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MAIN ARTICLE

Determinants of re-operation for bleeding in head and neck cancer surgery

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Abstract

Objective: Post-operative bleeding in the head and neck area is potentially fatal. This 'real world' study sought to assess factors that increase the risk of re-operation for post-operative bleeding in head and neck cancer surgery.

Methods: A total of 456 patients underwent surgery for head and neck cancer (591 operations). The primary endpoint was re-operation for bleeding.

Results: The rate of re-operation for bleeding was 5 per cent of all operations. Re-operation for bleeding was an independent risk factor for 30-day mortality (odds ratio = 5.27, $p = 0.014$). Risk factors for re-operation because of bleeding included excessive (more than 4000 ml) fluid administration (over 24 hours) ($p < 0.001$), heavy alcohol consumption ($p = 0.014$), pre-operative oncological treatment ($p = 0.017$), advanced disease stage ($p = 0.020$) and higher tumour (T) classification ($p = 0.034$). Operations with more excessive bleeding (700 ml or more) were associated with an increased risk ($p = 0.001$) of re-operation for post-operative bleeding. Moreover, the risk of re-operation was significantly higher in patients undergoing microvascular surgery compared to those who had no oncological treatment pre-operatively (18 *vs* 6 per cent, $p = 0.001$).

Conclusion: The 30-day mortality risk increased over 5-fold in patients undergoing re-operation for bleeding.

Key words: Reoperation; Surgery; Postoperative Hemorrhage; Mortality; Head And Neck Cancer

Introduction

Intra-operative bleeding in the head and neck region complicates the identification of important structures, and post-operative bleeding in this area may be fatal. Contemporary publications concerning post-operative bleeding in head and neck oncological surgery are scarce.

The rate of post-operative bleeding in patients undergoing transoral surgery of the oropharynx (including both transoral laser surgery and transoral robotic surgery) is 3.6–5.4 per cent.[1,2] Sixty-seven per cent of these patients required operative intervention. Tonsil primaries and more advanced tumour (T) stage tumours were most likely to bleed.[2] In thyroid surgery, the need for re-operation has ranged from 1.2 to 4.2 per cent.[3,4]

In earlier reports in the field of thyroid surgery, independent predictors for re-operation have included age, gender, type of surgery, malignant histology and higher T classification.[2–4] The risk factors for re-operation because of bleeding in head and neck cancer surgery in general remain largely unknown, although surgical complications have been reported to be related to higher intra-operative fluid administration and greater estimated intra-operative blood loss.[5] There is an unmet need to identify clinical risk factors for post-operative haemorrhage. Moreover, it is not known whether re-operation for bleeding affects the occurrence of cardiac and cerebrovascular events and survival in patients undergoing head and neck cancer surgery.

This study sought to assess the factors that increase the risk of re-operation because of bleeding, and the possible relationship between re-operation for bleeding and cardiac and cerebrovascular events and 30-day mortality.

Materials and methods

This investigation is a part of wider protocol assessing thrombotic and bleeding events in patients undergoing surgery (ClinicalTrials.gov identifier NCT02563470).[6–8] This retrospective study was conducted in a tertiary care centre of Turku University Hospital. The catchment area of the hospital covers approximately one million inhabitants.

All head and neck cancer patients ($n = 456$) treated in the institute between 1999 and 2008 were included in the study. Patients receiving palliative treatment

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were not excluded. Patients whose treatment was not completed in the study institute or whose treatment was started in another institute were excluded. Data were collected, by the first author of this article, from referral letters, patient files, anaesthesiology reports, intensive care unit reports, a laboratory database, a radiology database, electrocardiograms and pathology reports. The total number of operations was 591.

This study was conducted in accordance with the Declaration of Helsinki 2002. The study protocol was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland.

Tumour classification

Primary T classification and disease stage was documented according to the 2010 American Joint Committee on Cancer tumour–node–metastasis staging system.

Endpoints

The primary endpoint of this study was a re-operation for bleeding. Re-operation for bleeding as a risk factor for major adverse cardiac and cerebrovascular events, including acute coronary syndrome, decompensated heart failure, new-onset atrial fibrillation, transient ischaemic attack, stroke, pulmonary embolism and venous embolism, and all-cause mortality, was evaluated during a 30-day follow-up period.

The secondary endpoint was estimated intra-operative bleeding. The study population was divided into two groups based on the amount of median bleeding. Operations with bleeding equal to or higher than the median were evaluated separately.

