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ScienceDirect
British Journal of Oral and Maxillofacial Surgery 50 (2012) 227–232
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Safety of a regimen for thromboprophylaxis in head and neck cancer microvascular reconstructive surgery: non-concurrent cohort study

T.K. Blackburn [a,d], K.R. Java [b,*,e], D. Lowe [c], J.S. Brown [c], S.N. Rogers [c]

[a] *University Department of Oral Maxillo-Facial & Facial Plastic Surgery, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom*
[b] *Foundation Year 1, Warrington General Hospital, Lovely Lane, Warrington WA5 1QG, United Kingdom*[f]
[c] *Mersey Regional Maxillofacial Unit and Head and Neck Cancer Centre, University Hospital Aintree, Liverpool, England L9 7AL, United Kingdom*

Accepted 22 March 2011
Available online 14 July 2011

Abstract

We aimed to assess bleeding complications after increasing the thromboprophylactic dose of dalteparin from 2500 to 5000 units 12 h preoperatively in line with guidance on risk stratification and appropriate pharmacological thromboprophylaxis. We evaluated two groups of patients for confounding factors and bleeding, a prospective consecutive high dose group ($n = 29$), and a retrospective low dose group ($n = 30$) who had had ablative and microvascular reconstructive surgery for oral or oropharyngeal cancer. The bleeding index over 5 days (range 40–60) was used as an objective measure of perioperative bleeding. The null hypothesis was that there was no difference in the bleeding index between the two groups. We found no significant difference in the mean bleeding index between the two groups ($p = 0.56$) (mean (SD) bleeding index in the high dose group 45.3 (26.1), and 48.7 (18.1) in the low dose group). The 95% confidence interval (CI) was −1.51 lower to 0.83 higher in the high dose group. Five patients (2 (7%) in the high dose, and 3 (10%) in the low dose group) were returned to theatre with bleeding complications. There was a trend to a higher failure rate of free flaps in the high dose group (4 (13%) complete, and 1 partial failure compared with 1 (3%) complete and 1 partial failure in the low dose group). There were no symptomatic thromboembolic events in either group. An increased dose of dalteparin did not seem to increase conventional surgical bleeding complications, which was consistent with the null hypothesis at evidence level 2b, but a larger sample is needed to explore its impact on venous thromboembolic events and on the failure of microvascular free flaps.

Keywords: Venous thromboembolic event; Oral and maxillofacial surgery; Head and neck oncology; Thromboprophylaxis; Bleeding risk; Bleeding index

Introduction

International guidelines and consensus statements recommend the assessment of individual patients for the risk of venous thromboembolism, the existence of a local protocol for thromboprophylaxis, and audit of the protocol.[1–5] Major head and neck cancer surgery carries a greater risk of venous thromboembolism than more minor head and neck operations,[6] and routine thromboprophylaxis has been recommended for patients undergoing surgery for cancer.[7] In 2006, the local protocol for thromboprophylaxis was updated in the Mersey Regional Maxillofacial Unit and Head and Neck Cancer Centre. This resulted in the dose of dalteparin (a low molecular weight heparin) being increased

* Corresponding author. Tel.: +44 151 529 5283; fax: +44 192 529 5288.
E-mail address: kapiljava@hotmail.com (K.R. Java).
[d] Formerly Specialist Registrar, University Hospital Aintree.
[e] Formerly Senior House Officer, University Hospital Aintree.
[f] http://www.headandneckcancer.co.uk/.

0266-4356/$ – see front matter
doi:10.1016/j.bjoms.2011.03.265

to high-risk patients including those undergoing microvascular reconstructive surgery. In addition to the intended reduction in the risk of venous thromboembolism, pharmacological thromboprophylaxis in microvascular surgery has perioperative implications regarding the relation between timing and amount of the first dose with the risk of bleeding complications[8–10] and the risk of microvascular anastomotic thrombosis.[11–14]

A non-concurrent cohort (before and after) study was designed to assess the safety of a change in protocol in which the first dose of dalteparin was increased from 2500 to 5000 units 12 h preoperatively for patients undergoing major head and neck surgery with microvascular reconstruction. The efficacy of prophylaxis with the increased dose was not assessed. We selected this group of patients because there is a relative lack of published data on the subject, and the potential hazards – for example, a haematoma contributing to compromise of the microvascular circulation, are particularly relevant.[15]

