Preoperative Low-Molecular Weight Heparin Chemoprophylaxis in Head and Neck Free Flap Reconstruction

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Abstract

Background: The safety of preoperative chemoprophylaxis for deep venous thrombosis (DVT) prevention in patients undergoing head and neck oncologic surgery with free tissue transfer (HNS-FTT) remains undetermined. Methods: Retrospective chart review of HNS-FTT patients receiving versus not receiving intraoperative subcutaneous enoxaparin (Px-LMWH) was performed. Outcomes included estimated blood loss (EBL), hematoma, flap compromise, DVT or pulmonary embolus (PE). Fisher's exact test and Wilcoxon Rank Sum test were performed between groups (p-value < 0.05). Results: 44 of 134 patients (33%) received Px-LMWH. There was no significant difference in EBL, hematoma, or flap complications between groups. Patients without Px-LMWH had higher rates of DVT and PE ($p = 0.999$, 0.09, respectively). Conclusion: Px-LMWH can be used in major head and neck reconstructive surgery without increased intraoperative blood loss or postoperative complications. Larger studies will need to be done to determine the impact of Px-LMWH on DVT and PE in this patient population.

ABSTRACT

Background: The safety of preoperative chemoprophylaxis for deep venous thrombosis (DVT) prevention in patients undergoing head and neck oncologic surgery with free tissue transfer (HNS-FTT) remains undetermined.

Methods: Retrospective chart review of HNS-FTT patients receiving versus not receiving intraoperative subcutaneous enoxaparin (Px-LMWH) was performed. Outcomes included estimated blood loss (EBL), hematoma, flap compromise, DVT or pulmonary embolus (PE). Fisher's exact test and Wilcoxon Rank Sum test were performed between groups (p-value < 0.05).

Results: 44 of 134 patients (33%) received Px-LMWH. There was no significant difference in EBL, hematoma, or flap complications between groups. Patients without Px-LMWH had higher rates of DVT and PE ($p = 0.999$, 0.09, respectively).

Conclusion: Px-LMWH can be used in major head and neck reconstructive surgery without increased intraoperative blood loss or postoperative complications. Larger studies will need to be done to determine the impact of Px-LMWH on DVT and PE in this patient population.

KEY POINTS

1. Preoperative LMWH has the potential to prevent thrombotic events and its use is recommended by several surgical subspecialties.
2. Preoperative low-molecular weight heparin (LMWH) therapy is not widely used in head and neck oncologic and reconstructive surgery due to concerns over adverse events.

3. Our results show preoperative LMWH given on the day of surgery is safe and does not increase blood loss or adverse events.
4. Given the morbidity of thrombotic events, preoperative LMWH should be administered to patients undergoing major head and neck surgery with reconstruction.
5. The effect of preoperative LMWH on thrombotic events in this patient population should be explored at a multi-institutional level.
6.

INTRODUCTION

Perioperative venous thromboembolism (VTE) remains a significant contributor in morbidity and mortality. Studies estimate rates of VTE between 1.2-1.9 per 1000 person years[1,2,3]. 20% of VTE is associated with a cancer diagnosis, and cancer patients are at a 4-7 times increased risk of VTE events[4,5,6]. Cancer patients who develop VTE have a 3-fold increased risk of death from subsequent pulmonary embolus (PE) as compared to non-cancer patients[7].

Several factors go into the increased risk of VTE for patients with a cancer diagnosis, including dehydration, chemotherapy, and neoplastic activation of the clotting cascade[8]. Surgery is an independent risk factor for cancer-related VTE, with patients undergoing oncologic surgery having twice the risk of VTE as non-cancer patients undergoing similar procedures[9,10]. Unfortunately, development of VTE in cancer patients increases the risk of recurrent VTE and is an independent predictor of mortality[11].

There has been increasing interest in the role of preoperative chemophrophylaxis in preventing the downstream morbidity and mortality from VTE in cancer patients. Guidelines from the European Society of Medical Oncology, the American Society of Clinical Oncology, and the American College of Chest Physicians recommend preoperative chemical prophylaxis for cancer patients undergoing surgery with either low-molecular weight heparin (LMWH) or unfractionated heparin (UFH)[12,13,14]. A large cohort study examining the safety of preoperative chemoprophylaxis in major oncologic surgery found no increased risk of bleeding complications and a significant decrease in VTE rates in patients who received preoperative VTE[15].