A history of heavy alcohol consumption was also recorded, defined as the consumption of 20 or more units of alcohol weekly.

Statistical analysis

Data are presented as counts, medians (interquartile ranges or ranges) and frequencies (percentages) where appropriate. Continuous variables were analysed using an independent samples *t*-test. Categorical variables were analysed using a chi-square test. Univariate and multivariate analyses were used to evaluate possible predictors for re-operation because of bleeding. Adjusted odds ratios, 95 per cent confidence intervals (CIs) and *p*-values were calculated for each predictor. Significance was set at $p < 0.05$. Analysis was performed with SPSS Statistics software, version 22.0, for the Mac operating system (SPSS, Chicago, Illinois, USA).

Results

Altogether, 456 patients and 591 operations were evaluated. The rate of re-operation for bleeding was 5 per cent of all operations (31 out of 591). Re-operation for bleeding occurred within the first 2 days (median, 2 days; range, 0–17 days) in 58 per cent of cases (18 out of 31 cases). One patient suffered fatal post-operative haemorrhage.

In a binary logistic regression analysis, the univariate predictors of re-operation for bleeding were: fluid administration exceeding 4000 ml within the operation day (over 24 hours) (odds ratio = 4.88, 95 per cent CI = 2.20–10.81, $p < 0.001$); intra-operative bleeding of 700 ml or more (odds ratio = 3.55, 95 per cent CI = 1.70–7.41, $p = 0.001$); a history of heavy alcohol consumption (odds ratio = 2.67, 95 per cent CI = 1.23–5.92, $p = 0.014$); pre-operative oncological treatment (odds ratio = 2.46, 95 per cent CI = 1.17–5.15, $p = 0.017$); advanced disease stage (odds ratio = 1.42, 95 per cent CI = 1.06–1.90, $p = 0.020$); and higher T classification (odds ratio = 1.42, 95 per cent CI = 1.03–1.97, $p = 0.034$). Moreover, the risk of re-operation was significantly higher in patients who underwent microvascular surgery with pre-operative oncological treatment, compared to the same operation with no pre-operative oncological treatment (18 per cent *vs* 6 per cent, $p = 0.001$). There was no significant difference in flap survival in patients who underwent re-operation for bleeding compared to those who had no re-operation ($p = 0.234$). Patient-related factors such as co-morbidities, older age, gender, smoking or prior antithrombotic medication (including aspirin and oral anticoagulation) had no effect on re-operation risk.

Re-operation for bleeding was an independent risk factor for 30-day mortality post-operation (odds ratio = 5.27, 95 per cent CI = 1.39–19.96, $p = 0.014$). The cause of death at 30 days for all patients who underwent re-operation was cardiovascular (coronary artery disease or heart failure), and one-third of patients who died had a history of heart failure. Nevertheless, re-operation for bleeding was not an independent risk factor for 30-day cardiac and cerebrovascular events.

Median estimated intra-operative bleeding was 700 ml (interquartile range = 800). Median post-operative drain output was 240 ml (interquartile range = 298) and median drainage time was 4 days (interquartile range = 2). Operations with more excessive bleeding (700 ml or more) were associated with an increased risk ($p = 0.001$) of re-operation because of post-operative bleeding.

The characteristics of the operations are presented in Table I. The following procedures predisposed the patients to a higher risk of intra-operative bleeding: operations involving microvascular reconstruction (82 radial forearm flaps, 16 latissimus dorsi flaps, 14 fibula flaps, 1 crista iliaca flap) or reconstruction using a pedicled regional flap (12 pectoral flaps, 9 temporal flaps, 1 sternocleidomastoideus flap, 1 trapezius flap), salivary gland operations with neck dissection, and major sinonasal surgery.

Patients with a higher disease stage ($p < 0.001$) and T classification ($p < 0.001$) suffered more profuse bleeding intra-operatively (Figure 1).

