**Title: The Use of Thrombin-based Haemostatic Matrix in Head and Neck
Reconstructions: a Potential Risk Factor for Pulmonary Embolism**

Running title: haemostatic matrix & pulmonary embolism

Study type: Case series

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Abstract

Introduction

Haemostatic agents including thrombin based haemostatic matrix are widely used in patients undergoing cardiac, vascular and spinal surgery. These agents promote local hemostasis through activation of the clotting cascade. To our knowledge this case series is the first report of pulmonary embolization associated with Floseal following head and neck oncology resection and free flap reconstruction.

Methods

We present five patients who were diagnosed with symptomatic pulmonary embolism after oncologic head and neck free flap reconstructions in 2014 and 2015.

Results

There were five patients consisting of three males and two females. The mean age was 67 years, ranging from 60 to 74 years. Pulmonary embolism occurred between three and 30 days with a mean of 12 days. Four out of the five reported cases showed involvement of more than one lobe, and two cases had bilateral pulmonary involvement. All but one patient underwent infratemporal fossa dissections as part of the cancer resection. 10 mls of floseal was applied to the pterygoid plexi in the four patients to achieve haemostasis. All patients received heparin infusion followed by warfarin therapy for at least six months with no mortality or complications relating to pulmonary embolism to date.

Discussion

Although inconclusive due to study design and small numbers, this series raises the possibility that there may be an association between the use of haemostatic matrix in head and neck oncologic reconstructions and pulmonary embolism. Haemostatic matrix must be used in caution when there is direct contact with venous endolumens such as the pterygoid plexus and soleus.

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Introduction

In 1 study evaluating 7 million discharged hospital patients, postoperative VTE was the second most common complication¹. It accounts for approximately 10% of hospital deaths annually², and patients who survive VTE are at risk for further complications, including recurrent VTE, pulmonary hypertension, venous stasis, and complications of long-term anticoagulation²⁻⁴. In addition, VTE substantially adds to length of hospital stay and inpatient costs of affected patients⁵.

Surgical oncology inpatients are generally considered one of the highest-risk groups for VTE^{2, 6, 7}. When compared with patients undergoing non-head and neck reconstruction, patients undergoing oncologic head and neck procedures were older, underwent longer anesthesia, spent more days in the hospital, and were more likely to need free flaps⁸. Chen et al analysed 1591 patients who underwent head and neck reconstructions and reported a 0.44% incidence of symptomatic PE⁹.

Haemostatic agents including thrombin based haemostatic matrix are widely used in patients undergoing cardiac, vascular and spinal surgery¹⁰. The collagen or gelatin granules from these agents restrict blood flow and provide a physical matrix to support clot formation, while delivering thrombin to exposed microvessels to activate clotting. Recent studies suggest that this may potentially activate systemic coagulation resulting in thromboembolic events¹¹⁻¹³. Safaee et al analysed 467 patients who underwent craniotomies for meningioma and found a significant association between the volume of Floseal[®] used intraoperatively and the incidence of post-operative pulmonary embolism. In an experimental animal study, Ritschl et

al investigated the thromboembolic risk of three different tissue glues (fibrin, FloSeal ® or TachoSil ®) in vascular anastomosis and reported a significant increase in thromboembolism in the experimental groups¹².

To our knowledge this case series is the first report of pulmonary embolization associated with Floseal following head and neck oncology resection and free flap reconstruction.

Methodology and patients

A retrospective analysis of all head and neck free flap reconstruction operations at Royal Melbourne Hospital was completed between January 2007 and June 2015. A significant increase in pulmonary embolism was noted in 2014 - 15 (5 of 72, 6.9%), compared to the baseline incidence of pulmonary embolism in our institution from 2007 to 2013 (4 of 266, 1.5%) (Fisher's exact test 2 tailed P value = 0.024).

We present five patients who were diagnosed with symptomatic and clinically significant pulmonary embolism in 2014 and 2015.

There were five patients consisting of three males and two females. The mean age was 67 years, ranging from 60 to 74 years (Table 1). Pulmonary embolism occurred between three and 30 days with a mean of 12 days. Four out of the five reported cases showed involvement of more than one lobe, and two cases had bilateral pulmonary involvement.

