Management of Persistent Epistaxis Using Floseal Hemostatic Matrix

PROTOCOL IDENTIFYING NUMBER
001

PROTOCOL VERSION DATE
June 8, 2015

GENERAL INFORMATION

Name and title of the investigators and sub-investigators responsible for the trial with address and phone numbers

Dr. David Côté
1E4.07 WMC, 8440 112 Street
University of Alberta Hospital
Edmonton, AB, T6G 2B7
780-407-4490

Dr. Adrian Mendez
1E4.07 WMC, 8440 112 Street
University of Alberta
Edmonton, AB, T6G 2B7
780-407-4490

Alexander Hopkins BSc.
3-007 Li Ka Shing
University of Alberta
Edmonton, AB, T6G 2R3
arhopkin@ualberta.ca
780-407-4490

Study Summary

Title	Management of Persistent Epistaxis using Floseal Hemostatic Matrix
Short Title	Floseal Epistaxis Study
Protocol Number	001
Phase	Phase 4 Clinical Trial
Methodology	Randomized open-label Trial
Study Duration	1 Year
Study Center(s)	Single-Center, University of Alberta
Objectives	We wish to observe the effectiveness of Floseal Hemostatic Matrix in aborting persistent epistaxis with the end of bleeding being our primary outcome. We also wish to include measures of patient comfort and cost analysis of epistaxis treatment.
Number of Subjects	60
Diagnosis and Main Inclusion Criteria	Adult patients presenting for Otolaryngology Head and Neck Surgery consult in the Emergency Department with persistent epistaxis.
Study Product, Dose,	Floseal Hemostatic Matrix, 5mL
Duration of administration	30 Minutes
Reference therapy	Standard nasal packing using gauze by a trained Otolaryngology resident
Statistical Methodology	This study is powered based on a non-inferiority analysis to compare the efficacy of Floseal at achieving hemostasis. We will perform standard chi-square statistical analysis to determine the significance of these outcomes.

Table of Contents

List of Abbreviations

HREB	Health Research Ethics Board
OHNS	Otolaryngology Head and Neck Surgery

1 Background

1.1 Investigational Agent

Floseal Hemostatic Matrix. This agent is a health Canada approved treatment option that is already in use in a number of hospital settings. It is a hemostatic sealant composed of a human thrombin containing fraction and a collagen gel-like fraction. It is applied to the area of active bleeding to achieve rapid hemostasis.

1.2 Preclinical Data

Floseal has been previously shown to achieve hemostasis more effectively than traditional methods in a number of clinical settings. These include cardiac surgery, spinal surgery and topical bleeding. Gel like hemostatic agents have additional advantages such as ease of use, conformity to irregular surfaces and their bio absorbable properties eliminate the need for removal. A prospective clinical trial using 10 patients at the University of Alberta has already been conducted, however it was not a randomized clinical trial and did not look at outcomes in addition to hemostasis. We wish to expand upon this knowledge in the context of epistaxis in this study.

1.3 Risk/Benefits

Potential benefits to participating in this study include: A potentially faster and more effective way to achieve hemostasis and abort bleeding. An increased level of comfort and less pain compared to traditional nasal packing.

Potential risks to participating in this study include: A very small theoretical risk of transmission of human viruses due to the Floseal product containing human thrombin. This treatment is already a standard of care that is currently in use in the University of Alberta Hospital therefor the risks are no greater than what a patient might be exposed to already. Risks might also include discomfort from the placement of the packing or FloSeal in the nasal cavity.

1.4 Dose Rationale

Floseal Hemostatic Matrix comes in a standard size (5mL) and we will be using this dosing to achieve hemostasis.

1.5 Trial Conduct

This study will be conducted in compliance with the protocol approved by the University of Alberta Health Research Ethics Board (HREB), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB except where it may be necessary to eliminate an

immediate hazard to a research subject. In such case, the deviation will be reported to the HREB as soon as possible.

1.6 Population

Adult patients presenting to the Emergency Department at the University of Alberta who have persistent epistaxis and require OHNS consult.

