL trial, both the dosing amounts of DE (150 mg and 220 mg) were found to be as effective as 40 mg enoxaparin (once daily), started the evening before surgery 8. In comparison, 30 mg enoxaparin taken twice a day in the RE-MOBILIZE trial was more effective in preventing VTE than DE administered between 6-12 h after surgery.[10] The lower efficiency of DE in comparison to enoxaparin was suggested to be either due to strong and extended enoxaparin dosing or possibly due to delayed administration of DE.

Even though the general consensus exists about the use of DE as a promising anticoagulant in preventing VTE, as with any newly approved drug, some aspects of the treatment, such as the time of administration of the first dose, are still subject to debate. [22] Although the recommended time for initiating DE administration, according to the National Institute of Health and Clinical Excellence (NICE), is within 1-4 h post-surgery, [23] there are concerns regarding increased risk of bleeding events due to early initiation of thromboprophylaxis22. Data from a randomized, double blind study analysis of BISTRO-II trial showed that early administration of DE (within 2 h post-surgery) was more effective and safe, without any associated increase in clinically significant bleeding, than delayed treatment initiation (> 4 h).[16] Another report also suggests the initiation of DE treatment between 1-4 h post-surgery based on its pharmacokinetic profile. [24]

The fear of augmented bleeding, resulting in potential complications, due to early administration of anticoagulants has led to a standard practice of delayedthromboprophylaxis in most of the USA and Canada. [25, 26] Given the severe consequences related to any anticoagulant drug, there is an urgent need for evidence from clinical and research studies comparing the effectiveness and safety of initiating DE treatments at different times. Although the current studies record clinically relevant major bleeding events, [2] the reduction in bleeding due to different DE administration initiation times has not yet been studied. Thus, the primary aim of this study was to examine this variable in isolation by evaluating the relationship between the time of DE administration (0-4 h vs. > 4h post-surgery) and the respective blood loss after elective TKR. The amount of peri-operative blood loss was quantified for patients divided in to two groups (0-4 h vs. > 4h post-surgery) to assess its association with the DE administration time, and to inspect for any associated clinically significant bleeding trend. The secondary aim of the study was to audit the department regarding the timing of DE administration. BNF guidance regarding dabigatran said that it should be given in 0-4 h post-operation or once haemostasis was achieved. The senior authors practice is to give DE at 4 hours post surgery or delay this if there is perceived higher risk of bleeding in an individual patient, to allow adequate time for haemostasis to be achieved.

II. MATERIALS AND METHODS

Patients aged 40-years or older who underwent an elective total knee replacement were eligible for enrolment in this study. Patients selected in this retrospective cohort study went through their TKR surgery between 1st January 2010 and 31st May 2012, performed by a single surgeon at single hospital in the UK. Two groups were formed which differed in regard to the time of DE administration initiation. Patients from one group received the first dose of DE between 0-4 h post-operatively, while the other group received it >4 h after the surgery. Pre- and post-operative data were collected from the patients' records of the management. The sample size of 71 was initially selected for convenience and the selection was made on the first name basis sorting alphabetically. Among the 71 patients selected, notes for 12 patients could either not be obtained or had unsatisfactory information for analysis. Seven patients had to be excluded from the study as four of them were given enoxaparin instead ofdabigatran as VTE prophylaxis, and the other three had been taking warfarin before the operation. Thus, a total of 52 patients were included in this retrospective study. The patients were split into two groups of 21 patients (DE administration between 0-4 h post-surgery) and 31 patients (DE administration > 4 h post-surgery). Patients older than 75 years or with renal impairment received dose of 75 mg initially and 150 mg from day 2 onwards. Patients with no impairment or under the age of 75 should receive 110 mg initially and 220 mg from day 2 onwards.

The date of birth and date of surgery of the patients were used to determine their age at the time of operation. Their length of stay in the hospital was recorded from the electronic version of the discharge summary sheet. Height and weight as well as the DE administration time and dosage were obtained for all patients from the drug chart. The nurse's signatures were used to confirm the drug administration. The tourniquet off time, as recorded in the anaesthetic notes, was considered as the end of operation time. The tourniquet off time was not mentioned for two of the patients. Therefore, the end of operation time was considered from beginning of surgery and the total tourniquet time as recorded by the surgeon. Patients' admission and discharge notes were also studied to ascertain if there were any events of deep vein thrombosis and pulmonary embolism in patients up to six weeks post-operatively.

