กาวไฟบรินช่วยลดระยะเวลาการใส่ท่อระบายน้ำเหลือง หลังการผ่าตัดเต้านมในผู้ป่วยมะเร็งเต้านม

นายแพทย์ปิยะ เตียวประเสริฐ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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FIBRIN SEALANT REDUCES THE TIME OF DRAIN REMOVAL IN POSTOPERATIVE MODIFIED RADICAL MASTECTOMY IN BREAST CANCER PATIENTS

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ปิยะ เตียวประเสริฐ: กาวไฟบรินช่วยลดระยะเวลาการใส่ท่อระบายน้ำเหลืองหลังการผ่าตัดเต้านมในผู้ป่วยมะเร็งเต้านม (Fibrin sealant reduces the time of drain removal in post operative modified radical mastectomy in breast cancer patients). อ.ที่ปรึกษา : ศ.นพ. จิตร สิทธิอมร, อ.ที่ปรึกษาร่วม :รศ.นพ. ประดิษฐ์ สมประกิจ และนางสาว วีนัส อุดมประเสริฐกุล ; 67 หน้า. ISBN 974-333-559-5

วัตถุประสงค์ : เพื่อเปรียบเทียบระยะเวลาการถอดท่อระบายน้ำเหลืองหลังการผ่าตัด Modified radical mastectomyในผู้ป่วยมะเร็งเต้านมระยะแรก ระหว่าง การใช้ กาวไฟบรินกับยาหลอก

รูปแบบการทดลอง : การทดลองทางคลินิกแบบสุ่มทดลอง

สถานที่ทำวิจัย : โรงพยาบาลพระมงกุฎเกล้า

ผู้ป่วย : ผู้ป่วยหญิงที่ได้รับการวินิจฉัยโรคมะเร็งเต้านมระยะแรก จำนวน 64 ราย ผู้ป่วยกลุ่มที่ 1 ถูกสุ่มให้ได้รับ Fibrin sealant จำนวน 30 ราย อีกกลุ่มหนึ่งได้รับยาหลอกจำนวน 34 ราย

การรักษา : หลังจากผู้ป่วยทั้ง 2 กลุ่ม ได้รับการผ่าตัด modified radical mastectomy ก่อนการเย็บปิดผิวหนัง ในกลุ่มทดลองได้รับ กาวไฟบรินขนาด 250 IU (2 มล.) สำหรับกลุ่มควบคุมได้รับ normal saline ปริมาณเท่ากันฉีดพ่นใต้ผิวหนังบริเวณรักแร้และฐานเต้านมเช่นเดียวกัน หลังจากนั้นได้เก็บข้อมูลระยะเวลาที่ใส่ท่อระบาย,ระยะเวลาการอยู่โรงพยาบาล, อัตราการเกิดการสะสมของน้ำเหลืองภายหลังการถอดท่อระบาย และผลแทรกซ้อนที่เกิดขึ้น

ผลการรักษา : ในกลุ่มที่ได้รับ กาวไฟบรินสามารถถอดท่อระบายน้ำเหลืองออกได้ ใช้เวลาโดยเฉลี่ย 8 วัน ในขณะที่กลุ่มควบคุมใช้เวลาโดยเฉลี่ย 9 วัน อย่างไรก็ดี ไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในระหว่าง 2 กลุ่ม นอกจากนั้น ระยะเวลาการอยู่โรงพยาบาลในกลุ่มทดลองจะสั้นกว่ากลุ่มควบคุม 1 วัน, อัตราการเกิดการสะสมของน้ำเหลืองภายหลังการถอดท่อระบายเป็น 33.33% ในกลุ่ม กาวไฟบรินและ 23.5% ในกลุ่มควบคุม และไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุปการทดลอง : การใช้ กาวไฟบรินฉีดพ่นในระหว่างการผ่าตัด modified radical mastectomy ในผู้ป่วยมะเร็งเต้านมนั้น ไม่สามารถช่วยลดระยะเวลาการใส่ท่อระบายน้ำเหลืองภายหลังการผ่าตัดลงได้ อย่างมีนัยสำคัญทางสถิติ ซึ่งผลจากการศึกษาครั้งนี้อาจจะเกิดจาก ปริมาณของ กาวไฟบริน บริเวณที่ทำการฉีดพ่น ตลอดจนอุปกรณ์ที่ใช้ในการฉีดพ่น การศึกษาในตัวแปรเหล่านี้อาจนำมาซึ่งประสิทธิภาพที่ดีขึ้นของ กาวไฟบริน

ภาควิชา.....การพัฒนาสุขภาพ.....

สาขาวิชา.....การพัฒนาสุขภาพ...

ปีการศึกษา...2542.....

ลายมือชื่อนิสิต.....

ลายมือชื่ออาจารย์ที่ปรึกษา.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

: 4175378930 MAJOR HEALTH DEVELOPMENT
KEY WORD: FIBRIN SEALANT/TIME/DRAIN/MODIFIED RADICAL MASTECTOMY/BREAST CANCER
PIYA TEAWPRASERT, M.D.: FIBRIN SEALANT REDUCES THE TIME OF DRAIN REMOVAL IN POST OPERATIVE MODIFIED RADICAL MASTECTOMY IN BREAST CANCER PATIENTS. THESIS ADVISOR PROF. CHITR SITTHI-AMORN, M.D., Ph.D., THESIS COADVISOR: ASSOC.PROF. PRADIT SOMPRAKIT, M.D., M.Sc., AND Ms. VENUS UDOMPRASERTGUL, M.Sc., 67 pp. ISBN 974-333-559-5

Objective : To compare the time of drain removal in the patients with early stage of breast cancer treated by modified radical mastectomy between the use of fibrin sealant and placebo.

Design : A randomized placebo controlled clinical study.

Setting : Phramongkutklao Hospital

Patients : 64 patients diagnosed of stage I or II of breast cancer with fulfillment of criteria were enrolled in the study. The patients were randomly divided into fibrin sealant treated group and control group. The fibrin sealant treated group consisted of 30 patients while the control groups consisted of 34 patients.

Intervention : Both groups were treated with modified radical mastectomy. Before closing the incision, in the treated group, 2 ml of 250-IU fibrin sealant were applied over the operative area and in the control group, 2 ml of normal saline were applied. The time of drain removal, length of hospitalization, post-catherter removal collection and other complications were measured.

Results : It took approximately 8 days for fibrin sealant group and 9 days for control group before the drain could be removed. Although fibrin sealant could reduce the period of drain insertion, there is no significant difference between this main measurement of clinical outcome. The patients in the fibrin sealant treated group stayed in the hospital for 9 days which is approximately a day shorter than that of the patients in the control group, however, there is no significant difference. The collection of the fluid under skin flap was recorded on the first day after removing the drain and also at 4 weeks after the operation. Without significant difference, the fluid collection was detected in 33.33% of the patients in fibrin sealant treated group and 23.5% in the control group. No severe side effect of the fibrin sealant was detected.

Conclusions : The result of using fibrin sealant in modified radical mastectomy showed no significant difference to the placebo in terms of the time of drain removal. The effectiveness might be a result of the amount of fibrin sealant, area of application and the application devices. Further studies to determine the importance of these factors should be done to provide proper usage of this preparation before routine clinical usage will be recommended.

ภาควิชา...การพัฒนาสุขภาพ.....
สาขาวิชา.....การพัฒนาสุขภาพ...
ปีการศึกษา...2542.....

ลายมือชื่อนิสิต.....
ลายมือชื่ออาจารย์ที่ปรึกษา.....
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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CHAPTER 1

INTRODUCTION

Carcinoma of the breast is the most common site-specific cancer in women and also the leading cause of cancer mortality in the woman between 40 to 44 years of age. Breast cancer accounts for 32 percent of all female cancers and is responsible for 19 percent of the cancer-related deaths in woman[1]. Breast cancer is unusual prior to the age of 30 years, but its frequency increases with each decade thereafter. Most patients are between age of 40 to 70 years. Over 98 percent of all cancers of the breast are carcinomas that arise from the epithelium of mammary duct.