1.7 Literature

1. Cote D, Barber B, et al. Floseal Hemostatic Matrix in Persistent Epistaxis: A Prospective Clinical Trial. *J Oto Surgery*. 2010; 39:3:304-308
2. Oz MC, Cosgrove DM 3rd, Badduke BR, et al. Controlled clinical trial of a novel hemostatic agent in cardiac surgery. *Ann Thorac Surg*. 2000;69:1376-1382.
3. Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. *J Card Surg*. 2003;18:486-493.
4. Renkens KL Jr, Payner TD, Leipzig TJ, et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. *Spine*. 2001;26:1645-1650.
5. Nasso G, Piancone F, Bonifazi R, et al. Prospective, randomized clinical trial of the FloSeal matrix sealant in cardiac surgery. *Ann Thorac Surg*. 2009;88:1520-1526.

2 Trial Objectives

The objective of this study is to observe the effectiveness of Floseal Hemostatic Matrix as a treatment option for persistent epistaxis in patients requiring OHNS consult. We will determine effectiveness based on its ability to abort bleeding as well as outcomes of patient comfort and ease of treatment. Even if Floseal has equal effectiveness in treating nosebleeds as traditional packing, if it is much more comfortable for patients then it may be the favorable treatment.

3 Trial Design

3.1 Primary Study Endpoints/Secondary Endpoints

The primary endpoint of this study will be when hemostasis is achieved and there is no longer any active bleeding from the nasal cavity. Our secondary endpoint will be two days following the intervention when we obtain the telephone questionnaire results from the patients about pain level and comfort of the treatment.

3.2 Study Design/Type

This study will be a prospective randomized, open-label clinical trial.

1. Otolaryngology Service consulted for persistent epistaxis by Emergency department

2. Otolaryngology resident determines whether patient meets inclusion/exclusion criteria for the study

3. Informed Consent is obtained and participants are given a chance to ask questions

4. Participants will be randomized using a sealed envelope system to either experimental or control group

5. Group A receives traditional nasal packing

   Group B receives treatment using FloSeal Hemostatic Matrix

6. Both Groups are followed to observe the primary endpoint of hemostasis (end of bleeding)

7. Hospital care or discharge continues as normal

8. Patients are telephoned or visited as inpatients 48 hours later to complete the comfort questionnaire

3.3 Randomization

This study will be randomized in an allocation concealment fashion with a randomized treatment group already established in an envelope in the treatment room prior to patients being enrolled in the study. The direct care team therefor has no control over the chosen treatment for the patients. Due to the nature of the treatment it is not possible to blind this study to either the direct care team or patient.

3.4 Trial Treatment

Patients in this trial will be receiving Floseal in the nasal cavity by a trained OHNS resident. The amount of Floseal required to stop bleeding and cover the wound site may vary. Floseal is packaged as a 5mL syringe set that requires set up before use. Detailed instructions on the use of Floseal sealant are provided in the Floseal safety monograph (attached in the ethics application) and residents will all have proper training.

3.5 Duration

The duration of treatment for patients in this study will be no longer than the standard practice treatment for their condition. Total time from admission to the Emergency Department and being seen by OHNS consult to achieve hemostasis using either Floseal or standard nasal packing may be variable, but should take no longer than a few hours. There will be an additional telephone survey completed at the patients discretion two days following their involvement in the study.

3.6 Discontinuation

Patients will be undergoing all aspects of the study under the supervision of a physician or research coordinator and will therefor be encouraged to express any concerns they have so they can be addressed as promptly as possible. We will minimize risk by providing the physicians involved with the most training possible to ensure placement of the treatment is done as easily and accurately as it can be. Patients who wish to withdraw from the study will be able to do so at any time and will be informed of this upon obtaining consent for the study.

As this is a minimal risk trial with a product that is already in the use in hospital settings it is very unlikely that we will need to discontinue the entire trial. In the unlikely event that this would occur, we would disclose the reasoning to the HREB and all other necessary regulatory agencies.

3.7 Data Identification

For this clinical trial we will need to have access to patient records to observe our primary endpoint of hemostasis as well as our secondary outcomes of patient comfort and a cost analysis. To obtain informed consent we will need the patients name and signature. For our statistical analysis we will need patient age and gender. To perform the patient comfort survey we will need the participant telephone number and email address.