All surgeries were performed in a standard fashion utilizing the same implant (MRK, Matortho Ltd) and sequence of surgery. All patients have been routinely given preoperative dose of antibiotic prophylaxis (cefuroxime), and on induction dose of

tranexamic acid iv. At the end the surgical field has been infiltrated with 0.25% Marcaine with adrenaline 1:200k 40ml. In all cases patient have been given TED stockings pre-operatively and had mechanical support (calf pumps) during the surgery and within first 24 hours.

III. STATISTICAL ANALYSIS AND GRAPHICAL PRESENTATION

The peri-operative blood loss was compared between the two groups of patients using the Nadler's formula [28]:

$$V = EBV * \ln\left(\frac{Htc_0}{Htc_1}\right)$$

where V = blood loss (l); EBV = blood volume (l); Hct_0= preoperative haematocrit; Hct_1= haematocrit on the first post-operative day.

The patient's blood volume was estimated using the following formula:

$$EBV = \left(K_1 * Height^3\right) + \left(K_2 * weight\right) + K_3$$

where Male: K1 = 0.3669, K2 = 0.03219, K3 = 0.6041 and Female: K1 = 0.3561, K2 0.03308, K3 0.1833.

IV. RESULTS

Of 71 patients initially enrolled for the study, 52 patients were finally included in the analysis. Out of these 52 patients, there were a total of 18 males and 34 females. The descriptive data of these patients is presented in Table 1. Except the timing of DE administration, there were no significant group differences. Pre-assessment notes have been reviewed in all 71 patients during the selection of the study group, to make sure that patients enrolled in the study have not been on any anticoagulation prior to surgery.

Table 1: Patient information

Group	Male:Female	Age (years)	BMI	Length of stay (days)	Blood loss (litres)
0-4 h	6:15	71	33	5	0.331
>4 h	12:19	70	32	5	0.331

The patients were split into two groups: the first group (21 patients) received their first dose of dabigatran between 0-4 h after surgery according to the BNF guidance, whereas the second group (31 patients) was administered the drug > 4 h after the surgery.

Two patients in the 0-4 h group were suspected of having DVT on clinical examination. This was confirmed by ultrasound in one of those two cases. One patient in the > 4h group was suspected of having DVT on clinical examination but ultrasound showed patent veins.

Time given by prescriber for drug to be given was the same as administration time of drug in all cases. The peri-operative blood loss was compared between the two groups of patients using the Nadler's formula to evaluate the association of DE administration time with clinically significant bleeding trends. The results show that there was no difference in the calculated mean blood loss between the two groups (Fig. 1). The mean blood loss for the 0-4 h group was 331ml (95% CI: 142-549), compared with 331ml (95% CI: 195-458) for the > 4 h group ($p > 0.05$). This shows no reduction in bleeding by performing a delayed DE administration. There was also no difference in the length of hospital stays for patients from the two groups (Fig. 2). The mean hospital stay for the 0-4 h group was 5.5 days (95% CI: 4.1-6.9), which was also the same for the > 4 h group patients (95% CI: 2.9-8.2) ($p > 0.05$).The trend in the blood loss reduction with respect to DE administration time is graphically represented in Fig. 3, which does show a reduction in blood loss as dabigatran administration is delayed. Although graphically there appears a small correlation this does not appear clinically significant.

Figure 1: Blood loss comparison between the two groups of patients with regard to two different times of DE administration initiation (1-4 h vs. ≥ 4 h post-surgery)

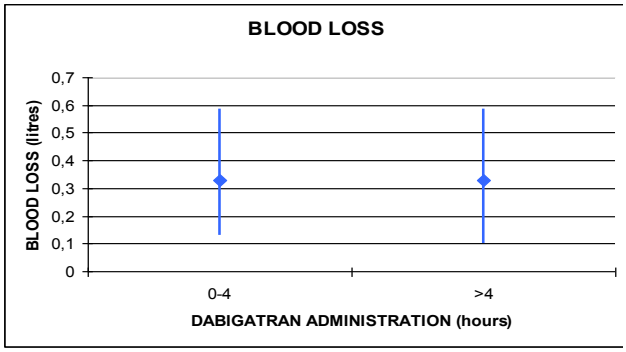


Figure 2: Length of hospital stay comparison between the two groups of patients with regard to two different times of DE administration initiation (1-4 h vs. ≥ 4 h post-surgery)