Major head and neck surgery with free tissue reconstruction represents a relatively small subset of all major oncologic surgery and large studies on VTE in this patient population are lacking. Prospective studies have found VTE rates as high as 13% in patients undergoing head and neck cancer surgery without chemoprophylaxis[16]. However, other centers report a low VTE rate and the addition of chemoprophylaxis has been implicated in increased risk of bleeding complications[17,18]. The decision to use preoperative chemoprophylaxis in major head and neck surgery remains controversial, with the risk of bleeding complications coinciding with a potential for failure of free flap reconstruction from hemorrhage or hematoma.

The purpose of this study was to examine the use of preoperative VTE chemoprophylaxis with LMWH in patients undergoing head and neck cancer surgery with microvascular reconstruction, and the impact on operative time, blood loss, hemorrhagic complications, overall free flap survival, and thrombotic events.

METHODS

An IRB-approved retrospective review was conducted at our academic institution of all head and neck patients undergoing free flap reconstruction over a 5 year period. During this time, one faculty member used preoperative chemical VTE in the form of subcutaneous 40mg of low molecular weight heparin (LMWH) administered in the pre-operative area or immediately on entry in the operating room. Subsequent doses of LMWH were administered starting post-operative day one. Two faculty members used either no chemoprophylaxis, or an intraoperative dose of intravenous heparin at the time of venous anastomosis. For the purposes of analysis, patients who received intravenous heparin were excluded to avoid confounding data. As such, only patients who received perioperative enoxaparin were compared with only patients who received no chemoprophylaxis.

All patients received sequential compression devices (SCDs) in the operating room. Prescription anticoagulation, including aspirin, was held prior to surgery per hospital guidelines. Post-operatively patients were started on prophylactic chemical prophylaxis with daily 40mg LMHW as well as daily aspirin at 81mg or 325mg per surgeon preference. Patients who were on prior systemic anticoagulation other than aspirin were restarted on their home anticoagulant per surgeon preference and were excluded from the analysis final.

Post-operative monitoring was standardized for all patients. At our institution, all patients receive arterial and venous implantable dopplers for anastomosis monitoring. In the rare case implantable dopplers are not available, patients undergo monitoring with manual doppler checks of the main pedicle. All patients undergo hourly flap checks by the nursing team for the first 48 hours, and q2 hour flap checks for the next 48 hours. Resident checks occur 2-3 times a day.

Data on patient sex, tumor site, tumor stage, and history of prior treatment were recorded. Surgical data recorded included free flap type, duration of surgery and estimated blood loss, the latter two of which were determined from the anesthesia record. The incidence of post-operative surgical site hematoma, donor site hematoma, blood transfusion, partial flap loss or complete flap loss were recorded based on chart documentation. Hematoma formation was recorded if inpatient documentation mentioned a blood collection at either the operative of donor site. Partial flap loss was defined as a non-viable portion of the free flap reconstruction noted on clinical exam with or without operative debridement. Complete flap loss was defined by loss of the entire free flap with or without salvage. Transfusion requirements included a Hgb level < 6 and symptomatic hypotension not responsive to initial fluid bolus.

Assessment of DVT was based on physical exam findings of swollen extremity and/or pain, or abnormal lab values. Initial assessment with ultrasound of the affected extremity was performed to confirm the diagnosis. Assessment of PE was undertaken for patients on a symptom-based approach which included assessing for tachycardia, hypoxia, and tachypnea. A thin-slice contrasted CT was used to confirm the diagnosis of PE. All patients with DVT or PE were started on systemic anticoagulation.

Fisher's exact test was used to assess proportions of categorical variables between patient groups, while Wilcoxon Rank Sum test was used to assess distributions of continuous variables. A p-value < 0.05 implied statistical significance in this study. Statistical calculations were performed using statistical software R, version R 3.6.3.