Surname and First Name

Telephone Number

Email Address

Age at time of data collection

Health Care Number

Hospital Discharge Date

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

Adult patients with persistent epistaxis that present to the Emergency Department at the University of Alberta Hospital and require OHNS consult for their ongoing epistaxis.

4.2 Exclusion Criteria

For this trial we will exclude any patients taking anticoagulant medication or other blood thinners.

4.3 Subject Withdrawal

Patients will be undergoing all aspects of the study under the supervision of a physician or research coordinator and will therefor be encouraged to express any concerns they have so they can be addressed as promptly as possible. We will minimize risk by providing the physicians involved with the most training possible to ensure placement of the treatment is done as easily and accurately as it can be. Patients who wish to withdraw from the study will be able to do so at any time and will be informed of this upon obtaining consent for the study. They will be instructed to speak with any member of the direct care or research team to withdraw him or herself from the study. Patients will not be replaced as this study has a rolling enrollment and we will continue until we acquire the proper number of participants. Data from the withdrawn participants will be discarded, however we will keep the record of the patient themselves and follow-up with them as we would any other patient in the study (if they are willing) to monitor for any adverse events and ensure patient safety.

4.4 Treatment of Subjects

The amount of time from patient admission to the emergency department until they are seen by an OHNS resident may be variable due to extraneous circumstances. Upon consult by OHNS if the patient meets the criteria for the study, informed consent will be obtained by a member of the research team (not the direct care team). They will have an opportunity to ask questions and sign the consent form.

a. Participants will be randomized using a sealed envelope system to either experimental or control group

b. Group A receives traditional nasal packing by a trained OHNS resident (merocel gauze)

Group B receives treatment using 5 mL of Floseal Hemostatic Matrix by a trained OHNS resident

c. Both Groups are followed to observe the primary endpoint of hemostasis (end of bleeding)

d. If hemostasis is not promptly achieved (as determined by the direct care team) than additional measures will be taken to arrest bleeding just as they would in any other non-study situation

e. Hospital care or discharge continues as normal

f. Patients are telephoned or visited as inpatients 48 hours later to complete the comfort questionnaire

We will have extra follow-up with these patients to observe the effects of our treatment on patient comfort and allow for the opportunity of a study debrief. This will occur two

days following their treatment and should last no more than five minutes over the telephone.

4.5 Medication

All other medication required by the patient or medications they are already taking will be continued and will not interfere with the progression of this study.

5 Assessment of Efficacy

5.1 Efficacy Parameters

Efficacy of the Floseal Hemostatic Matrix will be determined by observing whether patients receiving either the Floseal or control treatment require additional measures to abort bleeding. Our primary endpoint is hemostasis, however if hemostasis is not adequately achieved, as determined by the OHNS resident providing direct care, than additional measures will be taken to abort bleeding and this will signify our primary endpoint.

5.2 Method and Timing

The research team will review the data obtained following each patient enrolled in the study to ensure that the protocol is being followed appropriately and that the primary and secondary endpoints are being appropriately recorded.

6 Assessment of Safety

6.1 Safety Parameters

Patient safety throughout this trial will be monitored by both the direct care team and the research team. The direct care team will be able to contact the research team at any time to report and concerns that may arise regarding patient safety. The research team will also periodically (2-3 weeks) check in with the direct care team to ask about any concerns that they might have.

6.2 Method and Timing

Assessing safety will be the responsibility of the direct care team following the enrollment of each patient in the study. Safety concerns will be brought to the attention of the research team immediately if they are to arise. The research team will seek out concerns on a 2-3 week basis with the direct care team. Concerns will be recorded and

kept securely with the rest of the trial data on an encrypted computer in the research office.

6.3 Adverse Event Reporting

Any adverse events occurring throughout the duration of this study will be promptly addressed and brought to the attention of the University of Alberta HREB as well as Health Canada if the situation dictates.

If any unseen safety concerns were to arise the protocol would be stopped and reviewed to determine the source of safety concerns. As this study is only observing one step in the treatment of the patient, their hospital care will be continued as required in all cases.

6.4 Adverse Event Follow-up

The direct care team will report any adverse events to the research team. The research team will follow-up with the patients in person or via telephone for the duration of treatment or until the adverse event has resolved. This study will not interfere with the normal care and treatment of these patients either before or after participation in the study.