Discussion

Head and neck cancer operations are often extensive, lengthy surgical procedures, with a high risk of

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TABLE I
BASELINE CHARACTERISTICS OF OPERATIONS

Operation	Operations (*n*)*	Disease stage (median (IQR))	Blood loss (median (IQR); ml)	Drain output (median (IQR); ml)	Drainage duration (median (IQR); days)	Re-operations for post-operative bleeding (*n*)
Panendoscopy ± tonsillectomy	132	–	N/A	N/A	–	5
Local resection in oral cavity	119	2 (1)	N/A	N/A	–	0
Local resection + neck dissection	33	2 (1)	N/A	188 (130)	3 (3)	4
Neck dissection	68	2 (2)	N/A	306 (237)	4 (2)	1
Removal of submandibular or parotic gland + neck dissection	5	3 (3)	1000 (2075)	285 (272)	4 (2)	0
Resection + temporal plasty	15	4 (1)	1000 (988)	N/A	2 (1)	1
Resection + temporal plasty + neck dissection	6	4 (1)	2000 (500)	303 (199)	4 (2)	1
Resection + pectoral plasty + neck dissection	11	2.5 (1)	1300 (1238)	336 (521)	5 (2)	1
Resection + microvascular reconstruction + neck dissection	109	3 (1)	1200 (1050)	308 (327)	4 (1)	15
Laryngectomy	18	2 (1)	500 (425)	77 (86)	3 (1)	1
Laryngectomy + neck dissection	6	3 (1)	550 (225)	229 (677)	4 (10)	1
Laryngopharyngectomy + neck dissection + microvascular reconstruction	9	3 (2)	1400 (1200)	145 (235)	4 (2)	0
Sublabial rhinotomy	19	3 (1)	800 (600)	N/A	N/A	0
Other operation	41	–	N/A	N/A	–	0

*Total $n = 591$. IQR = interquartile range; N/A = not available

morbidity and even mortality. It is important to recognise those patients with an increased risk for post-operative complications. In this study, we used retrospective, unselected, real-life patient population data to analyse the risk factors for re-operation because of post-operative bleeding.

Profuse intra-operative bleeding and excessive fluid administration, a history of heavy alcohol consumption, pre-operative oncological treatment, and a higher disease stage predisposed patients to re-operation for post-operative bleeding. Moreover, re-operation for bleeding was a major predictor of 30-day mortality after surgery.

Knowledge of peri- and post-operative bleeding risks is important for the surgeon and anaesthesiologist for pre-operative planning of the operation, intra-operative fluid administration and reservation of blood products. This study shows that features of more advanced disease such as higher stage, T classification and type of operation have a major influence on the rate and volume of intra-operative bleeding in head and neck cancer surgery, and on the need for re-operation because of bleeding. Higher stage and T classification indicate more invasive disease with angiogenesis,[9] and usually deeper resection is needed. More advanced disease increases the probability of post-operative bleeding; the bleeding is more difficult to handle on the ward and interventions in the operating theatre are often needed. In line with our findings, earlier publications showed that patients with a higher T classification have a higher post-operative bleeding rate in oropharyngeal cancer and in gastric cancer.[2,10] In addition, mean tumour size was larger in the re-operation group, in patients who underwent gastrectomy for gastric cancer.[11]

The 30-day mortality rate after re-operation was 5 times higher compared to those who did not undergo re-operation, and the cause of death was cardiovascular in all cases. Post-operative bleeding has previously been associated with decreased survival after thyroidectomy.[12] Moreover, in patients undergoing gastrectomy, post-operative morbidity was closely associated with other measures of poor outcome, including re-operation and mortality.[13] Similarly, in cardiac surgery, re-operation for bleeding has been associated with higher 30-day mortality rates.[14] Mechanisms of bleeding-related poor prognosis include decreased oxygen delivery due to anaemia, hypoperfusion, lactataemia and the discontinuation of drugs. Nevertheless, poor prognosis may also be partly related to the fact that patients with more advanced cancer have a worse prognosis.

There is evidence to suggest that prior radiotherapy, peri-operative transfusion and flap reconstruction significantly increase the risk of peri-operative complications, including post-operative haematoma.[15] In our study, pre-operative oncological treatment was a risk factor for re-operation because of bleeding. During the study period, all patients who were evaluated as being competent by general health practitioners were treated with pre-operative chemo-radiation in our institute. Remarkably, those patients who underwent microvascular or pedicled regional flap reconstruction and had pre-operative oncological treatment had a higher risk of re-operation for bleeding.