RESULTS

A total of 134 patients were included. 44 (33%) received preoperative chemoprophylaxis (Px-LMWH). Full demographic data is show in in Table 1. Tumor staging was available for 35 patients in the Px-LMWH group and 73 in the control group. Nodal and metastatic staging was available in 33 patients in the Px-LMWH group and 70 patients in the control group. There was no significant difference in T, N, or M stage between the two study groups. The majority of patients (55%) had T3 or T3 primary tumors. The most common site of cancer was the oral cavity (53%), followed by larynx and oropharynx (13%). The most common free flap donor sites were the anterolateral thigh and radial forearm (39% and 40%, respectively). 26 (19.4%) of patients were taking preoperative aspirin (ASA) that was held prior to surgery.

Surgical data was analyzed and showed no significant difference in EBL between patients receiving preoperative chemoprophylaxis and those who did not (Table 2). There was a significant difference in surgical duration, with patients receiving LMWH having on average 98 minutes longer of an operative duration.

Post-operative data was similarly analyzed between patient groups (Table 3). There was no significant difference in the rates of blood transfusion between groups, with the majority (72%) requiring no blood transfusion during their stay. There was also no significant difference in rates of surgical site hematoma. Partial flap loss occurred in one patient and complete flap loss in four patients. There was no significant difference in the rates of flap failure between patient groups. No patients in the Px-LMWH group developed a PE and 1 developed a DVT ($p = 0.09$ and 0.9, respectively). Overall, DVT occurred in 3.7% of all patients, and PE occurred in 5.2%.

DISCUSSION

The use of preoperative chemical prophylaxis to prevent surgical VTE in head and neck surgery patients remains controversial, but of high importance to investigate. Mortality occurs in 6-11% of patients with isolated deep venous thrombosis (DVT); however, pulmonary embolus can result in mortality for up to a third of affected patients[4]. Several risk stratification methods exist for predicting which patients are at higher risk of VTE. Known risk factors exist and include age $>$ 60 years old, male gender, increased Charleston comorbidity score, bedrest $>$ 4 days, surgery duration $>$ 2 hours, inpatient stay $>$ 2 days, and malignancy[19,20]. Risk stratification in oncologic patients undergoing surgery is more nuanced. No one system can completely predict rates of VTE for each surgical subset, though several methods exist. The Caprini score (Figure 1) has been widely used to predict VTE risk due to ease of use, validation across multiple types of surgical patients, and a low risk of bias. Based on the model, the majority of head and neck cancer patients undergoing reconstruction would start at a baseline score of 8 (major surgery $>$ 6 hours, present malignancy, age $>$ 45 years old), placing them at a moderate risk of VTE. Other factors such as cast immobilization or cardiopulmonary comorbidity, the latter of which is seen in up to a third of patients undergoing major head and neck surgery, increase this risk to high with an estimated 2% risk of symptomatic VTE[21,22].

The use of preoperative VTE chemoprophylaxis has not been universally implemented in head and neck free flap patients due to variable rates of VTE and the potential for devastating complications from hematoma. Previous studies had reported low rates of VTE in otolaryngology patients undergoing surgery; however, recent studies have found rates of VTE in head and neck free flap patients may be higher than those previously reported[24]. Shuman et al additionally found a correlation with increasing Caprini risk score and the incidence of perioperative VTE in head and neck patients, with rates of VTE as high as 18.3% with a score of 9 or above[25].

Our study showed no increase in intraoperative blood loss, transfusion requirements, rates of hematoma, partial flap loss, or total flap loss with the use of preoperative chemoprophylaxis. There was a significant difference in surgical duration with the group receiving perioperative chemoprophylaxis having over an hour longer surgical duration. Several factors can play a role in operative time, including the difficulty and extent of planned resection, the timing of flap harvest, anesthetic considerations and practice differences between surgeons. The increased operative time seems independent to LMWH administration. Overall preoperative LMWH administration had a low rate of hemorrhagic or reconstructive complications in our study cohort. It should be mentioned that several outcome measures, including hematoma and flap compromise, are more dependent on post-operative factors than preoperative LMWH use. However, these were included for completeness and to assess if intraoperative LMWH had an unintended effect on the ability to provide adequate hemostasis. While our study was not powered to determine the occurrence of DVT or PE based on LMWH use, there was a higher incidence of both DVT and PE in the cohort who did not receive preoperative LMWH. This effect should be explored further as a multi-institutional prospective trial. Our study shows that preoperative LMWH administration can be done safely without increased morbidity from blood loss and with the potential to prevent thrombotic events.