7 Statistical Plan

7.1 Statistical Methods

As this study is comparing a single experimental group to a control group we will use a standard statistical analysis to compare both the primary outcome of hemostasis and the secondary outcome results of the pain and comfort questionnaire. This is a non-inferiority study and has been powered as such. We will use a chi-square test to determine significance of any difference between the treatment and control group.

7.2 Subject Population(s) for Analysis

We hope to have 60 patients total enrolled in this study (30 Floseal and 30 control). This sample size was chosen to provide the powering listed below. This level of significance is based on a non-inferiority trial. We chose this trial type because we seek to quantify the secondary benefits for this treatment, which is already in use. All randomized subjects will be included in the statistical analysis based on an intention-to-treat protocol.

7.3 Significance

This is a non-inferiority trial with a power of 0.8, a non-inferiority limit of 5% and a significance level of $P<0.05$.

7.4 Termination Criteria

Termination of this study will occur once we have enrolled the required number of patients or if there are any significant adverse events, which result in a decision by the research team to terminate the study.

7.5 Deviation Reporting

In the case that any changes to the statistical analysis of this trial may arise they will be fully disclosed. Any deviation from the original statistical plan will be amended and justified in the protocol and in the final report.

8 Direct Access to Source Data/Documentation

Throughout the study if direct access data is required for audit or other trial-related monitoring, it can be obtained by written request to Dr. David Cote. This includes access by any regulatory agency such as the University of Alberta HREB.

9 Quality Control and Quality Assurance

Data from the direct care team will be obtained in paper form and be scanned or otherwise transferred to electronic data kept on the research computer. Interim analysis will be done by the research team to ensure that data collection is continuing as per the protocol. The study coordinator (Alexander Hopkins) will review that data obtained following each patient enrolled in the study and ensure that it is being recorded in compliance with this protocol and good clinical practice requirements.

10 Ethical Considerations

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and University of Alberta research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Alberta HREB for formal approval to conduct the study. The decision of the HREB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the HREB. The formal consent of a subject, using the HREB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

For confidentiality purposes all data for this study will be coded and de-identified and kept on an encrypted secured database in the personal office of Dr. David Cote.

12 Supplements

Comfort Questionnaire

Patient Name: _____ Researcher Filling out this form: _____

Method of Contact (circle one): Telephone In Person

Behavioural Rating Scale

( ) No pain

( ) Pain present, but can easily be ignored

( ) Pain present, cannot be ignored, but does not interfere with everyday activities

( ) Pain present, cannot be ignored, interferes with concentration

( ) Pain present, cannot be ignored, interferes with all tasks except taking care of basic needs such as toileting and eating

( ) Pain present, cannot be ignored, rest or bedrest required

Box Scale

If a zero (0) means 'no pain', and a ten (10) means 'pain as bad as it could be', on this scale, what is your level of pain?

Pain during placement:

0 1 2 3 4 5 6 7 8 9 10

Pain during treatment:

0 1 2 3 4 5 6 7 8 9 10

Pain during removal (if applicable):

0 1 2 3 4 5 6 7 8 9 10

Information Letter and Participant Consent Form

Title of Study: *Management of Persistent Epistaxis Using Floseal Hemostatic Matrix*

Research Investigator/Study Coordinator:
Alexander Hopkins BSc.
3-007 Li Ka Shing
University of Alberta
Edmonton, AB, T6G 2R3
arhopkin@ualberta.ca
780-407-4490

Supervisor:
Dr. David Côté
1E4.07 WMC, 8440 112 Street
University of Alberta Hospital
Edmonton, AB, T6G 2B7
780-407-4490

Why am I being asked to take part in this research study?

You are being asked to be in this study because you have a nosebleed that has not stopped even after a first try at treatment in the Emergency Department. There are a number of treatment options for people in your situation and we are interested in studying which treatment has the best result at stopping bleeding quickly and is the most comfortable.

The most standard treatment for severe nosebleeds is a re-packing of the nose using gauze by a trained Ear, Nose and Throat (ENT) specialist; this is what half of the participants in this study will receive. The other half of participants will be treated again by a trained ENT specialist using a less common (but still used) treatment called Floseal Hemostatic Matrix. We hope to have approximately 60 people participating in this study by the end of data collection.

