Title - Wound problems following hip arthroplasty before and after the introduction of dabigatran

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As this study was audit based, ethical approval was given by the audit department.

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Wound problems in hip arthroplasty following introduction of dabigatran

Abstract

NICE guidelines have stated that patients undergoing elective hip surgery are at increased risk for venous thromboembolic events (VTE) following surgery and have recommended thromboprophylaxis for 28-35 days[1, 2]. However the studies looking at the new direct thrombin inhibitors have only looked at major bleeding. We prospectively looked at wound discharge in patients who underwent hip arthroplasty and were given dabigatran postoperatively between March 2010 and April 2010 (n=56). We retrospectively compared these results to a matched group of patients who underwent similar operations six months earlier when all patients were given dalteparin routinely postoperatively until discharge, and discharged home on 150mg aspirin daily for 6 weeks (n=67). Wound discharge after 5 days was significantly higher in the patients taking dabigatran (32% dabigatran n=18, 10% dalteparin n=17, p=0.003) and our rate of delayed discharges due to wound discharge significantly increased from 7% in the dalteparin group (n=5) to 27% for dabigatran (n=15, p=0.004). Patients who received dabigatran were more than five times as likely to return to theatre with a wound complication as those who received dalteparin (7% dabigatran n=4, vs. 1% dalteparin n=1), however, this was not statistically significant (p=0.18). The significantly higher wound discharge and return to theatre rates demonstrated in this study have meant that we have changed our practice to administering dalteparin until the wound is dry and then starting dabigatran. Our study demonstrates the need for further clinical studies regarding wound discharge and dabigatran.

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NICE guidelines state that patients undergoing elective hip surgery are at increased risk for venous thromboembolic events (VTE) following surgery and have recommended thromboprophylaxis for 28-35 days[1, 2]. They state patients can be given unfractionated heparin, low molecular weight heparins or the newer direct thrombin inhibitors. The new drugs have the advantage of being orally administered and have no need for coagulation monitoring[3]. However, studies looking at their efficacy have only looked at major bleeding. Wound discharge and the subsequent need for further operations and delays in discharge have not been examined. This study aims to report the effects of dabigatran on wound complications, infections and return to theatre in patients undergoing primary and revision total hip arthroplasty and hip resurfacing.

Methods

The study was conducted at a District General Hospital which operates on around 1350 joints per year. Six consultants and four associate specialists operated on patients during this time.

For the study group (group 1), we prospectively collected data on how long the wound took to dry in patients who underwent total hip arthroplasty, revision hip arthroplasty and hip resurfacings and were given dabigatran postoperatively

between March 2010 and April 2010 (Table 1). During this period, patients received a half dose (75 mg or 110mg tablet) on the day of surgery followed by a full dose (2x75mg or 2x110mg) on each subsequent day. The reduced dose was given to patients who were over 75 years old, had moderate renal impairment (creatinine clearance 30-50 ml/hr) or were taking amiodarone or verapamil as per the manufacturer's guidelines.

The control group (group 2) was a retrospectively matched group of patients who underwent the same operations by the same group of surgeons six months earlier between October 2009 and November 2009. During this period, all patients were routinely given dalteparin 5000 units subcutaneously from day one postoperatively until discharge and then 150mg aspirin daily for 6 weeks post discharge.

The average length of stay in our unit is 5 days. Patients are not discharged until their wounds are dry so the notes of the patients who stayed for longer than 5 days were examined. Those patients who were delayed for discharge due to wound discharge were documented.

All wounds were dressed with a Cosmopore dressing. These were changed when they were soiled or after 3 days. All patients wore anti-thromboembolic stockings for six weeks after surgery, received three doses of intravenous

prophylactic antibiotics and were encouraged to mobilise early in the post-operative period. Patients using warfarin were excluded from the study.

All patients were followed up for six months by searching the hospital database to ascertain if there had been any further admissions or appointments after their 6 week appointment for wound problems.