Method

Before and after cohorts, a prospective consecutive (high dose, $n = 29$), and a retrospective (low dose, $n = 30$) group of patients undergoing ablative and microvascular reconstructive surgery for oral or oropharyngeal cancer were included. The retrospective group consisted of patients treated before the introduction of the new protocol in March 2006. They were given a first dose of 2500 units of dalteparin 12 h preoperatively, and thereafter the ward protocol included 2500 units daily. The protocol introduced in March 2006 went through an audit cycle to assess adherence and feedback to staff, and it was audited again to ensure that maximum adherence was achieved between March and November 2006. Data on the prospective cohort were collected from November 2006 to June 2007 in a Microsoft Excel database and included operative and confounding factors (age; sex; use of aspirin, clopidogrel or dipyridamole before admission; type of microvascular flap reconstruction and outcome; duration of stay in critical care; and dose and duration of thromboprophylaxis). The primary outcome measure was the bleeding index and the secondary outcome measure was postoperative return to theatre for bleeding or evacuation of a haematoma. Preoperative use of warfarin was considered a factor for exclusion. The bleeding index (BI)[17,18] over 5 days (range 40–60) was used as an objective, surrogate measure of perioperative bleeding: BI = [preoperative haemoglobin (g/L)-day 4–6 postoperative haemoglobin (g/L)] + number of units of packed cells transfused in the interim. Criteria for blood transfusion were applied by the critical care and surgical team based on the local protocol of Hb less than 70 or symptomatic anaemia. Other surgical complications relating to outcome of the microvascular reconstruction were recorded to assess a potential negative trend.

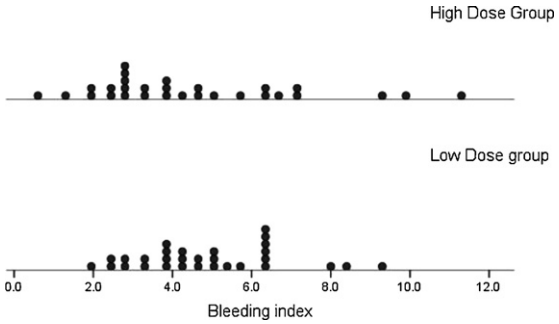

Fig. 1. Bleeding index values for the 29 high dose and 30 low dose patients: high dose group and low dose group.

Similar data collated for the retrospective group were retrieved from patients' notes, computerised haematology laboratory records, and the regional unit's comprehensive and contemporaneously maintained clinical database.

The null hypothesis was that the higher first dose of dalteparin would not be associated with an increased risk of bleeding. An interim power calculation (using SD 2.36) suggested a sample size of 22 for each group based on Student's *t*-test with 80% power to detect a mean difference in mean bleeding index of 20, with a probability of <0.05.

The *t*-test was used to compare bleeding index values between groups of patients. As some subgroups contained relatively few patients the non-parametric Mann–Whitney test was also used. Fisher's exact test was used to compare failure rates of flaps between the two groups. Correlation coefficients (Pearson or Spearman) were used to measure strength of association between bleeding index and age, duration of stay in intensive care, and duration on low molecular weight heparin. Multiple linear regression methods were used to assess the comparison of the two groups after adjusting for the effects of potential confounders.

Results

Data were collected for 68 eligible patients, 38 in the retrospective low dose group, and 30 in the prospective high dose group. Eight patients were excluded for not adhering to the protocol, one from the high dose group and seven from the low dose group. One further patient in the low dose group was excluded because prescription records were missing. No patients were excluded because of preoperative prescription of warfarin.

There was no significant difference in mean bleeding index values between the two groups ($p = 0.56$, *t*-test). Mean (SD) bleeding index values were 45.3 (26.1) for the 29 high dose patients, and 48.7 (18.1) for the 30 low dose patients (Fig. 1). The 95% CI for the difference in means was -1.51 to 0.83. Five patients (2 (7%) in the high dose and 3 (10%) in the low dose group) were returned to theatre with bleeding complications. There was a trend ($p = 0.25$ Fisher's exact test) to a