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Protocol Page

A Randomized Trial Evaluating the Use of Fibrin Tissue Adhesive Following Axillary Node Dissection in Patients with Melanoma
GS01-565

Core Protocol Information

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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective

To determine whether the use of a fibrin sealant applied to axillary soft tissues following node dissection can result in earlier drain removal.

1.2 Secondary Objectives

To determine the postoperative morbidity rate using fibrin sealant following axillary node dissection.

To assess patient-valuation of outcome by performing a cost-benefit analysis using a willingness-to-pay model.

To determine if serum levels, lymphatic fluids level, or cutaneous expression of vascular endothelial growth factor-D (VEGF-D), vascular endothelial growth factor-C (VEGF-C) or their receptor, vascular endothelial growth factor receptor-3 (VEGFR-3) correlates with nodal tumor burden or development of lymphedema in patients with melanoma.

2.0 Background

In 2000, 47,700 men and women were diagnosed with melanoma in the United States.[1] Many of these patients undergo axillary node dissection for staging and/or therapeutic purposes.

The most common short-term complication following axillary node dissection for patients with breast cancer or melanoma is seroma formation which may occur in up to 35% of patients.[2-5] Several techniques have been used in attempts to prevent seroma formation including the use of a suction drain inserted at the time of surgical dissection [6, 7] as well as the insertion of multiple drains[8], high and low suction drains[9] and post-mastectomy shoulder immobilization.[10]

The use of drains in the postoperative period has several disadvantages. First, the drain requires proper management to assure patency. Additionally, there is associated discomfort and limited mobility with the presence of a drain. There is also a theoretical risk of infection with prolonged drainage, as a drain is thought to serve as a portal for bacterial entrance into the deep tissues.[11] A technique that would allow earlier drain removal or potentially eliminate the need for a drain altogether might decrease morbidity and cost while enhancing patient rehabilitation and satisfaction, and allowing earlier commencement of adjuvant therapy.

Fibrin tissue adhesive is the name given to products, originally made from plasma proteins that mimic the last step of the physiological coagulation cascade.[12] These products when applied locally to the site of "injury" are thought to enhance hemostasis, adhesion and provide a matrix for peptides to enhance wound healing. Additionally, fibrin plays a central role in wound healing by inducing chemotaxis of polymorphonuclear granulocytes and promoting the initial inflammatory phase of the healing process.[13]

Preliminary Data
Fibrin tissue adhesives have been commercially available in Europe since 1978 and have been used for numerous procedures in all fields of surgery.[12, 14]

Several randomized trials have demonstrated the utility of fibrin tissue adhesives in a variety of surgical settings. For example, randomized trials have favored fibrin tissue adhesives in the setting of intraoperative control of hepatic bleeding[15] and intraoperative control of bleeding cancellous bone at sternal and iliac crest donor sites.[16]

However, other trials have reported conflicting results with the use of fibrin tissue adhesives. For example, in a trial of 56 patients randomized to fibrin tissue adhesive after distal pancreatectomy, there was a decrease in postoperative fistula formation from 40% to 15.4% ($p = 0.04$)[17] while D'andrea et al. demonstrated no difference in the rate of fistula formation between the control and fibrin tissue adhesive groups in 97 patients undergoing pancreatectomy.[18]

Axillary Node Dissection for Breast Cancer
Fibrin tissue adhesives have previously been shown to be effective in reducing seroma formation in animal models for mastectomy.[19-22] However, there have been conflicting reports of the efficacy of fibrin sealant in reducing seroma formation in humans undergoing axillary dissection.[23-28]

There have been three prospective, randomized trials in humans that have reported a benefit in using fibrin tissue adhesives in the setting of axillary node dissection for breast cancer. The first study, performed at the University of Virginia Health Sciences included 21 patients to evaluate the efficacy of fibrin sealant in decreasing total serous drainage from the axilla.[24] The fibrin sealant was composed of bovine thrombin and autologously donated fibrinogen. Their results demonstrated that the cumulative volume of axillary drain seroma fluid for 3 days was reduced by 268 mL or 57%. The day of axillary drain removal was reduced by 3 days or 43 percent (6.9 ± 1.19 to 3.9 ± 1.70 days in the treatment group).[24] Within the small group studied, this difference was statistically significant.