In the past three decades, there is a significant progress in multimodality therapy for the treatment of breast cancer. The integration of these modalities is to enhance survival and to employ conservation surgical principles. The surgical treatment of breast cancer concerns the treatment of potentially curable cancer that is confined to the breast and regional lymph nodes. For early stages of breast cancer, surgical removal provides a reasonable chance for cure. The procedure of choice of

early breast cancer is either modified radical mastectomy or conservative breast surgery.

Modified Radical Mastectomy (MRM) refers to a procedure combining a total mastectomy and removal of axillary lymph nodes in continuity with the mastectomy specimen. This is currently the most widely used procedure to treat operable breast cancer and is the alternative to breast sparing procedure. Modified Radical Mastectomy leaves the pectoralis muscle intact, providing a soft tissue covering over the chest wall and a normal appearing junction of the shoulder with the anterior chest wall and avoiding the hollow defect inferior to the clavicle that accompanies the removal of the pectoralis muscle. The patient will be left with intact musculature around the shoulder and a situation well suited to prosthetic reconstruction.

Modified Radical Mastectomy require axillary lymph node dissection. The axillary lymph node dissection is performed for three objectives, which are to control of tumor growth at this site, to detect of node metastasis and to determine total number of nodes that contain metastases. Dissection of the clinically uninvolved axilla does not contribute to the cure of breast cancer.

A complete axillary node dissection provides excellent protection from recurrence at this site. Less than 1.4 percent of patients have recurrence in the axilla after this operation. No further local treatment to the axilla with irradiation is warranted, as it lead to increase in the risk of lymphedema of the arm without providing appreciable benefit. A complete dissection (levels I to III) provides optimal information about the presence and extent of axillary nodal involvement and provides better protection against axillary recurrence in the presence of multiple nodal involvement (more than three involved nodes) than does lesser dissection (levels I to II).

The extent of axillary dissection is necessary to reliably detect nodal metastases if they are present. The dissection has been the subject of multiple studies and is a matter of controversy. Accuracy in this respect is important since the presence of nodal metastasis is the primary indication for systemic adjuvant hormonal therapy or chemotherapy. It is obvious that axillary node biopsy is unreliable, with a false-negative rate that approaches 60 per cent. There is also considerable variation in the reliability of a level I dissection; the accuracy is reported from 71 to 98 percent. A level II dissection, however, is generally agreed to have a high accuracy (90 to 99 per cent) and is the minimum extent of dissection for early invasive carcinomas.

The absolute numbers of involved nodes are directly correlated with prognosis independent of the total number of node removed. The most accurate prognostic information is provided, therefore, by complete axillary node dissection.

Because the irradiation of the axilla with clinically negative findings is as effective as the dissection of the axilla in preventing tumor recurrence at this site, it may be chosen as a reasonable alternative if the information obtained from a dissection is not useful for the patient management and not necessary for prognosis.

Anesthesia of the skin of the axilla and the lateral scapular area is to be expected and extends down the inner side of the upper arm if the intercostal brachial nerve is not preserved. This effect often results in paresthesias and variable degrees of discomfort described as sensations of tightness, swelling, and tingling. Lymphedema of the upper extremity is an immediate or ultimate sequel of axillary dissection in 6 to 8 percent of cases. Although it is usually mild, it can become unsought and functional handicap in some cases. Both trauma to and infection of the arm can invite lymphedema. Irradiation of the dissected axilla or the supraclavicular area also increases its frequency.

Complications after axillary lymph node dissection include seroma formation [2-6], infection[5,7-9], hematoma [4], wound dehiscence and necrosis of the skin flap with 5-53%, 8-12%, 3%, 5% of incidence,respectively.[4] The most common of these complications is seroma formation. After dissection of lymph nodes in axilla, closed-suction catheter drains are important to evacuate blood and serum and to keep the tissues in apposition, minimizing the risk of seroma formation. Two large catheters are inserted percutaneously for drainage. They are usually introduced through separate stab wounds made in the lower flap posteriorly. One catheter is directed up to the axilla and may be anchored to serratus muscle. The other catheter is secured anterior to pectoralis major muscle for drainage from under the skin flaps. Although there are no conclusive data about the best time to remove these devices, the incidence of seroma formation increase if they are removed too early. On the other hand the incidence of wound infection increase if they are remain for too long, especially more than 10 days. Based on empirical evidence, the catheters probably should be removed when the drainage is less than 40 ml per 24 hours, or 8 days after surgery[1].

These devices cause uncomfortable felling for the patients, inducing pain and limiting arm movement. The present of axillary drains requires proper management by nurse and patients to assure effectiveness. In addition, there is a risk of infection, as it

serves as a portal for bacterial entrance into the deep tissue. Most surgeons attempt to remove these devices as early as possible.

Any methods that could reduce the time of drain removal would cut off these undesirable problems. The purpose of this study is to compare whether fibrin sealant application after modified radical mastectomy of early breast cancer can decrease the time of drain removal when compared to placebo.

CHAPTER 2

LITERATURE REVIEWS

Breast cancer is one of the most common malignancy found in Thai women. Early stages (stage I and II) are defined as stage in which the tumor are confined within the breast and the axillary area. The principle treatment of the early stage of breast cancer is surgery. Modified radical mastectomy, the preferable procedure, requires axillary lymph node dissection. The most common post-operative complication is the seroma formation. The seroma is a collection of serous fluid other than pus or blood. Like hematomas, it provides an excellent culture medium for bacteria and this could lead to septic complications. In general, a small seroma is a result of liquefaction of necrotic fat while large seroma is usually associated with the operation that involve elevation of skin flaps and dissection of numerous lymphatic vessels. This seroma formation can be prevented by inserting closed suction drains beneath the flaps. Closed suction drains are firm, multiholed catheters made of polyvinyl chloride or silicone. The silicone material is softer, less irritating to the tissues and less likely to cause infection. These drains are particularly effective under large skin flaps, such as those encountered after radical neck or breast dissections. Closed suction drainage has lower incidence of infection secondarily caused by contamination

of the drain itself comparing to other drainage system and is mandatory in the presence of foreign body. However using closed suction drainage frequently cause a problems such as pain, limitation of arm movement and requirement of special care. Leaving these drains more than 10 days will cause the infections. Hence the time of drain removal is considered to be crucial which has to be balanced with its usefulness. Many studies tried to find the suitable method to reduce the seroma formation in order to decrease the period of drain insertion.

In 1990, Petrek, et al[12] evaluated the influence of early and delayed initiation of shoulder mobilization on postoperative drainage. The study were conducted by the enrollment of fifty-seven women with clinical stage I or II breast cancer. They were randomized to have either early (postoperative day 2) or delayed (postoperative day 5) shoulder motion. It was found that early or delayed time of exercise initiation had no effect on total amount or duration of drainage, either as an inpatient or outpatient. The two factors predicting greater drainage were large numbers of positive lymph nodes and no previous surgical biopsy (as in one-step procedure).

In 1991 Hahl et al[13] study on a contact Nd-YAG laser in mastectomy and axillary evacuation. Patients were allocated into three groups as group A for conventional operation, group B for contact Nd-YAG laser operation and group C for

conventional mastectomy with laser evacuation of the axillary lymph nodes. Contact Nd-YAG laser showed the significant reduction of peri-operative bleeding ($p < 0.01$) but post-operative wound seromas detected considering high (50% of the cases), especially in the patients underwent radical axillary lymph node dissection. No other complication was found.

In 1992 Petrek et al[14] postulated that multiple drains (instead of a single drain) might decrease postoperative fluid accumulation by their greater proximity to the points of leakage. 65 women with clinical stage I or II carcinoma of the breast were randomly grouped to have either single or multiple drains. They were also stratified for axillary dissection and modified radical mastectomy. For axillary dissection, randomization to multiple drains and single drain groups meant placement of four catheters in the axilla and one catheter in the axilla, respectively. For modified radical mastectomy, the patients who were randomized to multiple drain group, were received four catheters in the axilla and one catheter under the inferior flap. While the patients who were randomized to single drain group, had one catheter in the axilla and one catheter under the inferior flap. From this study, it has been concluded that single versus multiple drains had no clinically significant effect on the amount or duration of drainage. They also recommended the use of a single drain in the axilla after lymphadenectomy.