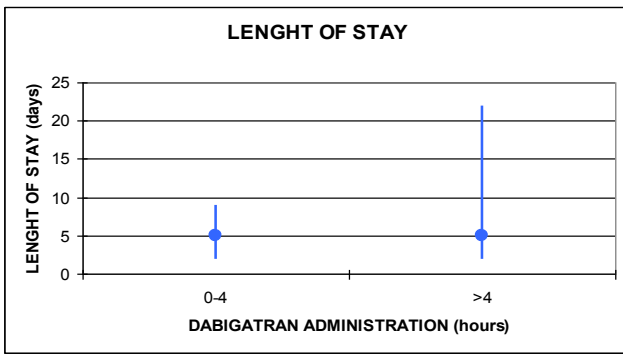
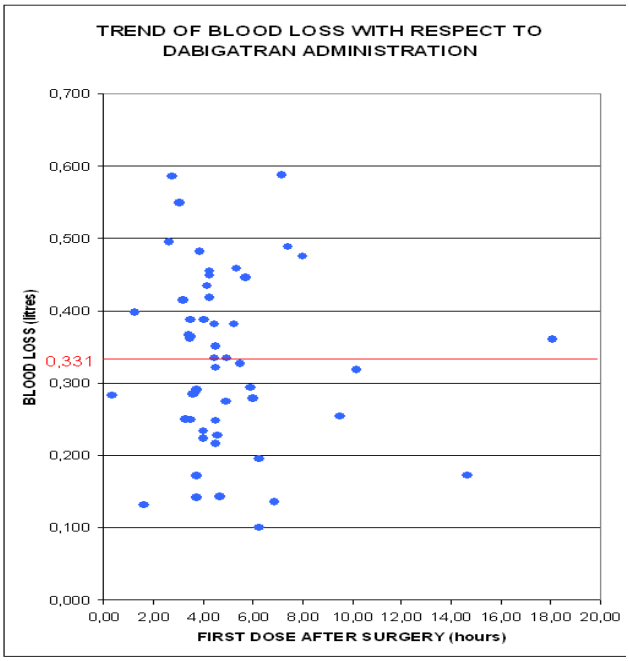
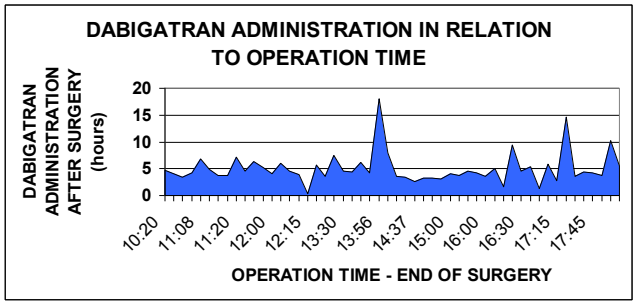


Figure 3: Graphical representation showing the trend of blood loss reduction with respect to DE administration initiation time.



The other aspect of this study was to investigate the delayed initiation of DE administration, > 4 h post surgery. BNF guidance suggests dabigatran should be given 0-4 h post-operation or once it is believed haemostasis was achieved. During the audit, it was hypothesized that the delay in initiating dabigatran treatment was more due to surgeon/anesthetist decision with regards to control of hemorrhage during surgery. The graph in Fig. 4 shows the time dabigatran administration initiation in relation to the operation time of the day. There are two peaks, the first around lunch time and the second at the end of the day, suggesting the surgeon's decision to delay the drug administration based on increased risk of bleeding rather than convenient timing of drug administration. In addition, the results discussed above also agree with the stated hypothesis. This is because if the delay in drug administration was actually made in high risk patients, the blood loss reduction between the two groups of patients should be presumed to be much larger than observed. However, the reliability of this analysis cannot be confirmed due to the small study size and the assumptions involved.

Figure 4: Graph showing the time of dabigatran administration initiation in relation to the operation time of the day.