The second randomized trial was performed in Europe and included 108 patients with breast cancer.[23] The treatment group received 2 ml of fibrin glue applied to the area of axillary dissection following lymphadenectomy. The cumulative volume of axillary drainage for 6 days was reduced by 48% (408 ml vs. 214 ml, $p = 0.001$) and the hospital stay was decreased by 21% in the treatment group. There was no difference in short-term or 6 month morbidity between the treatment and control group.[23]

The third study was a phase II, multi-center, prospective randomized trial which randomized 78 patients to 4 treatment arms.[26] Twenty-one patients in the control group did not receive fibrin sealant while the remaining 57 patients were treated with escalating dose of fibrin sealant

(4, 8 or 16 ml). The authors reported that 4 ml of fibrin sealant is sufficient to produce a 30% reduction in median time to drain removal (14.8 ± 9.6 days vs. 7.9 ± 3.7 days) and a 23% reduction in cumulative drainage over 4 days.[26]

There have also been 3 prospective, randomized trials that have reported that fibrin tissue adhesives are ineffective in reducing the volume of seroma drainage following mastectomy.[25, 27, 28] Uden's study [25] had relaxed criteria for time to drain removal (< 100 cc/ 24 hours) which would make discrimination difficult. Dinsmore's study [27] included only 27 patients and used a fibrin tissue adhesive with a low concentration of fibrinogen. In the trial by Vaxman et al.,[28] a significant difference in the volume of seroma drainage was seen in 40 patients, however, this did not result in a difference in drain duration.

To date, there are no published prospective trials using fibrin tissue adhesive in patients with melanoma. The lack of data in patients with melanoma together with the discrepancies in the published results in patients with breast cancer indicate the need for a properly designed, randomized study. The purpose of this prospective, randomized trial is to perform a study with sufficient statistical power to determine whether fibrin tissue adhesive is truly effective in reducing the time to drain removal following axillary node dissection in patients with melanoma.

Laboratory Correlative Studies

Lymphatic spread represents the most common first site of metastasis in patients with primary cutaneous melanoma and represents a significant clinical problem with respect to both treatment as well as treatment-related complications. While it is known that the lymphatic vasculature transports extravasated fluid, macromolecules, and even cells into the systemic circulation, little is known regarding the molecular mechanisms which regulate lymphatic vessels. Recently, vascular endothelial growth factor VEGF –C and VEGF-D have been shown to stimulate lymphangiogenesis and are regulated through their common receptor, VEGFR-3.[29] Interestingly, recent studies have demonstrated that inhibition of VEGF-C/VEGF-D signaling may inhibit lymphangiogenesis and induce regression of already formed lymphatic vessels, as well as lymphedema-like symptoms in experimental models.[30] Preliminary observations suggest that VEGF-D may be overexpressed in melanoma nodal metastasis. However, the role of these growth factors in human melanoma is currently unknown.

3.0 Background Drug Information

TISSEEL® VH Fibrin Sealant, prepared by Baxter Hyland Immuno, is a two-component fibrin sealant, vapor heated kit that contains the following substances in four separate vials:

1. Sealer protein concentrate (human);
2. Fibrinolysis inhibitor solution (bovine);
3. Thrombin (human);
4. Calcium chloride solution

TISSEEL® contains Fibrinogen (Sealer Protein) as the main active ingredient. Sealer Protein Concentrate is formulated as a sterile, non-pyrogenic, freeze-dried, vapor-heated powder preparation made from pooled human plasma. TISSEEL® also contains Thrombin, Calcium Chloride, and Fibrinolysis Inhibitor (Aprotinin) Thrombin is formulated as a sterile, non-pyrogenic, freeze-dried, vapor-heated powder preparation made from pooled human plasma. Both of these components are made from pooled human plasma. The two-step vapor heat treatment used in their manufacture has been shown to be capable of significant viral reduction.