In 1997, the influence of negative pressure on fluid production and complication rates after axillary dissection for breast cancer was studied by Bonnema et al[15] in a prospective randomized trial. Patients were randomized for either a high or a low vacuum drainage system. However, no statistically significant differences were found between the low vacuum group (n = 68) and the high vacuum group (n = 73) in volume (728 ml versus 780 ml) and duration (9.5 days versus 10 days) of seroma production. The drainage volume of the separately drained breast wound after mastectomy and lumpectomy was larger for the high vacuum system (55 ml versus 100 ml, P = 0.02).

The use of fibrin glue in the surgery of breast carcinoma was firstly introduced by Gioffre Florio et al[16] in 1993. Twenty-four patients operated for breast carcinoma with associated axillary node dissection were randomly assigned to two protocols. In the first group fibrin glue was applied intraoperatively while in the second group no complementary treatment was accomplished. A significant reduction of postoperative axillary secretion in the group treated by fibrin glue was observed.

In contrast, Vaxman and Kolbe[17] reported that fibrin glue did not reduce lymphorrhoea after axillary lymph node dissection. Twenty patients underwent

vaporization of fibrin glue (Tissucol®, 5 ml of 500 IU thrombin) only in the area of axillary dissection was compared with control group. The average volume of lymphorrhea in the lymph node dissection area was greater after use of fibrin glue (410.4 ml) than in controls (275.5 ml, p = 0.016). Drainage duration as well as duration of hospital stay were similar. In additioning to this report, Medl et al[18] also used the same preparation but more patients were enrolled. No significant effect on the total amount of lymph secretion was observed. They also concluded that the expected occlusion of the wound cavity by the application of fibrin glue after axillary lymphadenectomy did not lead to any advantage when compared with the control group.

Other preparation, bovine thrombin (20,000 units) was used in the study conducted by Burak et al[11]. Forty-nine patients were assigned to the treatment group and 52 to the control group. Significant risk factors for seroma formation included increased age, patient weight, initial 72-hour wound drainage, and low axillary dissection (LAD). They concluded that no statistically significant differences were observed between thrombin glue and control groups with respect to time to drain removal, and the incidence of other wound complications. With this rather disappointing result, this preparation has not been studied further.

In 1997 Moore et al[10] reported that fibrin sealant reduced serous drainage 57% of cumulative drainage at day 3 and allowed for earlier drain removal after axillary dissection. They concluded that local application of fibrin sealant significantly reduced the total drainage measured in patients undergoing MRM. Mean time to drain removal was 3.9±1.7 days in fibrin sealant group and 6.9±1.19 days in placebo group[10]. Moore mentioned the causes of negative results of fibrin glue in several studies[10, 15-17] might be because of suffer from a small volume of fibrin sealant applied, a limited number of enrolled patients or a prolonged period of time between sealant application and wound closure. He also reported a number of reasons of his positive findings. Firstly, adequate volumes to seal the axillary potential space were used and a large enough population of patients was enrolled to prove significant difference. Secondly, the method of fibrin sealant application, using specific spray device with immediate closure of the wound by a previous placed running suture and rapid a pressure application, enhanced adhesion of the skin flaps to underlying tissue. Finally, the concentration of fibrinogen and thrombin used may have enhanced sealant strength while at the same time maximized the speed of sealant formation.[10]

Recently, a prospective randomized trial was carried out to evaluate the efficacy of fibrin glue by Gilly et al[19] (1997). One hundred and eight breast cancer patients were randomized into two groups: group 1 (n = 58) without fibrin glue and

group 2 (n = 50) with 2 ml of fibrin glue applied to the axillary dissection area at the end of the lymphadenectomy procedure. Mean daily postoperative drainage and cumulative drainage volume of 6 days after the operation was significantly greater in the control group. The mean postoperative hospital stay was 10.1 days and 8.0 days in the control and treated groups, respectively (p = 0.006). One delayed seroma was observed in each group. Fibrin sealant seems to reduce daily postoperative drainage and hospital stay, but might not affect delayed seroma formation after axillary lymphadenectomy for breast cancer.

Fibrin sealant [10,11] or fibrin glue is a biologic adhesive that involves in the normal coagulation process, consisting of fibrinogen, fibronectin, thrombin, aprotinin, and calcium chloride. Fibrin sealant works as an adhesive by emulating the exudative phase of wound healing. Animal and clinical studies have demonstrated its efficacy in stabilizing anastomoses of the esophagogastric system, small intestine, and nerves. It is also effective in obtaining hemostasis at skin graft donor sites. Fixation of skin grafts with excellent take and without requiring any sutures or pressure dressing is achieved. Significantly increased stress, energy absorption, and elasticity values resulted from the use of a fibrin glue with a fibrinogen concentration of nearly 39 gram. per liter and a thrombin concentration of 200 to 600 units per ml. without adding factor XIII. Fibrin glue administered to tissue flaps of a mastectomy lowers the incidence of postoperative

seromas. Sealing of pancreatic injuries, resections, and anastomoses with fibrin glue may help to prevent the formation of fistula after pancreatic operations. Tissue adhesives may use the activity of growth factors to enhance healing in compromised wounds. The advantages of fibrin glue are not adequately recognized by many surgeons.

In this study, fibrin sealant is a fraction of human plasma and separated by plasma fractionation section of the National Blood Center, the Thai Red Cross Society. This fibrin glue is consisted of solution 1and 2 as following:

solution 1 contains 250 IU human thrombin and 2 mg of gentamycin in 1 ml of 40 mM calcium chloride solution and

solution 2 contains fibrinogen 10-12 mg and tranexamic acid 12.5 mg per 1 ml.

Fibrinogen has been quarantined from freeze dried cryoprecipitin and then heat treated at 60°C for 72 hr. Human thrombin passes two discrete virus elimination steps, solvent detergent techinque and nanofiltration.The accepted conditions for using of fibrin sealant are local hemostasis, suture support, tissue adhesion, wound care and sealing of body cavities. In addition, using fibrin sealant becomes more practical in plastic surgery, dental and oral surgery, nerve and microvascular graft. The only contraindication of fiber sealant is arterial and severe venous bleeding.

Fibrin sealant is for topical use only. The dosage depends on the extent of the surface to be covered, the volume of the defect to be filled, type and organ applied. The side effects of fibrin sealant [20-22] are those found in the transfusion of the compartment of blood. Allergic reactions of any constituents of human thrombin may occur. It has a lower risk of transfusion-transmitted diseases than other blood components is due to using quarantine cryoprecipitin as the source of fibrinogen. There are no other known side effects and adverse events for the topical use have been reported.

Application of fibrin sealant are as followed:

1.Thaw both solution at room temperature (20-25° C).

2.Draw up the solution 1 to first syringe and solution 2 to second syringe.

3.Put both syringes on the Sterile Spray Delivery Set.

4.Fix both syringes with syringe bridge and holder.

5.Connect air cannula to the pump throught 0.2 um filter (for major surgery with spray)

Fibrin sealant should be stored frozen below -20°C. The preparation may not be used beyond date of expiry given on the pack and container. After being thawed,

both solutions are stable up to 6 hours at room temperature (20 – 25°C). These preparations are for single use only.

CHAPTER 3

RESEARCH QUESTIONS AND OBJECTIVES

RESEARCH QUESTIONS

Primary research question

In postoperative modified radical mastectomy breast cancer patient, does fibrin sealant produce at least a 25% reduction in time of drain removal compared to placebo?

Secondary research questions

1. In postoperative modified radical mastectomy breast cancer patient, is there any difference in length of hospitalization between using fibrin sealant compared to placebo?
2. In postoperative modified radical mastectomy breast cancer patient, is there any difference in post catheter removal collection between using fibrin sealant compared to placebo?