V. DISCUSSION

Dabigatran etexilate is a new direct thrombin inhibitor effectively employed in many countries, including EU, Canada and USA for the prevention of VTE in patients undergoing TKR and THR surgeries. [11, 17, 23] The oral route of DE administration overcomes the obstacle limiting the extended LMWH prophylaxis, and thus can help more patients in continuing with their prophylaxis treatment even after discharge. [29] At present, studies addressing the correlation between the time of DE administration initiation and the respective blood loss in patients undergoing orthopaedic surgeries are almost negligible. The lack of such studies currently limits the utilization of a strong anticoagulant with confidence.

The study conducted here demonstrated that there was no difference in the amount of blood loss between the two groups of patients with different DE administration initiation times. The advantage of this study is that unlike other reports in the literature detailing the bleeding events or determining blood loss through the need for blood transfusion, a mathematical formula was used for the quantitative determination of peri-operative blood loss. The Nadler's formula, used in many studies, [30, 31] takes into consideration the gender, weight and height of the patient. The results showed that the null hypothesis stating that there is no difference in blood loss between the two dabigatran administration times (0-4 h vs. > 4 h) cannot be rejected. The non-difference in the calculated mean blood loss (Fig. 1) between the two groups and trend of blood loss reduction with respect to DE administration initiation time (Fig. 3) should alleviate fears in giving dabigatran as per the BNF guidance (0-4 h post-surgery). Hence, our results here, in agreement with other studies, [16, 24] suggest that treatment with DE is as safe for the prevention of VTE at an early administration time (0-4 h) as it is at a delayed time period (> 4h).

It seemed like the initialization of the first dose of dabigatran had more of a surgeon's decision based on high risk of bleeding than practical element of timing. In general, it can be assumed that the blood loss reduction between a high risk patient and a normal patient should be larger than between patients with equal risks of bleeding. The graph showing the relationship between the times of dabigatran administration with the operation time of the day may also suggests the role of the practical element, discussed above, in DE administration (Fig. 4).

The main limitation of this study was the smaller study size. Although it is clear that the reduction in blood loss between the two groups of patients was clinically insignificant, a more reliable and statistically significant result could be achieved with a larger patient population. This study was not intended to assess the venous thromboembolic events in relation to dabigatran administration timings as it done in bigger studies where all patients had bilateral venography (RE-MODEL and RE-MOTILIZE trials. The initial dose of dabigatran differed in patients ranging from 75 to 110 mg. Patients older than 75 years of age and/or with renal impairment, have been given reduced dose of 75 mg as initial dose. All other patients have been given 110 mg as initial dose. Doses starting on day 1 post operatively have been double of initial dose that means 150 mg or 220 mg.

Two patients in the 0-4 h group were suspected of having DVT on clinical examination. This was confirmed by ultrasound in one of those two cases. One patient in the > 4h group was suspected of having DVT on clinical examination but ultrasound showed patent veins. There was no significant difference in DVT occurrence in both groups but this can be limited by small amount of patient enrolled.

The study described here shows that there is no benefit in blood loss reduction by delaying the administration of dabigatran. The results obtained are also in agreement with the current NICE guidelines for preventing venous thromboembolism, and this study therefore recommends giving dabigatran 0-4 h post-operatively. We would suggest the administration of dabigatran strictly 3 h post-surgery (rather than 4 h) to increase the likeliness of all patients receiving the drug between that 0-4 h window. Studies like these should be promoted to conduct even larger randomized control trials to assess the benefits of delayed dabigatran administration, if there are any. The depth of knowledge gained from such studies as reported here should pave the way for further investigations on such issues, in addition to expanding our understanding on the efficiency of the drug in preventing VTE after TNR and THR operations.

VI. CONCLUSION

This report illustrates a significant step forward in determining an important aspect of DE administration by studying for the first time, the relationship between the time of DE administration initiation and its effects on the amount of blood loss. The efficacy and safety of DE administration was comparable at both times (0-4 h vs. > 4 h post-surgery). The DVT has been proved in one case in early dabigatran administration, which could be effected by small size study. We observed no clinically significant disadvantage concerningperi-operative blood loss when performing an early/late administration of the first dose of DE.

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