The fibrinolysis inhibitor solution (Aprotinin) is of bovine origin and is formulated as a sterile, non-pyrogenic solution containing 3,000 kallidinogenase inactivator units of Aprotinin, an inhibitor of proteases including plasmin.

When the two reconstituted components, the Sealer Protein and Thrombin Solutions, are mixed and applied topically they produce a viscous solution that quickly sets into an elastic coagulum.

3.1 Toxicity

TISSEEL® 5ml VH Kit is made from human plasma which may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been markedly reduced using three methods: (1) screening plasma donors for prior exposure to certain viruses, (2) by testing for the presence of certain virus infections (including HIV and hepatitis), and (3) by inactivating and removing certain viruses. Although the potential risk of virus transmission can never be totally eliminated, TISSEEL® VH fibrin sealant has been used in more than 6 million surgical procedures for over 20 years with no confirmed cases of viral transmission to date.[31,32]

As with any other plasma derivatives, anaphylactoid or anaphylactic reactions may occur in rare cases. No adverse events of this type have been reported during the course of clinical trials.

The fibrinolysis inhibitor solution (Aprotinin) TISSEEL® is of bovine origin. In cases of hypersensitivity to bovine proteins or after repeated administration, allergic or anaphylactic reactions can occur on rare occasions. TISSEEL® is contraindicated in individuals who are known to be hypersensitive to bovine protein.

4.0 Patient Eligibility

4.1 Part I - Inclusion Criteria

Patients that consent to participate.

Patients with melanoma who have undergone axillary dissection within the last six months as part of their surgical treatment will be considered for the study.

4.2 Part II - Inclusion Criteria

Patients that consent to participate.

Patients with melanoma that will be undergoing axillary node dissection as part of their operative management.

4.3 Part II - Exclusion Criteria

Patients with known hypersensitivity to bovine proteins.

Patient has undergone prior radiation therapy to the operative site.

Patient is pregnant or lactating.

Patient is steroid dependent within prior 6 months.

Patient has used aspirin or other anti-platelet drug (excluding Celebrex) within seven days of operation.

Patient has pre-existing lymphedema.

Patient has other pre-existing medical conditions with evidence of organ dysfunction as determined by principal investigator.

5.0 Treatment Plan

The protocol will consist of two parts:
Part I: Questionnaire development (pilot study)
Part II: Intervention

Part I: Questionnaire Development:
Prior to the accrual of patients on Part II, a preliminary questionnaire (see Appendix G) was given to a group of 20 patients who were identified as having already been treated at MDACC. Eligible patients had a diagnosis of melanoma and had an axillary nodal dissection performed within the last 6 months. A research nurse interviewed the 20 patients and asked a two-part questionnaire about what it was like to have a surgical drain following an axillary node dissection. The first part of the questionnaire focused on short-term lifestyle changes, averting behaviors, and expenditures related to having a drain. The second part of the questionnaire involved hypothetical scenarios of a 25% reduction in time to drain removal. The patients were asked to think about the hypothetical health benefit of early drain removal to reveal the maximum cost willing to pay in dollars for such a benefit. The questionnaire took approximately 20 minutes to complete.

The results of the preliminary questionnaire were used to create willingness-to-pay questionnaires 1A and 1B (see Appendix H) which will be administered as an option to patients in Part II of the study preoperatively (questionnaire 1A), and about 3-6 weeks postoperatively (questionnaire 1B) by the research nurse either in the clinic or by telephone interview. We will then use this information to quantitate the disutility of having a drain using a willingness-to-pay (WTP) analysis. Cost Benefit Analysis: cost (fibrin sealant, $) - benefit (WTP, $) = net benefit ($). The questionnaires will take approximately 20 minutes to complete.