RESEARCH OBJECTIVES

1. To compare the time of drain removal between using fibrin sealant group and placebo group

2. To compare length of hospitalization between using fibrin sealant group and placebo group

3. To compare the post catheter removal collection rate between using fibrin sealant group and placebo group

HYPOTHESIS

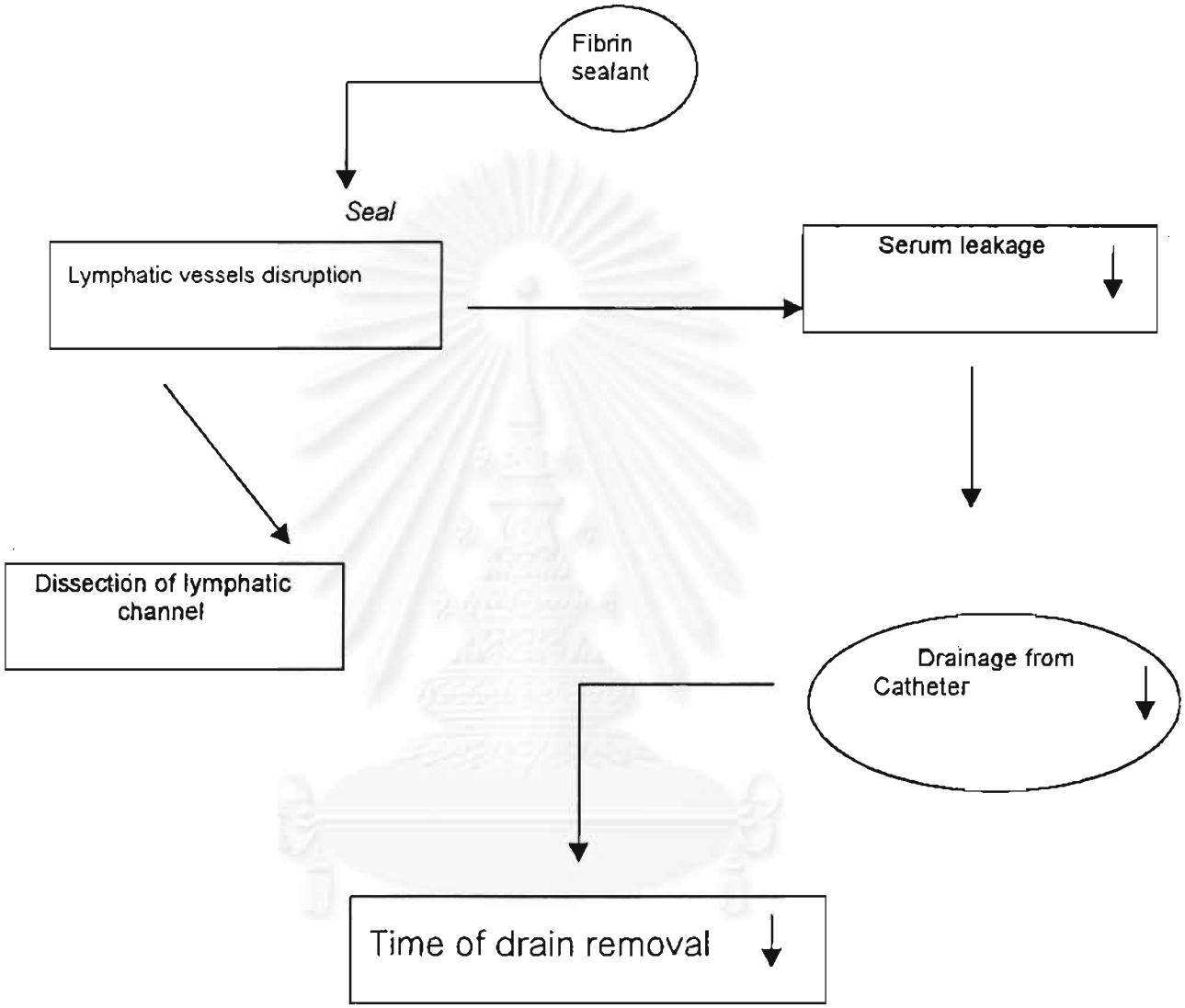
Null hypothesis

The time of drain removal in postoperative modified radical mastectomy breast cancer patients who using fibrin sealant group and placebo group are equal.

Alternative hypothesis

The time of drain removal in postoperative modified radical mastectomy breast cancer patients who using fibrin sealant group and placebo group are not equal.

CONCEPTUAL FRAMEWORK



KEY WORDS

Fibrin sealant, Time, Drain, Modified radical mastectomy, Breast Cancer

CHAPTER 4

RESEARCH METHODOLOGY

RESEARCH DESIGN

Double-blinded randomized controlled trial were conducted. The patients and the doctors, who evaluated the patients, were blinded to reduce the bias.

RESEARCH METHODOLOGY

Population and Sample

The target population was the Thai female patients who were diagnosed as having early breast cancer and underwent modified radical mastectomy.

Sample group

Female early breast cancer patients who were underwent modified radical mastectomy at Phramongkutklao Hospital. The eligibility criteria were

Inclusion criteria

1.Patients who are diagnosed as having breast cancer and underwent modified radical mastectomy

2.Patients who are admitted at Phramongkutklao Hospital.

3. Patients who give the informed consent for the study

Exclusion criteria

1. Use of chemotherapeutic, immunosuppressive agents or radiation

2. Pregnant and lactation

3. Patients with major underlying disease such as diabetes, and malnutrition.

4. Patients with known of hypersensitivity to fibrin sealant

SAMPLE SIZE ESTIMATION

Sample size estimation was calculated by the formula for comparison of means (the time of drain removal – day) between two different and independent group.

$$N / \text{group} = \frac{2\left(Z\alpha+Z\beta\right)^2 \sigma^2}{\left(X_1-X_2\right)^2}$$

$Z\alpha$= 1.96 [Type I error rate 5 %, 2-tailed] $Z\beta$= 1.28 [Type II error 10 %]

$\sigma^2 = [(n_1-1)S_1^2 + (n_2-1)S_2^2] / n_1+n_2-2 = [(21-1)1.7^2 + (21-1)1.19^2] / 40$

data from fibrin sealant study [10,19]

X_1 = mean of the time of drain removal in placebo group (days)

data from Phramongkutklao Hospital

X_2 = mean of the time of drain removal in fibrin sealant group (days)

Expected value of significant

$$N / group = \frac{2[1.96+1.28]^2 (2.15)^2}{(8-6)^2}$$

N/ group = 24.25 ~ 25

The time of drain removal was the main outcome. The t-test was used under assumption that the data observed completely from start to end. If the data could not be observed completely such as lost follow-up, withdrawal, deaths from causes other than the one under study, the survival analysis and Logrank test would be considered and the sample size estimation must be reevaluated.

RANDOMIZATION

1. Patients who were diagnosed as having breast cancer and underwent modified radical mastectomy

2.eligible criteria

3. Simple randomization procedure was performed by using random number table.

INTERVENTION

Definition

Fibrin sealant

Fibrin sealant or fibrin glue is a fraction of human plasma and is separated by plasma fractionation section of the National Blood Center. the Thai Red Cross Society

Placebo

0.9% Normal Saline

The post catheter removal collection

Post catheter removal collection is the accumulation of fluid in the surgical area under the skin and subcutaneous tissue after the catheters had been removed.

Maneuver

Step 1. The patients who met the eligible criteria were randomly allocated into two groups

Step 2. General information was recorded and informs consent was asked from the patients.

Step 3. Each patient received general anesthesia

Step 4. Standard modified radical mastectomy was performed in both groups. The details as followed:

The skin was wildly prepared with topical antiseptics. This included not only the involving breast, but the area over the sternum, supraclavicular region, shoulder, axilla, and collateral chest wall as well as upper abdomen on the involved side. An oblique elliptical incision was made that might include a short extension laterally up toward the axilla to ensure a better exposure for the axillary dissection and more cosmetically acceptable closure. The transverse segment of the elliptical incision included the nipple and an appropriate distance of 5-7.5 cm. beyond the limits of the tumor. The skin flaps were elevated to the level of the clavicle superiorly, to the edge of the sternum medially, to the costal margin inferiorly, and then laterally to the edge of latissimus dorsi muscle.

The fascia over the pectoralis major muscle as well as the breast was resected as subfascial dissection. The fascia was meticulously dissected off the pectoralis muscle without including any of the muscles within the gross specimen. The perforating intercostal arteries and vein near the sternal margin must be carefully ligated. The fascia over the edge of pectoralis major was incised. The lateral edge pectoralis minor was cleared of fascia, and several veins were ligated as they came off the axillary.vein. The loose tissue over axillary vein was incised and the vein wall gently exposed for a short distance beyond the subscapular vessels.