In this study, heavy alcohol consumption increased the risk of re-operation for bleeding nearly three-fold. Recent studies have reported controversial findings regarding the effects of heavy alcohol intake on the coagulation cascade. In their review, Pieters *et al.*

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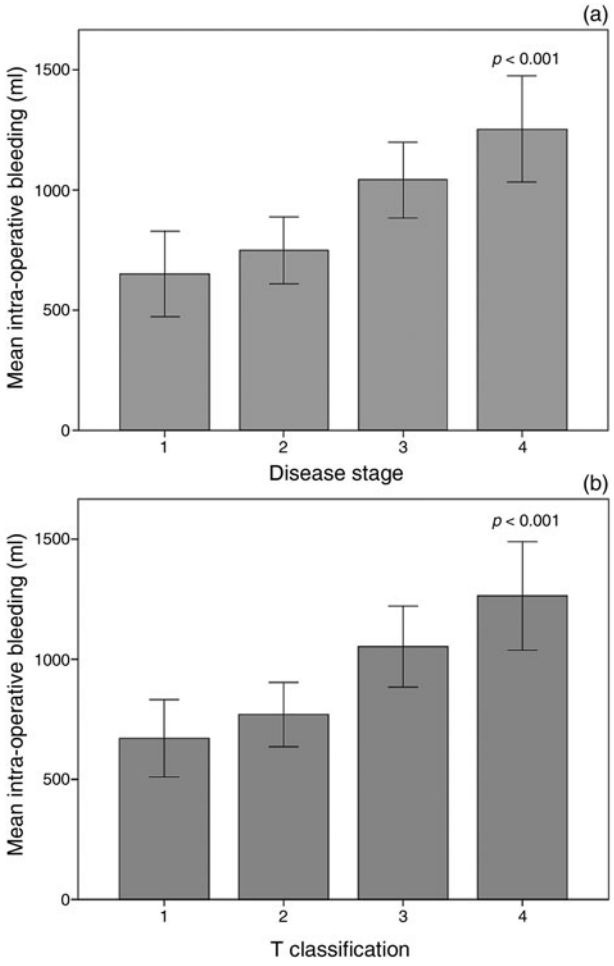

FIG. 1

The impact of (a) disease stage and (b) tumour (T) classification on intra-operative bleeding in head and neck cancer surgery (error bars represent 95 per cent confidence intervals).

stated that a higher alcohol intake seemed to reduce fibrinolytic activity, but altered the platelet function so that the platelets were not able to fully contribute to platelet plug formation.[16] Moreover, alcohol abuse is known to induce platelet apoptosis, which impairs *in vivo* haemostasis.[17,18]

Obviously, the type of surgery plays a major role in bleeding events. As expected, major head and neck surgery, such as microvascular surgery, reconstruction using a pedicled regional flap, salivary gland operation with neck dissection, and major sinonasal surgery predispose patients to greater intra-operative bleeding. Godballe *et al*. reported that the extent of an operation was an independent risk factor for re-operation after thyroid surgery.[4] In this study of head and neck cancer patients, the re-operation risk was nearly four times higher in operations where bleeding was equal or higher to the median (700 ml) of all operations. This is in line with a previous neurosurgery study, where the risk of post-operative extradural haematoma was higher in patients who had intra-operative blood loss of more than 800 ml.[19]

There is increasing evidence that both hypovolaemia and excessive fluid therapy may cause peri-operative problems.[20,21] In line with this reasoning, the present findings showed that the administration of fluids of more than 4000 ml peri-operatively (over 24 hours) was associated with a nearly five-fold increase in the risk of re-operation for bleeding. However, this result must be interpreted with caution, as the amount of fluids infused tends to increase together with the severity of bleeding, and the extent of the operation is related to the amount of fluids administrated.

Limitations

This study has all the limitations of a retrospective setting. However, this study provides practical information about the risk of re-operation for bleeding and the factors influencing that risk.

- **Post-operative bleeding after thyroidectomy and cardiac surgery is associated with decreased survival**
- **The extent of operation is an independent risk factor for re-operation**
- **This study indicates that, in head and neck surgery, re-operation for bleeding increases the 30-day mortality risk over 5 fold**
- **Risk factors for re-operation because of bleeding were: excessive fluid therapy, heavy alcohol consumption, intra-operative bleeding and pre-operative oncological treatment**

Conclusion

Re-operation for bleeding increases 30-day mortality rates by over 5 times in patients undergoing head and neck cancer surgery. The risk of re-operation is influenced by higher intra-operative bleeding and excessive fluid therapy, a history of heavy alcohol consumption, and pre-operative oncological treatment. Moreover, patients who underwent microvascular surgery had a higher risk of re-operation for bleeding.

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