All patients received routine pulmonary embolism prophylaxis with intra-operative subcutaneous injection of 5000 units of heparin before flap inset, and post-operative subcutaneous injections of 5000 units of heparin 12-hourly, compression stockings, venous

foot pumps and pneumatic calf compression devices. CT pulmonary artery scans were ordered only when patients developed persistent tachycardia for more than 24 hours, fever of more than 37.8 ° Celsius, and decreased oxygen saturation below 95%.

With patient 5 as an exception, all patients underwent infratemporal fossa dissections as part of the resection procedure, with significant bleeding from the pterygoid plexus. 10 mls of floseal was applied to the pterygoid plexi in the four patients to achieve haemostasis.

All patients received heparin infusion followed by warfarin therapy for at least six months with no mortality or complications relating to pulmonary embolism to date.

Patient 1

66 year old female with a previous T4N0 squamous cell carcinoma of anterior floor of mouth managed with anterior segmental mandibulectomy and free fibular flap reconstruction in 2010. Her other medical conditions include left mastectomy for breast cancer, 70 pack year smoking history (ceased 2010) hypertension and COPD. She takes regular tamoxifen for her ongoing management for breast cancer.

In 2014, she developed a recurrent 15mm right buccal mucosal well differentiated squamous cell carcinoma, staged T2N0Mx. She underwent wide local excision, right segmental mandibulectomy, partial maxillectomy and radial forearm free flap reconstruction. CTPA completed day four post operation for the indications outlined revealed acute pulmonary emboli involving several segmental branches in the right upper and middle lobes with a non-occlusive thrombus in the right lower lobar artery.

Patient 2

74 year old male presented with right posterior mandibular ulcer with associated odynophagia. This lesion was diagnosed stage T2N0 squamous cell carcinoma of the right retromolar trigone, posterior alveolar mandible. He has a past medical history of hypertension, COPD and 50 pack year smoking history.

He underwent WLE, subsigmoid segmental mandibulectomy, partial maxillectomy, right neck dissection (I-IV) and ALT free flap reconstruction. CTPA completed day three post operation revealed acute pulmonary emboli involving right upper, middle, lower lobe subsegmental arteries.

Patient 3

72 year old female presented with persistent ulcer at the base of left tongue. She was diagnosed with T3N1 squamous cell carcinoma of the left posterolateral tongue and floor of mouth. Her past medical history includes verrucous carcinoma in 1991 which was managed with marginal mandibulectomy and neck dissection. She has a 20 pack year smoking history. She underwent left segmental mandibulectomy, subtotal glossectomy, radical excision left infratemporal fossa and fibula free flap reconstruction. CTPA completed day 17 post-operation revealed acute pulmonary emboli involving the right middle lobe segmental pulmonary artery.

Patient 4

63 year old male presented with an enlarging ulcer located at his right floor of mouth. He was diagnosed with a T4N2b squamous cell carcinoma of the right floor of mouth. His medical

history includes hypertension, hyperlipidemia and COPD. He continued to smoke 15 cigarettes per day.

He underwent lateral-mandibulectomy (angle of mandible to contralateral canine), subtotal glossectomy, bilateral neck dissection and osteomusculocutaneous free fibula reconstruction.

Unfortunately, he returned to theatre day one post operation due to an arterial anastomosis thrombosis, where the arterial anastomosis was redone. The skin paddle was found to be non-viable and the FHL inset was used to cover bone and plate.

CTPA completed day six post-operation revealed acute pulmonary emboli involving bilateral segmental and subsegmental pulmonary arteries.

Patient 5

60 year old male with a previously treated T2N0 SCC right floor of mouth in India in 2010 with surgical excision and adjuvant radiotherapy. This was complicated by osteoradionecrosis of the mandible and a pathological fracture was subsequently confirmed on CT (Stage III). He was otherwise well with no significant medical history.

He underwent right segmental mandibulectomy and free fibula reconstruction.

His admission was complicated with temporomandibular joint dislocation secondary to soft tissue contracture which was addressed with reduction, local pedicled pectoralis major flap and split skin graft. This patient subsequently developed an orocutaneous fistula which was addressed with a radial forearm free flap.