A complete and through dissection of axilla was mandatory, beginning with dissection of Rotter's lymph nodes. Precautions were taken to avoid the medial and lateral nerve. The axillary fat and lymph node were mobilized off the chest wall and axillary vein. The long thoracic nerve as well as the thoracodorsal nerve should have been free of redundant tissue. The operative area was repeatedly inspected for any bleeding points. which were ligated. The wound was irrigated with saline, and a final inspection was made for hemostasis prior to closure. Two Radivac drain was inserted. They were introduced through separate stab wounds made in the lower flap

posteriorly. One catheter was directed up to the axilla. The other catheter was secured anterior to pectoralis muscle under the skin flap.

Before closing the skin incision in treatment group, the tip of the fibrin sealant spray applicator was inserted between the loose suture loops and sealant was applied onto the exposed axilla. In placebo group 0.9% Normal Saline is sprayed in the same fashion. After the spraying, skin flaps were closed.

Step 5. The skin incision was dressing by dried gauzes without any elastic bandage wrappings. Shoulder mobilization was recommended on the second postoperative day.

Step 6. The patients were observed and evaluated clinical as same as the post operative modified radical mastectomy patients. Therapy with analgesics and sedatives were allowed to all patients. 0.9% NSS with povidine solution were allowed for wound dressing.

Step 7. Daily drainage was measured by the staff nurses in the labeled jar every morning. The amount of the fluid was recorded in the chart. The resident evaluated the records and determined when to take the drain off by using the standard criteria.

OUTCOME MEASUREMENT

Outcome variables

1.The time of drain removal (days)

2. Length of hospitalization (days)

3.The post catheter removal collection rate

Primary outcome

The primary outcome was the time of drain removal (days)

Criteria to remove catheters

Catheters should be removed when the drainage is less than 40 ml per 24 hours (closed-suction drains must work properly)

Secondary outcome

1. Length of hospitalization: the operative day was counted as day zero.

Criteria for discharge

1. Normal recovery and no complication
2. Closed-suction drains should be removed

2. The post catheter removal collection

Criteria to diagnosed collection

1. Fluctuation of skin in the surgical area
2. Fluid accumulation was identified

Evaluation of post catheter removal collection

The patients were observed and evaluated clinical as same as the post operative modified radical mastectomy patients. After catheters were removed, axilla and chest wall were evaluated for collection. Post catheter removal collection will be evaluated 2 and 4 weeks after operation.

DATA COLLECTION

1. The current admission data were filled in a form and kept separately as a reference.

2. Types of treatment were not been written down in the OPD card to blind the physician. The patients were observed and evaluated clinical as same as the post operative modified radical mastectomy patients.

3. Daily drainage was measured by the staff nurses in the labeled jar every morning. The amount of the fluid was recorded in the chart. The resident evaluated the records and determined when to take the drain off by using the standard criterias.

4. After catheters were removed, axilla and chest wall was evaluated for collection. The time of drain removal was recorded.

5. After the patients were discharged, all patients were followed up at OPD surgery 2 and 4 week after operation by surgeons who did not know type of treatment. Axilla and chest wall was evaluated for collection. Length of hospitalization and the post catheter removal collection was recorded.

Baseline data

The baseline data were age (years), presenting sign and symptom, location of tumor, tumor size (centimeters), cancer staging, number of axillary node, level of dissection, operative time (minutes) and pathological characteristic

The outcome variables

1.The time of drain removal (days)

2. Length of hospitalization (days)

3. The post catheter removal collection rate

DATA ANALYSIS

All baseline data and outcome variables were collected and analyzed by microcomputer statistical program SPSS (version 7.5). All baseline data were compared before outcome variable analysis. Descriptive statistics of the baseline

continuous data were summarized as means, standard deviations and 95% Confidence Interval. For the baseline categorical data were analyzed as frequency distribution and percent as show in table 1.

Table1.Demographic and baseline data

Variable	Type of variable	Descriptive Statistics
1. age (year)	Continuous	Mean, S.D. 95% CI
2.presenting sign and symptom	Nominal	Frequency distribution, percent
3. location of tumor	Nominal	Frequency distribution, percent
4. tumor size (cm)	Continuous	Mean, S.D. 95% CI
5. number of node	Continuous	Mean, S.D. 95% CI
6. cancer staging	Ordinal	Frequency distribution, percent
7. level of dissection	Ordinal	Frequency distribution, percent
8. operative time (min)	Continuous	Mean, S.D. 95% CI
9. pathologic grading	Ordinal	Frequency distribution, percent
10. pathological characteristic	Nominal	Frequency distribution, percent

Table 2.The outcome variables

Variable	Type of variable	Statistics [p-value, 95% CI]
1. time of drain removal	Continuous	t-test or Mann-whitney test, Survival analysis with Logrank test
2. Length of hospitalization	Continuous	t-test or Mann-whitney test, Survival analysis with Logrank test
3. The post catheter removal collection rate	Nominal	Chi-square test or Fisher's exact test

The time of drain removal was the main outcome. The t-test was used under assumption that the data was observed completely from the start to the end. If the data could not be observed completely such as lost of follow-up, withdrawal, deaths from causes other than the one under study, survival analysis and Logrank test were considered. With completion of observation, the significant difference of the length of hospitalization was determined by T-test. Without completion of the observation as mentioned earlier, the data will be analyzed by survival analysis and Logrank test.

The post-catheter removal collection was the nominal data. This data will be analyzed by Chi-square test or Fisher's exact test if the expected value in a 2*2 table was less than 5

All statistical test were carried out using two-tail probability with $p<0.05$ as accepted significance.

ETHICAL CONSIDERATIONS

Ethical considerations of the fibrin sealant were considered. The study protocol must have been thoroughly explained to the patients before enrolling in the study and the face informed consent should have been obtained from patients.

From previous study this drug was effective without serious side effect. This intervention was reviewed by Phramongkutklao ethical committee for approval.

LIMITATIONS

Generalizibility

This study was conducted particularly for the patients treated by modified radical mastectomy. The usefulness of fibrin sealant would be proved only for this

procedure. The procedure apart from MRM such as breast preserving procedure might need more data.

Follow up

After being discharged, the patients might not come to see the doctors unless they had some problems. Some patients might not come to the exact follow-up date 2 and 4 week after operation. The patients who lost follow up will be contacted by telephone to ask about their clinical symptoms.

BENEFITS OF THE STUDY

The benefits will be a reduction of time to drain removal. This reduction will make patients more comfortable and less pain. Moreover, the other problems such as the limitation of arm movement and caring catheter system will be lesser. This would also reduce the risk of infection, an important postoperative complication. The length of hospitalization will be shorter as a result of this benefit so that the patients could go back to their normal activity.

Reduction of post-catheter removal collection is another benefit that we would expect from this treatment. If this complication can be prevented, it will be unnecessary for the patients to see their doctor after being discharged from the

hospital. However this outcome measurement is less important than the time to drain removal.

The benefits for the doctor would improve the situation of bed administration that appears to be a problem in most hospitals. The cost of hospitalization would be reduced as well. If the fibrin sealant group give better results without serious side effects, this treatment should be introduced as a standard treatment in modified radical mastectomy breast cancer patients.

CHAPTER 5

RESULTS

Study population

The study was conducted during March 1999 to January 2000 at the Phramongkutklao Hospital. During the study period, 64 patients who were diagnosed of stage I or II of breast cancer and met the eligible criteria were enrolled in the study. The patients were randomized into intervention group and control group. The interventions group, consisted of 30 early breast cancer patients who underwent modified radical mastectomy, followed by the fibrin sealant before closing the skin incision. The control groups consisted of 34 early breast cancer patients who underwent modified radical mastectomy followed by normal saline before closing the skin incision.