Results

The demographic patient data are given in Table 1. The age range, median age and male to female ratios were similar in both groups. Group 1 had a higher proportion of total hip replacements (95 %, n=53) compared with group 2 (87%, n=58) and there were no hip resurfacings in group 1 but this was not statistically significant. Group 1 had fewer operations done by consultants than group 2 (30% group 1 n=17, to 57% group 2 n=38) although the majority were performed by associate specialists (66% group 1 n=39, 37% group 2 n=29), which was statistically significant. The wound closure methods were similar in both groups (Figure 1).

The endpoints and complications are shown in Figure 2 and Table 2 respectively. There was significantly more wound discharge after 5 days in the patients taking dabigatran (32% dabigatran n=18, 10% dalteparin n=7, p=0.003) and the rate of delayed discharges due to wound discharge significantly increased from 7% in

the dalteparin group (n=5) to 27% for dabigatran (n=15, p=0.004). Patients who received dabigatran were more than five times as likely to return to theatre with a wound complication as those who received dalteparin (7% dabigatran n=4, vs. 1% dalteparin n=1), however, this was not statistically significant (p=0.18). During the first 4 weeks of the trial, 3 people were taken to surgery for wound washout and one of these was discharged on intravenous antibiotics.

Two patients in the dabigatran group were readmitted after discharge with a leaking wound which responded to intravenous antibiotics and one patient from this group was admitted five months after the initial operation for washout of an old haematoma around the hip replacement.

Discussion

Historically the risk of fatal PE was thought to be as high as 3%[4]. Now with improved anaesthesia, surgical technique and rehabilitation the risk is thought to be less than 0.5%[5-10]. There is an increased risk of VTE for some time after THR (DVT at mean of 22.5 days 6-37) and TKR (mean 5 days post op, 3-8)[5, 7, 11, 12]. Dahl et al stated that using thromboprophylaxis for 35 days instead of 7 days will nearly halve the rate of post operative venographically detected DVT[1, 13]and this has been recommended by the American College of Chest Physician (ACCP) guidelines [4]. The NICE guidelines to reduce venous thromboembolic events following surgery have been developed with these factors in mind.

Surgeons in the USA historically have used warfarin but this has problems with a narrow therapeutic index, the need for regular monitoring and frequent dose adjustments. European surgeons use low-molecular weight heparin (LMWH) but these need subcutaneous administration daily which may be difficult in an outpatient setting especially if required after early discharge[5, 15]. Dabigatran etexilate is a prodrug of dabigatran, a potent non-peptidic small molecule that specifically and reversibly inhibits both free and clot bound thrombin by binding to the active site of the thrombin molecule[16-19]. It has a rapid onset of action and estimated half-lives of 8–10 hours and 14–17 hours with single- and multiple-dose administration, respectively[20]. It does not need to have daily monitoring and as it is an oral tablet it is thought to have fewer problems with compliance than subcutaneous LMWH.

However some studies have shown that dabigatran caused more major bleeding in hips and more serious adverse events than enoxaparin with a higher rate of any and major VTE[3, 21]. Most of the studies are inconsistent in their reporting of major bleeding (defined as death related bleeding, bleeding into a critical organ and bleeding requiring transfusion of more than 2 units) but did not include bleeding that warranted a second surgery to stop bleeding[2, 15]. The studies did not look at wound complications.

Wound infection carries costs to the individual and the NHS in terms of longer hospital stays, prolonged antibiotic courses and the need for more surgery with costlier implants[22, 23]. Deep infection in hip prostheses is often associated with a discharging postoperative wound and early wound complications such as a draining haematoma carry a higher risk of developing late deep infection than those which healed uneventfully[24-26]. Even if the wound discharge itself does not cause the infection, the increased use of blood transfusion is associated with an increased risk of infection[27].

Our results show that the wound discharge after 5 days was highest in patients taking dabigatran (32% group 1, 10% group 2) which was statistically significant. Following the introduction of dabigatran, our rate of delayed discharges due to wound discharge rate went up from 7% in patients on dalteparin to 27% in patients on dabigatran, again statistically significant.