There are limitations to this study. As a retrospective cohort study, there exists a selection bias that could impact our findings. Our study cohorts had no significant differences in tumor stages and sites, rates of prior treatment, and types of reconstruction, making each population heterogeneous for study. The incidence of the outcome measures were low overall and our sample size may be underpowered to make a complete assessment about all outcomes based on this patient population. Additionally, while attempts were made to keep the patient cohort homogenous, a patient's individual comorbidities and variations in LMHW processing were not taken into account. Measurement of anti-Xa and antithrombin III levels can be useful in this regard to determine if the standard dose of perioperative chemoprophylaxis is biologically and clinically effective[23]. Finally, a rigorous method of assessing intraoperative and post-operative blood loss remains elusive in this patient population. Measurements of EBL are notoriously subjective and transfusion requirement can be patient and provider-dependent. However, clinical outcomes can provide a direct clinical reference for bleeding complications and are ultimately the end-point for assessing the safety of Px-LMHW

administration in reconstructive surgery.

In conclusion, we found that standard preoperative VTE chemoprophylaxis in the form of LMWH does not appear to increase rates of intraoperative blood loss in major head and neck surgery with reconstruction, and rates of post-operative complications are were comparable between treatment groups. An increase in operative time can be due to several factors, though does not seem to be related to LMWH administration or blood loss. Head and neck cancer patients undergoing surgical resection with free flap reconstruction remain a high-risk group for VTE and the downstream morbidity and mortality that accompanies these events. Preoperative LMWH can potentially decrease thrombotic complications while maintaining reconstructive outcomes and safety. Further work should focus on larger, prospective studies examining the impact of Px-LMWH on hemorrhagic complications and measure therapeutic endpoints of chemoprophylaxis administration. Multi-institutional prospective studies should be done to determine the effect of Px-LMWH on DVT and PE in this patient population.

1. Heit JA, Petterson TM, Farmer SA et al. Trends in the Incidence of Deep Vein Thrombosis and Pulmonary Embolism: A 35-Year Population-Based Study. Blood (2006) 108 (11): 1488.
2. Cushman, M, Tsai AW, White RH et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med (2004) 117(1): 19-25.
3. White, R. The epidemiology of venous thromboembolism. Circulation. 2003: 107:I-4-I-8.
4. Heit JA. The Epidemiology of Venous Thromboembolism in the Community. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28:370–372
5. Laporte S, Mismetti P, Décousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry, Circulation, 2008, vol. 117 (13): 1711-1716)
6. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study, Arch Intern Med, 2002, vol. 162 (11): 1245-1248
7. Gussoni G, Frasson S, La Regina M, et al. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry, Thromb Res, 2013, vol. 131(1):24-30
8. Falanga, F.R. Rickles. Pathophysiology of the thrombophilic state in the cancer patient. Semin Thromb Hemost, (1999). 25: 173-182
9. P. Prandoni. Antithrombotic strategies in patients with cancer. Thromb Haemost, (1997). 78:141-144
10. G.P. Clagett, J.S. Reisch. Prevention of venous thromboembolism in general surgical patients Ann Surg, 208 (1988), pp. 227-240
11. P. Prandoni, A.W.A. Lensing, A. Cogo, et al.The long-term clinical course of acute deep venous thrombosis. Ann Intern Med, 125 (1996), pp. 1-7
12. Mandala, M, Falanga, A, Roila F. Management of Venous Thromboembolism (VTE) in Cancer Patients: ESMO Clinical Practice Guidelines. Ann Oncol 2011; 22 (Suppl 6): vi85-vi92.
13. Lyman GH, Bohlke, K, Khorana AA et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015 Feb 20; 33(6): 654–656.
14. Gould MK, Farcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e227S-e277S.
15. Selby LV, Sovel M, Sjoberg DD, et al. Preoperative Chemoprophylaxis is Safe in Major Oncology Operations and Effective at Preventing Venous Thromboembolism. J Am Coll Surg. 2016;222(2):129-137.
16. Clayburgh, DR, Stott W, Cordiero T, et al. Prospective study of venous thromboembolism in patients with head and neck cancer after surgery. JAMA Otolaryngol Head Neck Surg. 2013 Nov;139(11):1143-50.
17. Gavriel H, Thompson E, Kleid S, et al. Safety of thromboprophylaxis after oncologic head and neck surgery. Study of 1018 patients. Head Neck. 2013 Oct;35(10):1410-4.