Table I. Baseline characteristics of the study population

	Intervention Group	Control Group
Number of patients	30	34
Age (year) (Mean±SD)	52.73 ±14.7	49.82±12.7
(Min-max)	(31-79)	(22-74)
Presenting signs and symptoms		
Self detected mass	27 (90%)	27 (79%)
Mastalgia	12 (40%)	19 (56%)
Nipple discharge	1 (3%)	0
Abnormal mammogram	1 (3%)	2 (6%)
Right breast	16 (53%)	15 (44%)
Left breast	14 (47%)	19 (56%)
Location		
Upper outer	17 (56%)	19 (55%)
Upper inner	2 (6%)	1(3%)
Lower outer	9 (30%)	10(29%)
Lower inner	1 (3%)	4 (11%)
Center	1 (3%)	0

Table I. Baseline characteristics of the study population (continued)

	Intervention Group	Control Group
Number of patients	30	34
Tumor size (cm.) (Mean±SD)	2.73 ± 1.2	2.94 ± 1
(Min-max)	(0.5-5)	(1-4.5)
Stage I	12	11
Stage II	18	23
Number of node dissections (Mean±SD)	15.60 ±6.3	16.09± 7.4
(Min-max)	(0.5-5)	(0.5-5)
Level of dissections	2	2
Operative time (Mean±SD)	162±36.3	170±32.4
(Min-max)	(115-180)	(120-250)

All of the patients enrolled in this study were completely followed up for the clinical outcome. Table I shows the distribution of the patient characteristics in both the treatment and the control groups. All patients were treated by modified radical mastectomy (MRM). Fibrin sealant was applied over the operative area in 30 patients in the treatment group while normal saline as a placebo was used in 34 patients in the control group. All the patients were female, the mean of age was 53 and 50 years old in the fibrin sealant treated group and control group, respectively. Presenting signs and symptoms of cases in this study were self detected mass, mastalgia and nipple discharge (Table I). One or more signs and symptoms could be presented in one patient. 90% and 79% of cases in intervention group and control groups presented with self detected mass while 40% and 56% of cases had mastalgia. Abnormal mammogram of routine checking was 3% and 6% in intervention and control group. Only a case of nipple discharge was in the intervention group. Lesions were detected in both sides with approximately the same proportion in both groups. Most lesions located in upper outer quadrant with 56% in intervention group and 55% in control group. The second most common location of the lesion in both groups was lower outer quadrant.

Twelve and 18 of the patients in the fibrin treated group were categorized as stage I and II respectively while 11 and 23 of the control group were in stage I and II, respectively (Table II). The mean of tumor size was 2.7 and 2.9 centimeters in diameter

in the fibrin sealant treated group and control group, respectively. The operative procedures such as incision lines, level of node dissection and dissection area were done by the same group of qualified surgeons in both groups. The amount of lymph node dissected from the specimens was the same in both groups with the average of 16 nodes. The operative time was 162 minutes in the fibrin treated group and 170 minutes in the control group.

Table II. Pathological characteristics of the study population

	Intervention Group	Control Group
Number of patients	30	34
Infiltrating ductal carcinoma		
Grade I	4 (14%)	5 (14%)
Grade II	13 (43%)	15 (44%)
Grade III	13 (43%)	14 (42%)
Lymph node positive for malignancy	14 (47%)	12 (35%)
Estrogen receptor positive	6 (20%)	8 (23%)

Table II shows the pathological findings of the specimens from the enrolled patients. All patients are infiltrating ductal cancer with 47 and 35 percentage of metastatic lymph nodes in fibrin sealant treated group and control group, respectively. Grading of pathological findings also showed the same percentage between two groups. Estrogen receptors were positive in 20% and 23% of cases in the intervention and control groups respectively.

There is no significant difference between 2 groups in terms of demographic and pathological characteristics.

Table III. The comparisons of clinical outcome

	Intervention Group	Control Group	p-value	95%CI
Number of patients	30	34		
Time of drain removal (day)(mean±SD)	7.9±2.1	8.97±2.9	0.11*	(-2.38)-0.24
Hospitalization (day)(mean±SD)	9.03±2.3	10.12±3.1	0.12*	(-2.48)-0.31
Post-removal collection	10 (33.3%)	8 (23.5%)	0.38**	

* Student t test

** chi-square test

Table IV. The comparisons of amount of discharge

	Intervention Group	Control Group	p- value
Number of patients	30	34	
Amount of discharge (ml)			
D1	101	104	NS*
D2	116	138	NS*
D3	88	94	NS*
D4	74	88	NS*
D5	67	71	NS*
D6	53	53	NS*
D7	40	44	NS*
D8	25	38	NS*
Total	564	630	NS**

*Student *t* test

**ANOVA for repeated measurement

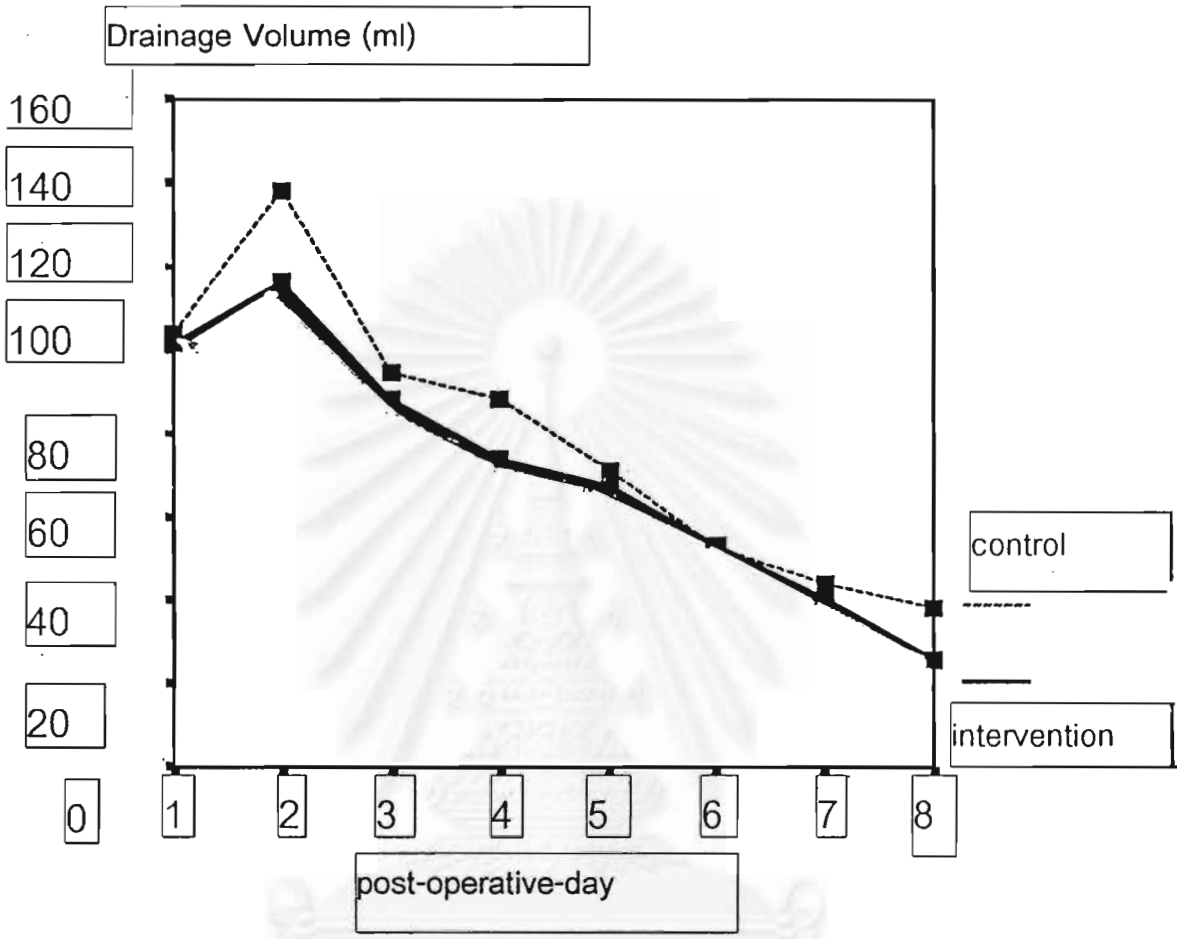


Figure 1. Means of Drainage Volume per Day

Clinical outcomes

Table III shows the comparisons of clinical outcome at the end of the study between 2 groups. Clinical outcomes were measured as described earlier. The main outcome of the treatment is the period between the end of operation to the time that closed suction drain was removed. It took approximately 8 days for fibrin sealant group and 9 days for control group before the drain could be removed. Although fibrin sealant tended to reduce the period of drain insertion, there was no significant difference between this main measurement of clinical outcome.