Patients who received dabigatran were more than five times as likely to return to theatre with a wound complication as those who received dalteparin (7% vs 1%) although this was not statistically significant. One patient on dabigatran was discharged on six weeks of intravenous antibiotics as his wound continued to discharge after 3 washouts. No patients in group 2 were discharged on intravenous antibiotics. Two patients treated with dabigatran were readmitted after discharge with a leaking wound which responded to intravenous antibiotics and one patient treated with dabigatran was admitted five months after the initial

operation for washout of an old haematoma around the hip replacement. There were no such admissions for any of the patients in group 2. Surgery needed either during the initial admission or on a subsequent admission was not statistically significant but we feel this is a reflection of the small numbers in our studies.

The number of patients staying over 5 days was statistically significantly higher in group 1 compared to group 2. Our results also show that the proportion of patients undergoing a revision total hip arthroplasty was higher in group 2 compared to group 1 (group 1 – 5%, group 2 – 7%). As revision hips tend to take longer to be discharged due to the increased complexity of their surgery, we feel that this difference would not account for the difference in discharge rates. The proportion of consultants who performed the operation was higher in group 2 compared to group 1 and this may have contributed to the lower wound discharge rate in group 2. However, the majority of operations in group 2 were performed by our associate specialty surgeons who are experienced surgeons.

Group 2 used staples more often as a closure method than group 1 (Group 1 n= 1, group 2 n= 15, Figure 1). However this was the group with fewer problems with wound discharge. A meta-analysis in the BMJ stated that staple usage was associated with an increased rate of superficial wound infection so we feel this change would not account for the difference in wound discharge and infection rates [28].

Although the comparative data set was collected retrospectively, we are confident that it reflects an accurate representation of our normal operative practice in this department. There were multiple surgeons in both the groups but they did not change between the two groups and all other local factors (antibiotic prophylaxis used, patients all going to a single, MRSA free ward post-operatively) remained the same. We are aware that the study size is small but we feel that the problems with the wound discharge, delayed discharge and need for further operative intervention in our patients who were started on dabigatran prior to their wound drying up meant we were unable to continue with this practice. After 3 weeks of dabigatran being given postoperatively, we felt the wound discharge and return to theatre rates were too high to continue and changed our practice to 5000 units of subcutaneous dalteparin until the wound was dry and then the patients were started on the manufacturer recommended dose of dabigatran and continued for 35 days of anticoagulation in total. We collected prospective data on these patients (see table 3 for patient demographics) and no further patients in the next 4 weeks needed their wounds washed out.

These findings were similar to a number of presentations at the recent 2011 British Hip Society meeting where the newer direct thrombin inhibitors were shown to have prolonged oozing, an increased number of wound problems and an increase in the overall return to theatre rate compared to aspirin or heparin[29-32].

Conclusion

Based on this study we no longer prescribe dabigatran from the day of surgery but rather prescribe dalteparin until the wound is dry postoperatively and then the patient is discharged home on dabigatran. Our study demonstrates the need for further clinical studies regarding wound discharge and dabigatran.

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Tables and figures:

Table 1 - Demographics

	Group 1 (Dabigatran)	**Group 2 (Dalteparin)**	**p-value**
Number	56	67	
Female:Male	32:24	39:28	1.0
Age Range (years)	38-90, median 70	31-94, median 70	0.88
Operation: THR	53	58	0.15
Revision THR	3	5	
Hip Resurfacing	0	4	
Surgeon grade: Consultant/ Associate Specialist	17/39	38/29	0.04*

* significant at 5%

Table 2 – Endpoints examined for each group

	Group 1	Group 2	p-value
Total number	56	67	
Median length of stay (days)	7.0 (range 3-32, IQR 5)	5.0 (range 1-60, IQR 3)	0.002*
Wound discharge after 5 days (%)	18 (32%)	7 (10%)	0.003*
Patient discharge delayed due to wound discharge (%)	15 (27%)	5 (7%)	0.004*
Surgery needed for wound whilst either inpatient or post discharge (%)	4 (7%)	1 (1%)	0.18
- whilst inpatient (%)	3 (5%)	1 (1%)	0.23
- post discharge (%)	1 (2%)	0 (0%)	0.46