CTPA completed day 30 post initial operation revealed acute pulmonary emboli involving the distal right lower lobe pulmonary artery and left lingual pulmonary artery.

Discussion

Patients undergoing oncologic head and neck reconstructions, compared to non-head and neck reconstruction, were older, underwent longer anesthesia times, spent more days in the hospital, and were more likely to need free flaps⁸. However, despite these potential risk factors, patients undergoing oncologic head and neck reconstructions have similar incidence of pulmonary embolism, ranging from 0% to 1.0%^{8, 14, 15} to patients undergoing general surgery procedures, ranging from 0.2% to 0.9%^{7, 16}. The low reported incidence may be due to the inclusion of patients who underwent less complex reconstructions utilizing local and

pedicled flaps^{8, 14, 15}. Although the incidence of symptomatic pulmonary embolism measured in our institute only included patients who have undergone free flap reconstructions, 6.9% incidence is nevertheless an outlier when compared to the current literature and the baseline incidence in our institution from 2007 to 2013 (1.5%). In this series, four of five patients who experienced symptomatic pulmonary embolisms underwent infratemporal fossa dissections and subsequent applications of 10mls of Floseal. Given that the use of Floseal in achieving haemostasis in the infratemporal fossa in our institute only commenced in 2014. It is hypothesized that exposing the pterygoid venous plexus endolumens to Floseal may be associated with the occurrence of pulmonary embolisms. This hypothesis is further supported by the absence of deep vein thrombosis (lower limb doppler ultrasound was completed in all patients with PE in our series). This differs to the reported prevalence of detectable DVT in patients with proven PE in the current literature ranges from 13 to 93%¹⁷⁻²⁰; although Diebold et al reported in a large autopsies series that 28% of patients did not have an identifiable source of PE on sectioning upper and lower extremity deep veins as well as deep calf veins²¹. In this series, this phenomenon could be explained by the fact that embolisms originated directly from the pterygoid plexus associated with Floseal use and lodge in pulmonary vessels via the retromandibular and external jugular veins. Floseal represents the new generation of topical hemostatic agents made from collagen or gelatin. Floseal is prepared by mixing together a proprietary gelatin matrix and topical thrombin immediately prior to its use. Both components are of bovine origin from traceable herds in the United States. The most common adverse events reported prior to the US Food and Drug administration recorded during and after the application of the hemostatic agents were anemia, atrial fibrillation, infection, and hemorrhage¹⁰. Pulmonary embolism has not been

listed in the possible complications associated with intraoperative use of Floseal.

Furthermore, no information regarding the recommended and toxic dose of Floseal is readily available from the manufacturer or the initial investigations^{10, 22, 23}. 10mls of Floseal was used in our institution as one package of Floseal contains 5mls of Calcium Chloride and 5mls of Thrombin in a vial. We believe that recommended and toxic dose of Floseal would be important in preventing an excessive amount of Floseal being used intraoperative.

There have been previous studies that identified the association between the use of Floseal and incidence of embolisms¹¹⁻¹³. In particular, there has been a report of a fatal pulmonary embolism by locally applied hemostatic matrix after surgical removal of spinal schwannoma¹³. An autopsy of this patient confirmed that the embolism directly formed from the Floseal matrix. In 467 patients who underwent craniotomy for resection of meningiomas, a significant association was found between the volume of Floseal used intra-operatively and the incidence of pulmonary embolisms ($p = 0.02$)¹¹. Furthermore, in a recent animal study by Ritschl et al, thromboembolic material was demonstrated significantly more frequently in the distally inserted micropore filter in all tissue glue groups, independent of tissue glue type.¹².