The secondary measurement of clinical outcome are the length of hospitalization, the post-removal collection and other complications such as skin necrosis, wound infections and wound dehiscence

The patients in the fibrin sealant treated group stayed in the hospital for 9 days which is approximately a day shorter than that of the patients in the control group, however, there was no significant difference. The collection of the fluid under skin flap was recorded on the first day after removing the drain and also at 4 weeks after the operation. Without significant difference, the fluid collection was detected in 33.33% of the patients in fibrin sealant treated group and 23.5% in the control group.

Table IV shows the amount of fluid drainage of both groups. The amount of fluid drainage of each group was comparatively plotted as shown in figure I. The amount of fluid drainage was highest on day 2 and then gradually decreased. The reduction of fluid reached the criteria to remove the drain with the average of 8 and 9 days in fibrin treated and control group, respectively. There was no statistical significant difference between the fibrin sealant and control group in terms of the daily amount and the total amount of fluid drainage.

Table V. The comparisons of complications

	Intervention Group	Control Group
Number of patients	30	34
necrosis of the skin flap	1(3%)	0
Infection	0	2 (6%)
Hematoma	0	0
Wound dehiscence	1(3%)	0
Skin flap irritation	1(3%)	0

Complications

One patient in the fibrin sealant treated group had a complication of skin necrosis. The area of skin necrosis was 1-centimeter width and 2-centimeter length on the incision line. Debridement, oral antibiotics and dressing of the wound were done to treat this complication. Itchiness was complainted by one patient in fibrin sealant treated group, the symptom subsided spontaneously within 1 day. Minor skin infection at the drainage site was detected in 2 patients in the control group whom were treated by oral antibiotics and wound dressing.

CHAPTER 6

DISCUSSIONS AND CONCLUSIONS

The most common complication of modified radical mastectomy is the collection of fluid under the skin flap on the breast area. The seroma formation is mainly a result of the leakage of the lymphatic vessel in the areas of operation especially in the axillar. The deeper level of axillary node was dissected, the more amount of fluid was detected. The seroma is also composed of liquefied necrotic fat since the operation disturbed the blood supply. Generally, closed suction drains beneath the flaps are a routine prevention of seroma formation in this kind of operation. The exact sites of the leakage in the operative area are difficult to identify so that the ligation of lymphatic vessels is not practical. A few procedures to reduce the leakage has been reported, these include pressure dressing of axilla and chest wall, early and delayed shoulder mobilization, contact laser, multiple drains and high-pressure vacuum drainage. No statistical and clinical significant reduction of fluid leakage had been shown by these methods.

Fibrin sealant, a biologic adhesive consisting of coagulation factors, has shown to close small leakage especially that found in the anastomoses of the

esophagogastric system, small intestine and vessels. It is also effective in obtaining hemostasis at skin graft donor sites. Fibrin sealant is now widely used in several areas of surgery such as wound care, neurosurgery, dental and oral surgery.

A few groups of researchers were interested in these biological glue for prevention of the leakage after modified radical mastectomy. However its usefulness is still inconclusive. Different outcomes in these clinical trials might be a result of different volume, concentration, preparation and source of fibrin sealant. In addition, the devices and method of application have also been using in different ways. The fibrin sealant was used to be a bovine origin. Because of the allergic reaction after using bovine fibrin and the possibility of unknown harzadous organisms, human fibrin has been developed and used. Recently the development of autologous fibrin has been done to reduce the risk of HIV infection.

In Thailand, there is no commercial fibrin sealant available right now. Fortunately, the fibrin sealant can be produced with reasonable price by blood centers in the academic health institutes such as the Siriraj Hospital and the National Blood Center, Thai Red Cross Society. Fibrin sealant produced by the National Blood Center, the Thai Red Cross Society is composed of 2 solutions. Solution 1 and 2 separately contains thrombin and fibrinogen. This study shows the effectiveness of the fibrin glue

comparing to placebo in the breast cancer patients underwent modified radical mastectomy.

The main outcome measurement was the time of drain removal that was not statistically different in both fiber sealant treated group and control group. Comparing of the amount of fluid drainage between two groups, there is no difference in term of daily amount and total amount of fluid drainage. These results are comparable to the results of previous studies. The reason behind the indifference might be due to the amount of the fibrin used in this study. Gilly et al[19] (1997) reported a significant reduction of drainage volumes by using 2-ml fibrin sealant sprayed over the operative area. However, the same amount but different application method used in other study [10,11] showed controversial results. With reasonable price, 2 ml of fibrin sealant was chosen in the present study. The areas of application would determine the outcome as well, however, the exact leakage areas were hardly identified. The higher amount of fibrin would cover more possible area of lymphatic leakage. There was also a report of using 5 ml with a succession.

The methods and devices of application were also different among the previous studies. Studies that applied fibrin sealant by spraying via cannula gave a better result comparing to others. Each solution of commercial fibrin sealant passes through its own cannula and mixed together in the main cannula. Via multiple holes at

the end of the main cannula, the mixed solution is then sprayed on the operative areas. This system would appear to work particularly well since the mixture is thoroughly combined before an application on the areas. Because there is no commercial spraying devices available, we used the device produced by the Thai Red Cross Society which may function compatibly . This device was consisted of two syringes with a no.21 needle. Each syringe contained a difference solution. The needles were curved in order to put their tips together in a main plastic tube. Both solutions would then pass through this main tube and be scattered by an air pumping system. This system might be inferior to the commercial one as the solution would not well mixed and the operative area would less covered.

During the insertion of the drainage, the patient would suffer from pain, limitation of the movement, caring of the drainage system and limitation of the patient's activity. Moreover the drainage might increase risk of nosocomial infections. Early removal of the drain is considered to be physically, mentally and financially important for the patients. For patients' view, earlier removal of the drain, even a day, seems to be important. In this study, the drain in the fibrin sealant treated group could be removed a day earlier than the control group. For the doctor's view, early removal of the drain is considered to be important in terms of bed administration and cost of hospitalization. However, 2 days or more appear to be a reasonable period for the

reduction of time to drainage removal. For bed administration, a complete treatment of some particular operative treatment such as acute appendicitis and laparoscopic cholecystectomy, could be done within 2 days. Importantly cost of treatment per head would be reduced.

In the present study, 1-day difference in the period of drain removal between the treated and control group, were observed but this was no statistically significant. If the sample size were calculated by using 1 day in difference, 123 patients each group would be needed for the significance. However, only 1 day is not important in terms of cost and clinical benefit. Comparing the cost of fibrin sealant, at least 2 day in the reduction of time to the drain removal will provide satisfactory. Hence it is not necessary to include more patients in this study in order to reach statistical significance. Considering the 2-day difference in the period of drain removal as being clinical important and statistical significant, patient number enrolled in this study was enough.

The length of hospitalization, the secondary outcome measure, depends on the time of drain removal. In parallel to this primary outcome, the time of hospitalization was also reduced for 1 day in the treated group. In the Army Hospital, the drain must be removed before the patients were discharged. In contrast, in some general

hospitals patients are discharged with the drain on and followed up for drain removal later. So the length of hospitalization might not be vital in some hospitals. Moreover the length of hospitalization after drain removal is also influenced by a few factors such as wound dressing, further adjuvant chemo-and/or radiotherapy, bureaucracy of administration and insecurity of the patient.

The important complication after drain removal is fluid collection under skin. Although treatment of this condition, aspiration and compression, is not complicated but it is uncomfortable for the patient. This collection might also be a source of infection so this condition is considered as the other important outcome measure. This condition can be easily detected by simple physical examination and mostly occur during a week after removing the drain. Although the follow-up period for each patient might not the exactly the same. Most patients come to see the doctor within three to four weeks after operation because they had to receive the final pathological reports which are the most important information for further treatment such as adjuvant chemotherapy or hormonal therapy. In the present study, the follow-up time for each patient covered the period that this complication might occur.