Part II:
5.1 Preoperative

After consents for operation and study participation are signed, patients will be registered for the trial by the research nurse. Patients will be randomized using a computerized randomization scheme.

Patients will be randomized to two groups:

Group I Treatment Group: Patients will receive fibrin sealant following completion of axillary dissection.

Group II Control Group: No fibrin sealant.

The results of the randomization will remain in a sealed envelope. The surgical team will be blinded until the surgical dissection is completed.

All patients will have a 10 cc specimen of blood collected prior to surgery.

5.2 Intraoperative

Patients will be brought to the operating room within one week of randomization.

All patients will receive prophylactic antibiotic coverage at the time of surgery with Ancef or, if an allergy to cephalosporins exists, the antibiotic of choice of the surgeon.

Patients with melanoma will undergo a standard Level I-III axillary node dissection.

During surgery, a specimen of normal viable skin, full thickness, 5 mm x 3 cm from the non-margin portion or the edge of incision will be obtained. This will not impact the closure.

At the completion of the procedure, once bleeding has been controlled in the surgical site, the exposed surgical surfaces will be blotted dry. The surgeon will then be informed of the patient's randomization status.

If the patient is randomized to Group I (Treatment Group) the circulating nurse will proceed with the preparation of the TISSEEL® (Thrombin component diluted 1:100) as described in Appendix I. The product will then be applied as a thin, uniform coating over the exposed soft tissue of the chest wall and axilla.

Patients in both treatment groups will have a 19-French Blake closed suction drain inserted into the axilla and secured with a nylon suture. The wound will then be closed allowing the fibrin sealant to seal the apposed tissues.

5.3 Postoperative

All patients will be given identical postoperative instructions:

- Minimize activity of the involved extremity (no exercises, no abduction beyond 90)
- No lifting of objects weighing more than 10 pounds
- May shower after 48 hours

Serous drainage will be measured daily by the patient/family/home health agency and recorded on the provided data sheet. The axillary drain will be removed once the cumulative serous drainage volume ≤ 30 ml / 24 hours for 2 days or maximum of 21 days has elapsed since surgery.

The first post-op day, all patients will have a 10 cc specimen of blood obtained and the contents of the drain will be collected.

5.4 Laboratory Correlates

The laboratory studies will be performed under the direction of Jeffrey Gershenwald, M.D. (Departments of Surgical Oncology and Cancer Biology). Specified blood samples pre- and postoperatively will be obtained by qualified personnel and processed for serum. VEGF-D and VEGF-C serum levels will be measured by enzyme-linked immunosorbent assay (ELISA). Lymph fluid will also be analyzed for these growth factors using ELISA kits as well. Skin specimens will be analyzed for VEGF-C, VEGF-D, VEGFR-3 expression by immunohistochemical staining.

6.0 Pretreatment Evaluation

6.1 A complete history including age and smoking history will be obtained within 2 weeks of randomization. Past medical history will record any history of connective tissue disorders, diabetes or medication usage.

6.2 Physical examination including height and weight will be recorded within 2 weeks of surgery.

6.3 Pregnancy test for women of child-bearing potential if indicated.

7.0 Follow-Up Data Collection

7.1 Wound Surveillance

Inpatients – For patients who are admitted to the hospital, the wound will be monitored by the surgeon for evidence of wound complications (bleeding, skin necrosis, hematoma, etc.) in the first 24 hours after surgery and daily until discharge.

Outpatients – The patients will be instructed in catheter care according to nursing protocol. The amount of drainage must be recorded for each day (24 hour period) including the day the drain is removed.