IQR = interquartile range

*significant at 5%

Table 3 – Demographics of Group 3

	Group 3 (Dalteparin until wound dry then Dabigatran)
Number	19
Female:Male	12:7
Age Range (years)	48-89, median 73
Operation: THR	15
Revision THR	4
Hip Resurfacing	0
Surgeon grade: Consultant/Associate Specialist	11:7
Median length of stay (days)	7 (range 5-22, IQR=3)
Wound discharge after 5 days (%)	3 (15%)
Patient discharge delayed due to wound discharge (%)	3 (15%)
Surgery needed for wound whilst either inpatient or post discharge (%)	0

Figure 1 – Wound closure methods

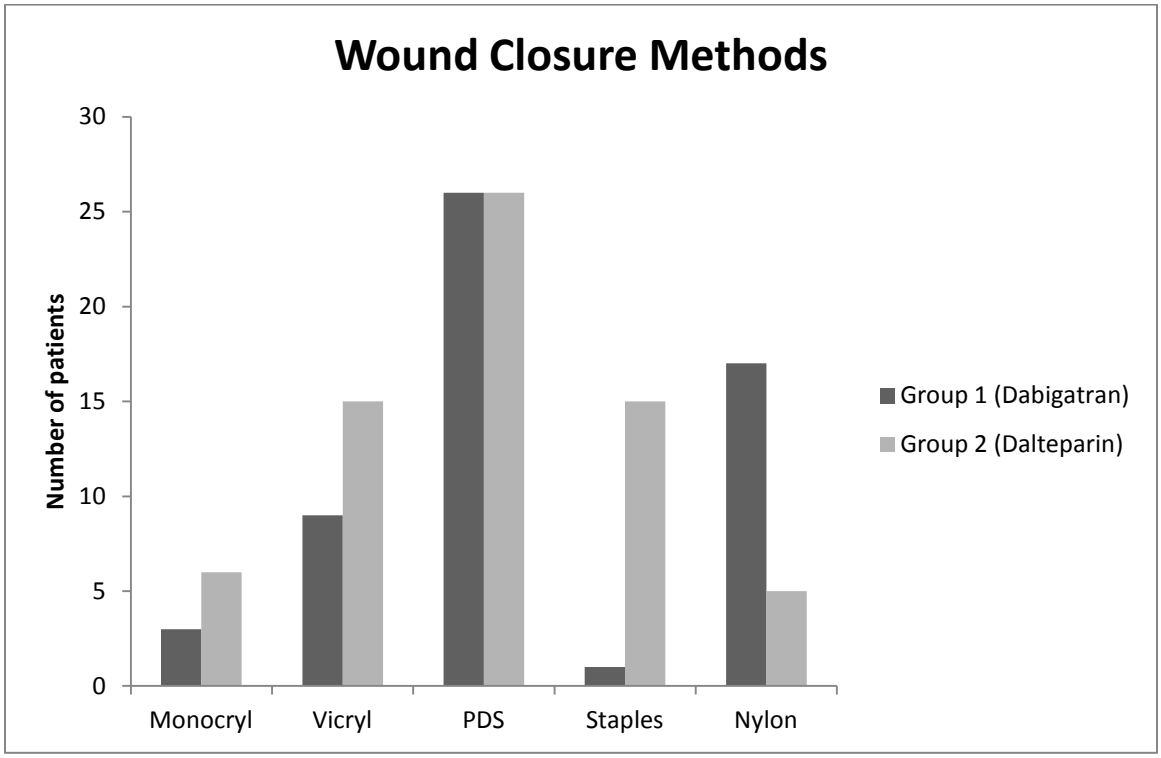

Figure 2 – Complications