DVT/PE was associated with increased risk of in-hospital mortality (OR, 3.1; $P < .001$), postoperative surgical complications (OR, 2.1; $P < .001$), acute medical complications (OR, 1.9; $P < .001$), and significantly increased length of hospitalization and hospital-related costs.⁵ Hence, prevention is key to improving patient outcome and health care expenses. Venturi et al proposed categorising plastic surgery procedures to moderate or high risk based on whether the operation is less or more than one hour respectively; and patients moderate or high risk based on whether there are less or more than four risk factors respectively. According to this

guideline, all patients and operations in our series belong to the high risk group²⁴. In head and neck surgery, Moreano et al identified pneumatic compression devices to be the only statistically significant modifiable variable in increasing or reducing the chances of developing VTE⁹. Meta-analysis has shown that pneumatic compression devices also decrease DVT in patients undergoing general surgical procedures by over 60%²⁵. Compared with no prophylaxis, subcutaneous heparin and low molecular weight heparin have been shown to reduce VTE risk by at least 60%.^{2,7}

In a study by Chen et al, all patients had received prophylactic anticoagulation consisting of aspirin and low molecular weight heparin; they also wore pneumatic compression devices before ambulation and before the start of anesthesia⁸. Innis et al recommends only early mobilization with the possible adjunct of pneumatic compression stockings in most low-risk patients, either mechanical or pharmacologic prophylaxis for moderate-risk patients, and chemoprophylaxis only in high risk patients and patients undergoing high-risk procedures of long duration or immediate reconstruction.²⁶ Gavriel et al demonstrated that there is a significant increase in haematoma or bleeding from the surgical site with using chemoprophylaxis, however this study did not include patients who underwent free flap reconstructions¹⁴.

In our series, all patients received strict administration of low molecular weight heparin and pneumatic compression devices before the start of anaesthesia and ambulation, followed by post-operative subcutaneous injections of 5000 units of heparin 12-hourly, compression stockings, venous foot pumps and pneumatic calf compression devices. Interestingly, Safaee demonstrated in a multivariate analysis of patients who received Floseal intra-operatively for resection of intracranial meningioma, that age, tumour histology, and use of anticoagulants

for DVT prophylaxis did not have significant influence over the incidence of VTE¹¹. This supports the mechanism described by Steinestel et al that topical application of Floseal can result in lodgement of Floseal particles in pulmonary vessels resulting in pulmonary embolism¹³. In this proposed mechanism, the causation of pulmonary embolism is not related to blood coagulation alone and would render traditional anticoagulation ineffective in the prevention of VTE.

Limitation

This case series is limited by its design and small patient numbers. Further investigation is warranted to compare the incidence of pulmonary embolism in patients who receive thrombin-based haemostatic matrix intraoperatively to a control patient group of similar demographics, cancer diagnoses and operative variables.

Conclusion

Although inconclusive due to small number and retrospective study, this series raises the possibility that there may be an association between the use of haemostatic matrix in head and neck oncologic free flap reconstructions and pulmonary embolism. Haemostatic matrix must be used in caution when there is direct contact with large venous endolumens such as the pterygoid plexus and soleus.

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Patient	Age	Gender	Diagnosis	Operation	PE post-op (days)	LOS	CTPA	DVT
1	66	F	T1N0 right buccal mucosa SCC	WLE, segmental anterior mandibulectomy, ND (I-IV), partial glossectomy, tracheostomy, free radial forearm flap	4	27	Right upper and middle lobe segmental arteries	NAD
2	63	M	T2N2b right floor of mouth SCC	Right hemimandibulectomy, WLE tongue, bilateral ND + free fibula flap	6	14	Bilateral segmental and subsegmental pulmonary arteries	NAD
3	74	M	T2N0 right retromolar trigone, posterior alveolar mandible SCC	WLE, Subsigmoid segmental mandibulectomy, ND (I-IV), ALT free flap	3	21	Right upper, middle, lower lobe subsegmental arteries	NAD
4	72	F	T3N1 left posterolateral tongue, floor of mouth SCC	Left hemimandibulectomy, subtotal glossectomy, lip split, free fibular flap	17	34	Right middle lobe segmental pulmonary artery	NAD
5	60	M	Right mandibular ORN	1) Right segmental mandibulectomy, free fibular reconstruction. 2) Pectoralis major reconstruction with SSG. 3) Right free radial forearm flap	30	63	Distal right lower lobe and left lingula pulmonary arteries	NAD

Table 1. Table illustrating demographics and clinical details of five patients who were diagnosed with symptomatic and clinically significant pulmonary embolism post oncologic head and neck free flap reconstructions

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