18. Moubayed SP, Eskander A, Mourad MW, et al. Systematic review and meta-analysis of venous thromboembolism in otolaryngology-head and neck surgery. Head Neck. 2017 Jun;39(6):1249-1258
19. Bahl V, Hu HM, Henke PK, et al. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg. 2010 Feb; 251(2):344-50.
20. Spyropoulos AC, Hussein M, Lin J, et al. Rates of venous thromboembolism occurrence in medical patients among the insured population.Thromb Haemost. 2009 Nov; 102(5):951-7.
21. Damain D, Esquenazi J, Duvvuri U, et al. Incidence, outcome, and risk factors for postoperative pulmonary complications in head and neck cancer surgery patients with free flap reconstructions. Journal of Clinical Anesthesia, Volume 28, Pages 12-18
22. Ciolek PJ, Clancy K, Fritz M et al. Perioperative cardiac complications in patients undergoing head and neck free flap reconstruction. American Journal of Otolaryngology. 38(4):433-437
23. Louis SG, Van PY, Riha GM et al. Thromboelastrogram-guided enoxaparin dosing does not confer protection from deep venous thrombosis: a randomized controlled pilot trial. J Trauma Acute Care Surg. 2014 Apr;76(4):937-42
24. Thai, L, McCarn, K, Stott, W et al. Venous thromboembolism in patients with head and neck cancer after surgery. Head & Neck. 2013, 35(10).
25. Shuman, A. G., Hu, H. M., Pannucci, C. J., et al.Stratifying the risk of venous thromboembolism in otolaryngology. Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery, 2012. 146(5), 719–724.

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Each risk factor = 1 point

- Age 40-59 years
- Minor surgery planned
- BMI $\geq$ 30mg/m^2
- History of prior major surgery (<1 month)
- Swollen legs (current)
- Varicose veins
- Sepsis (<1 month)
- Abnormal pulmonary function (COPD)
- Acute myocardial infarction (<1 month)
- Congestive heart failure (<1 month)
- History of IBD
- Medical patient currently at bed rest

Each risk factor = 2 points

- Age 60-74 years
- Arthroscopic surgery
- Major open surgery (> 45 minutes)
- Laparoscopic surgery (> 45 minutes)
- Prior cancer (except non-melanoma skin cancer)
- Present cancer (Except breast and thyroid)
- Confined to bed (>72 hours)
- Immobilizing plaster cast
- Central venous access

Each risk factor = 3 points

- Age $\geq$ 75 years
- History of VTE
- Family history of VTE
- Present chemotherapy
- Positive Factor V Leiden
- Positive Prothrombin 20210A
- Positive Lupus anticoagulant
- Elevated anticardiolipin antibodies
- Elevated serum homocysteine
- Heparin-induced thrombocytopenia (HIT)
- Other congenital or acquired thrombophilias

For women only (1 point each)

- Pregnant or post-partum
- History of unexplained or recurrent spontaneous abortion
- Oral contraceptives or hormone replacement therapy

Caprini risk category based on total risk score

Total score	Category
0-4	Low
5-8	Moderate
$\geq$9	High

Each risk factor = 5 points

- Major surgery lasting > 6 hours
- Stroke (<1 month)
- Elective major lower extremity arthroplasty
- Hip, pelvis, leg fracture (< 1 month)
- Acute spinal cord fracture or paralysis (< 1 month)
- Multiple traumas (< 1 month)

Figure 1: Caprini risk factors and total risk score ***(BMI = body mass index; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; VTE = venous thromboembolism)***