The fluid collection will occur if the drain is removed too early. Any treatment that can reduce the time of drain removal should decrease or at least, should not

increase the post-catheter removal collection as well. Although treated with fibrin sealant seem to reduce the time of drain removal by 1 day, the fluid collection after drain removal detected in the treated group (33 %) seem to be higher than the control group (23 %). This increase might be of concern by the surgeon, however, the difference in the number of post-catheter removal collection detected between these 2 groups is not statistical significance. Other complications in the fibrin-treated group were minor such as skin necrosis, wound dehiscence and irritation. The treatments were local wound care and oral antibiotics with no requirement of hospitalization and major procedure of treatment.

Conclusions

In conclusion, using fibrin sealant after modified radical mastectomy in the treatment of early breast cancer showed no significant difference in the time of drain removal comparing to the control group. There is also no difference of the length of hospitalization and also the post-catheter removal collection. A significant adverse reaction of fibrin sealant was not found. The result in the present study might be affected by the amount of fibrin sealant, area of application and the application devices. Further studies to determine the importance of these factors should be done to provide proper usage of this preparation. Routine clinical usage will be then recommended. Moreover because the fibrin sealant needs the freezer that provide

constant temperature below -20°C to keep its properties, its usage will be limited in the urban area.

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APPENDICES

Appendix A.

Data Collective Form

Baseline Data:

Name _____Age_____ [years]

1. Code No _____ Hospital No _____

2. Presenting sign/symptom _____

3. Side RT // LT

4. Location _____

5. Tumor size _____ [cm]

- ■ T0: No evidence of primary tumor
- ■ T1: Tumor 2 cm or less in greatest dimension
- ■ T2: Tumor more than 2 cm but not more than 5 cm in greatest dimension

6. Number of node _____ [axillary dissection]

7. Level of dissection ■ 1 ■ 2 ■ 3

8. Operative time _____ [min]

Date of surgery ___/_____/1999 Start at _____ End at _____

Surgeon _____

Pathologic cell type _____ grade _____

Nodal status +//- ER +//-

The Outcomes

Drainage volume [ml] D1 _____ D2 _____ D3 _____ D4 _____

D5 _____ D6 _____ D7 _____ D8 _____

D9_____ D10 _____ D11 _____ D12 _____

Primary

9. time of drain removal _____ [day]

Date of drain removal ___/___/ 1999___

Secondary

10. Length of Hospitalization _____ [day]

Date of Admission ___/___/1999 Date of discharge ___/___/1999

11. The post Catheter removal collection ■ Yes ■ No

12. Other complication ■ Yes ■ No

[E.g. Skin necrosis _____

13. Follow up 2 wk after operation ■ Yes ■ No

Complication_____

14. Follow up 4 wk after operation ■ Yes ■ No

Complication_____

Appendix B.

Patient Information Sheet

การใช้กาวไฟบรินใสในแผลผ่าตัดเพื่อลดระยะเวลาการใส่ท่อระบายน้ำเหลืองในผู้ป่วยที่รับการผ่าตัดรักษามะเร็งเต้านม

ชื่อผู้ทำวิจัย นายแพทย์ปิยะ เตียวประเสริฐ กองศัลยกรรม รพ.พระมงกุฎเกล้า

จุดประสงค์ เพื่อศึกษาว่า การใช้กาวไฟบรินใสในแผลผ่าตัด จะช่วยลดระยะเวลาการใส่ท่อระบายน้ำเหลืองในผู้ป่วยที่รับการผ่าตัดรักษามะเร็งเต้านมหรือไม่

ทำไมถึงต้องศึกษาเรื่องนี้

มะเร็งเต้านมเป็นมะเร็งที่พบได้บ่อย การผ่าตัดเพื่อรักษามะเร็งเต้านมนั้นจำเป็นต้องใส่ท่อระบายน้ำเหลืองเพื่อลดปัญหาการเกิดการสะสมของน้ำเหลืองบริเวณแผลผ่าตัด ดังนั้นหลังการผ่าตัด ผู้ป่วยจะมีท่อระบายน้ำเหลืองใส่อยู่ในบริเวณแผลผ่าตัด การใส่ท่อระบายน้ำเหลืองนั้นมีข้อดีคือ ลดปัญหาการเกิดการสะสมของน้ำเหลืองบริเวณแผลผ่าตัด แต่ก็มีข้อเสีย เช่น เกิดอาการเจ็บปวด, ขัดขวางการเคลื่อนไหวของไหล่ และเพิ่มอัตราการติดเชื้อถ้าใส่ไว้นานเกินไป ศัลยแพทย์หลายๆท่านพยายามหาวิธีที่จะลดระยะเวลาการใส่ท่อระบายน้ำเหลืองลงเพื่อให้เกิดประโยชน์ต่อผู้ป่วยสูงสุด การศึกษาครั้งนี้จะทำให้ทราบว่ากาวไฟบรินช่วยลดระยะเวลาการใส่ท่อระบายน้ำเหลืองหรือไม่

ผู้ป่วยคนไหนสามารถเข้าร่วมการศึกษาได้

ผู้ป่วยมะเร็งเต้านมระยะที่ 1,2 ที่ยังไม่มีการกระจาย ลุกลามไปยังส่วนอื่นๆ ของร่างกาย และได้รับการรักษาด้วยวิธีการผ่าตัด แพทย์ของท่านจะทำการตรวจและตรวจสอบว่าท่านสามารถเข้าร่วมการศึกษานี้ได้หรือไม่

อะไรจะเกิดขึ้นสำหรับผู้ป่วยที่เข้าร่วมศึกษาครั้งนี้

ถ้าท่านเข้าร่วมการศึกษา แพทย์ของท่านจะแจ้งรายละเอียดของท่านไปยังผู้ที่ทำวิจัย เพื่อจะดูว่าท่านจะได้รับการกาวไฟบรินหรือไม่ผ่านคอมพิวเตอร์โดยการสุ่ม ผู้ป่วยทุกคนจะได้รับการรักษาด้วยกันผ่าตัดเต้านมแบบมาตรฐาน แต่มีบางคนอาจได้รับกาวไฟบริน ร่วมด้วยในระหว่างการผ่าตัดและบางรายจะได้รับยาหลอก ขึ้นอยู่กับชนิดของการสุ่มด้วยคอมพิวเตอร์

ท่านจำเป็นต้องเข้าร่วมการศึกษาหรือไม่

ขึ้นอยู่กับท่านเอง แพทย์จะดูแลท่านอย่างดีที่สุด ไม่ว่าท่านจะเข้าหรือไม่เข้าร่วมในการศึกษาครั้งนี้ และท่านจะถอนตัวจากการศึกษาได้ทุกเวลา โดยไม่ทำให้ผลการรักษาเสียไปเพราะแพทย์จะดูแลท่านอย่างดีที่สุดเหมือนเดิม

การให้กาวไฟบรินทำอย่างไร

การให้กาวไฟบริน จะทำในระหว่างการผ่าตัดโดยหลังจากแพทย์ทำการผ่าตัดเต้านมและต่อมน้ำเหลืองบริเวณรักแร้ออกหมดแล้ว จะใช้กาวไฟบรินฉีดพ่นในบริเวณท่อทางเดินน้ำเหลืองบริเวณรักแร้ ก่อนการใส่ท่อระบายน้ำเหลืองและเย็บปิดผิวหนัง

การให้กาวไฟบรินมีผลข้างเคียงหรือไม่

จากการศึกษาวิจัยในต่างประเทศและประเทศไทยพบว่าการใช้กาวไฟบรินฉีดพ่นในบริเวณอวัยวะต่างๆ เช่น บริเวณ ตับ หลอดเลือด เส้นประสาท ช่องปากและฟัน ไม่มีผลข้างเคียงใดๆ ต่อผู้ป่วย แต่ถ้าพบอาการข้างเคียงใดๆเกิดขึ้นแพทย์ก็สามารถให้การบำบัดอาการต่างๆ ด้วยยาได้

ถ้าท่านมีปัญหากรุณาติดต่อ

นายแพทย์ ปิยะ เตียวประเสริฐ

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