Drain Removal – Drains will be removed once the cumulative serous drainage drops to ≤ 30 ml / 24 hours for 2 consecutive days or a maximum of 21 days for axillary node dissection. Removal of the drain may be performed at an outside institution by a local physician once the criteria have been reached. Patients will be instructed to contact the protocol research nurse to verify that drain removal criteria have been met prior to removal.

Follow-Up - Follow-up wound examination will be performed by the local primary physician or in the MDACC Melanoma Clinic between 1-4 weeks post-op and at approximately 6 weeks following surgery. A 10 cc specimen of blood will be obtained 2-3 weeks and 3-6 months after surgery. The contents of the drain will be collected from patients during the first day after surgery, during the first return follow-up visit to M.D. Anderson Cancer Center, and during drain removal (unless these latter 2 dates are the same). A voluntary 4 mm punch biopsy will be performed using local anesthesia on patients within the first 6 months of follow-up.

7.2 Secondary Objectives

Postoperative complications will be recorded by the protocol nurse and verified by the attending surgeon. Specific clinical information including occurrence of fever with symptoms or signs of infection, will be obtained by telephone if the patient is unavailable for a clinic visit.

Wound infection will be defined by the following criteria:

Culture positive seroma aspirate with clinical evidence of infection (i.e. fever, cellulitis)

Cellulitis as judged by a clinician requiring antibiotics or more aggressive wound management and responding appropriately to treatment.

Clinically significant postoperative seroma formation will be ascertained at a 6 week follow-up visit or telephone contact. Seroma will be defined as a fluid collection in the axilla that is symptomatic and requires treatment with a drainage procedure (i.e. aspiration).

8.0 Data Collection Tools

Part I - Pilot questionnaire (Appendix G) will be used.

Part II - Data sheets (Appendices A and B) will be used to capture patient information including:

Preoperative Assessment:
Risk Factors: smoking, obesity (BMI > 30)
Prior therapy
Date of randomization

Intraoperative Assessment:

Surgeon
Date of procedure
Perioperative antibiotics
Procedure performed
Indication (i.e., after positive sentinel node biopsy or for clinically evident disease)
Estimated blood loss
Length of operation

Post-Operative Assessment:
Date of drain removal
Wound complications: infection, seroma, wound necrosis or dehiscence, clogged drain, hematoma, etc.
Final pathologic assessment: diagnosis, number of nodes examined, number of tumor involved nodes
Tumor stage

Patients will be instructed in catheter care according to nursing protocol and given instructions on completing the drain output forms. The amount of drainage will be recorded for each day (24 hour period) including the day the drain is removed.

Part II - Willingness-to-pay preoperative questionnaire 1A and willingness-to-pay postoperative questionnaire 1B (Appendix H) will be used.

9.0 Statistical Considerations

This is a single-institution, randomized, phase III trial of the fibrin tissue adhesive (TISSEEL®) versus no fibrin tissue adhesive (control) in patients with melanoma undergoing nodal dissection of the axilla. The primary outcome, is time-to-drain removal (T). The null median for the group based on historical experience without fibrin glue is 14 days (Table 1) with an accrual rate of 7 patients per month. A group-sequential design with up to two tests using O'Brien-Fleming early stopping boundaries for both superiority and futility will be used, with overall type I error probability .01 and power .95 will be used. The goal will be to detect a 4 day drop in mean time-to-drain removal. A maximum of 95 patients will be accrued to obtain a sample size of 90 assuming a 5% rate of patients who are inevaluable. Based on a two-sample Z-score test statistic, within in each subgroup the interim test cutoffs will be +/- 3.64 to reject the null hypothesis of no difference and +/- .632 to stop for futility, with a final test cutoff of +/- 2.57 to reject the null. The anticipated study duration will be roughly 12 months.

Table 1.

Subgroup	Disease	Type of Surgery	Accrual Rate (patients/month)	Historical Median # Days to Drain Removal
1	Melanoma	Axillary node dissection	7	14

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