Before you make a decision one of the researchers will go over this form with you. You are encouraged to ask questions if you feel anything needs to be made clearer. You will be given a copy of this form for your records.

What is the reason for doing the study?

Floseal Hemostatic Matrix is a treatment that is already approved by Health Canada, and is currently in use in a number of hospital settings. **In this study we want to know whether *Floseal* is more or less effective than simply packing the nose alone and whether it is more comfortable.**

What will I be asked to do?

The amount of time required for the actual treatment in this study will be no longer than if you were not participating in the study. There will also be a comfort questionnaire that will be completed over the telephone and should take no more than 10 minutes to complete.

The treatment you will receive (either Floseal or traditional gauze packing) will be determined using randomization. Meaning you will have a 50/50 chance for which group you will be placed in. The doctor treating you will have no control over which group you are assigned to. In this study we will need to access your medical records to observe the effectiveness of the treatment and whether additional steps (such as hospital admission) were taken.

Process

- Upon completion of reading this letter you will have the opportunity to ask questions about the study and decide whether you would like to participate or not.
- If you choose to participate you will sign the informed consent form.
- You will receive a random treatment assignment and the physician will perform the assigned treatment (either Floseal or traditional packing).
- Your care will continue as it normally would without participation in this study.
- You will be contacted 48 hours following treatment and asked a few short questions about how you felt with the treatment.

What are the risks and discomforts?

As previously mentioned, Floseal is already an approved treatment for use in Canada. Should the Floseal not work in stopping the nosebleed, you may need to be re-packed and go to the operating theatre for surgical clipping of the nose vessels. There are very few risks associated with the use of Floseal. As some of the components of the Floseal Matrix come from human plasma, there is a very rare theoretical risk of transmitting an infectious agent although this has never previously been reported. Similarly, a component of the matrix is derived from bovine (cow) sources and if you have a history of allergy to cow products please let us know.

It is not possible to know all of the risks that may happen in a study, but we have taken all reasonable safeguards to minimize any known risks to a study participant. If we find out anything new during the course of this research, which may change your willingness to be in the study, we will tell you about these findings.

What are the benefits to me?

Based on what we currently know about both the nose packing and Floseal treatments, it is possible that the Floseal treatment will be more comfortable and less painful than traditional packing. However, you may not get any benefit from being in this research study. We hope that the information from this study may help inform doctors how to best treat other people with severe nosebleeds in the future.

Do I have to take part in the study?

Being in this study is your choice. If you decide to be in the study, you can change your mind and stop being in the study at any time, and it will in no way affect the medical care that you are entitled to.

In the event of opting out of the study your data will be withdrawn and discarded in a confidential manner. If you do withdraw from the study once it has started, we will attempt to follow up to ensure no complications arose a result of the study.

Will my information be kept private?

Any personal information or data we record about you will be kept confidential. No data relating to this study that includes your name will be released outside of the researcher's office or published by the researchers. We will make every legal effort to make sure that your information is kept private.

The investigator or their study staff may need to look at your personal health records throughout the study. Any personal health information that we get from these records will be only what is needed for the study.

By signing this consent form you are saying it is okay for the study team to collect, use and disclose information about you from your personal health records as described above. After the study is done, we will still need to securely store your health data that was collected as part of the study. At the University of Alberta, we keep data stored for a minimum of 5 years after the end of the study.

If you leave the study, we will not collect new health information about you, but we may need to keep the data that we have already collected.

What if I have questions?

If you have any questions about the research now or later, please contact **Alexander Hopkins [780-660-1059]**.

If you have any questions regarding your rights as a research participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has no affiliation with the study.

Conflict of Interest

We have no conflict of interest to declare.

CONSENT

Title of Study: Management of Persistent Epistaxis Using Floseal Hemostatic Matrix
Principal Investigator: Dr. David Côté **Phone Number:** 780-407-4490
Study Coordinator: Alexander Hopkins **Phone Number:** 780-407-4490

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to leave the study at any time, without having to give a reason and without affecting your future medical care or without penalty?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your study records, including personally identifiable health information?	☐	☐

Who explained this study to you? _____

I agree to take part in this study (Circle One): Yes No

Signature of Research Participant _____

(Printed Name) _____

Date:_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT