Effects of Topical Tranexamic Acid in Immediate Prepectoral Breast Reconstruction: A Paired, Double-Blind, Randomized Controlled Trial

Tyler Safran MD

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AUTHOR: Tyler Safran MD

SUPERVISORS: Dr. Tassos Dionisopoulos & Dr. Joshua Vorstenbosch

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“If I have seen further than others, it is by standing upon the shoulders of giants.”

-Sir Issac Newton

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LAY ABSTRACT:

Breast cancer affects one in every eight women and the majority will undergo mastectomy and implant-based breast reconstruction. Excess fluid accumulation around the breast implant in the form of excess blood (hematoma) or fluid (seroma) can lead to devastating complications including infection and excessive scarring around the implant. Although surgeons consistently strive to minimize bleeding and place drains to minimize fluid collection, the reported rates of hematoma and seroma remain at 3.4% and 6.7%, respectively. Topical administration of tranexamic acid (TXA) may reduce fluid accumulation and reduce the incidence of the aforementioned complications. Tranexamic acid is a safe medication that helps prevent postoperatively bleeding. Patients who underwent bilateral breast mastectomies with immediate reconstruction were enrolled in this RCT. One breast was randomized to receive 3g of TXA in 70cc of normal saline (100cc total) and the other received 100cc of normal saline alone. Post-operatively, daily drain outputs and complications were be recorded. Immediate implant-based breast reconstruction treated with 3% topical TXA decreased post-operative fluid production and rates of complications. Topical TXA during breast reconstruction may represent a safe, cost-effective, and simple adjunct that could improve patient safety and postoperative outcomes in breast reconstruction.

STRUCTURED ABSTRACT:

BACKGROUND:

Breast cancer affects one in every eight women, the majority of whom will undergo treatment with mastectomy and implant-based breast reconstruction[1]. Excess fluid accumulation around the breast implant in the form of hematoma or seroma can lead to devastating complications including infection and capsular contracture. Although surgeons consistently strive for meticulous intra-operative hemostasis and place drains to minimize fluid collection, the reported rate of seroma and hematoma remains at 6.7% and 3.4%, respectively[2]. Topical administration of tranexamic acid (TXA), an antifibrinolytic agent, may reduce fluid accumulation and reduce the incidence of the aforementioned post-operative complications. The proposed paired, double-blind, randomized control trial aims to investigate if TXA treated breasts will exhibit less postoperative fluid production and secondarily decrease the incidence of hematoma, seroma, infection, and capsular contracture compared to placebo treatment.

METHODS:

This paired, double-blinded, randomized-controlled trial enrolled patients undergoing bilateral breast mastectomies with immediate reconstruction between January and July 2021. In each patient, one breast was randomized to receive 3g of in 70cc of normal saline (100cc total), and the other received 100cc of normal saline alone. The blinded solutions were soaked in the mastectomy pocket for five minutes before implant placement. Postoperatively, daily drain outputs, complications, and baseline demographics were recorded.

RESULTS:

53 eligible patients representing 106 breasts were enrolled. All patients underwent bilateral nipple-sparing mastectomies. After randomization, TXA was placed in the right breast in 56.6% (n=30) of patients. The use of topical TXA resulted in a mean drain output reduction of 30.5% (RANGE: -83.6% - 26.6%). Drains on the TXA treated breast were eligible for removal 1.4(RANGE: 0-4) days sooner than the control side. TXA treated group had three complications (5.67%) versus 15 (28.3%) in the control group (Odds Ratio: 0.1920, p= 0.0129). Specifically, for operative hematomas, the TXA group had none(0%) versus three in the control group (5.7%)(Odds Ratio: 0.1348, P=0.18).

CONCLUSION:

In conclusion, soaking the mastectomy bed with 3% topical TXA before implant insertion leads to a decrease in drain output and a decrease in complications. Topical administration of TXA represents an option to decrease complications in breast reconstruction.

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Chapter 1: Introduction

1.1: Background

Breast cancer affects one in every eight women, the majority of whom will undergo treatment with mastectomy and implant-based breast reconstruction[1]. The American Society of Plastic Surgery in 2019 announced that breast reconstruction demonstrated a year-to-year increase of 8% and was performed in over 100,000 patients that calendar year[1]. Breast cancer reconstruction has shown to have an improvement in patient's reported outcomes in physical, psychosocial, and sexual well-being domains[2]. One consistent issue seen in breast reconstruction is the relatively common complications associated with implant-based breast reconstruction. Even with advances in prosthetic devices, reconstructive techniques, and mastectomy flap quality, recent reviews have demonstrated that surgical complications can arise in up to 20% of cases[3]. Aside from complications arising from mastectomy flap skin necrosis, the majority of complications arise from excess fluid accumulation around the breast implant. This fluid accumulation takes the form of hematoma or seroma can lead to devastating complications including infection and capsular contracture. Residual blood in the breast pocket does retain and pull fluid given the osmotic gradient and persistent inflammation[4,5]. Additionally, the residual hematoma is an excellent nidus for bacterial infection[6]. This excess fluid can lead to patients requiring urgent surgical intervention or can exacerbate more chronic inflammatory complications such as capsular contracture[7].

Although surgeons consistently strive for meticulous intra-operative hemostasis and place drains to minimize the fluid collection, the reported rate of seroma and hematoma remains at 6.7% and 3.4%, respectively[8]. Additionally, drains themselves are cumbersome to the patients and may represent a source of bacterial contamination[9]. Moreover, there is no evidence or consensus for the optimal duration or number of drains required. It is important, therefore, to attempt to minimize their length of insertion and output[9].

One possible solution to reduce drain outputs is the topical administration of tranexamic acid (TXA). As an antifibrinolytic agent, TXA prevents the breakdown of formed blood clots which helps to maintain hemostasis[10]. Topical TXA is safe, effective at preventing bleeding, has limited systemic absorption, and shows no difference relative to placebo for thromboembolic events (DVT/PE), stroke, myocardial infarction, or death[11]. Residual blood in the mastectomy pocket contributes to seroma formation due to its high oncotic pressure; infection due to its abundance of nutrients, and capsular contracture due to its highly inflammatory properties. It follows that TXA could reduce the incidence of excessive post-operative fluid and thus reduce the frequency of complications. The paired, double-blind, randomized control trial described here compares postoperative fluid production and incidence of complications in individual breasts (one breast randomized to topical TXA, the other to topical saline) in patients undergoing bilateral mastectomy with immediate implant-based breast reconstruction.

Tranexamic acid inhibits fibrinolysis by reversibly binding four to five lysine receptor sites on plasminogen[12]. This reduces the conversion of plasminogen into plasmin, preventing fibrin degradation, and preserving the framework of fibrin's matrix structure[12]. Therefore, tranexamic acid prevents the breakdown of already formed blood clots, which help ensure adequate hemostasis, but does not *cause* thrombosis, which is a critical consideration after surgery[11]. Tranexamic acid also directly inhibits the activity of plasmin with weak potency and blocks the active site of urokinase plasminogen, and in turn, stabilizes existing clots[11]. Lastly, TXA may also exert anti-inflammatory effects on the tissue by blocking plasmin activation of the complement cascade[13]. Studies have shown that TXA administration led to less upregulation of proinflammatory genes and an increase in anti-inflammatory genes[14]. The reduced inflammation secondary to TXA treatment can help prevent excessive fluid buildup and decrease rates of capsular contracture.

The use of TXA in PO (oral) or IV (intravenous) forms has been limited to episodes and events where the risk of bleeding outweighs the low risk of thrombo-embolic events. In mastectomy, where the risk of hematoma is not rare, topical TXA administration may be still quite effective for local hemostasis without the systemic side-effects, which are still very rare in PO/IV forms but need to be avoided, especially in the setting of malignancy and the corresponding increased risk of thrombosis. The plasma concentration of topically applied TXA has been shown to be approximately 90% less than when the medication is administered intravenously[16]. TXA is also listed on the World Health Organization’s List of Essentials Medicines and is quite inexpensive[17].

In one of the largest trauma trials to date, the CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage), the efficacy and safety of TXA IV was assessed in over 20,000 adult trauma patients and no increase in thromboembolic events was reported[18]. However, as stated In one correspondence, the precision of the safety estimate was not able to rule out an increased risk of VTE[19]. This, however, includes IV formulation, not topical administration[20]. To date, no trial has since shown an increased risk of VTE in IV administration of TXA.

In 32 of the 66 surgical trials on topical TXA, topical TXA was either poured (wound irrigation) or sprayed directly onto the operative site. Thirty-seven trials involving 3,408 patients reported blood transfusion data comparing topical TXA to placebo[16]. Compared to placebo, the use of topical TXA reduced the odds of receiving a blood transfusion significantly (OR 0.29, 95% CI (0.20 to 0.40); $P < 0.001$)[16]. Twenty-four studies (2,154 patients) reported blood transfusion data comparing topical to IV TXA[16]. When compared to the intravenous administration of TXA, there was no significant difference between the two groups overall[16]. The concentration of topical TXA used in the trials ranged from 1 mg/mL to 100 mg/mL and dosage of topical TXA did not influence effectiveness of topical TXA used in the trials. Topical TXA resulted in a mean blood loss reduction of 276 mL compared to placebo[16]. In all studies, there was no difference between placebo for thrombo-embolic (DVT/PE), stroke, myocardial infarction, or death[16]. In one double-blind randomized controlled trial, high-dose (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg)[21]. It

showed a reduction of 43% without any significant complications[21]. Additionally, the US Department of Veterans Affairs released dosing guidelines for topical irrigation, including 3 grams in a 100ml dilution[22]. Since this study, it has become almost standard of care to utilize any route of TXA in a variety of orthopedic surgery techniques.

In breast surgery specifically, multiple articles describing TXA have recently been published. In two randomized control trials on breast reduction surgery and modified radical mastectomy, topical TXA was shown to decrease drain output significantly (TXA reduced mean drain production at 24 h with 110cc versus 144cc (mean difference 34 (95% c.i. 8 to 60) ml, $P = 0{\cdot}011$) as well as decrease clinically relevant hematomas[15,23]. Retrospectively, one study showed that topical TXA in implant-based breast reconstruction resulted in fewer bleeding events and complications. The same group, however, demonstrated that these effects were also seen in IV administration[24,25]. The simplicity, lower risk of systemic absorption, and possible advantage of direct contact to the surgical site make topical application favorable in these instances.

In breast reconstruction, a majority of patients will receive drains that evacuate fluid from the mastectomy pocket into an external reservoir. With prolonged drain outputs and bleeding, patients are at higher risks of infection and bacterial seeding of the pocket[26]. Interestingly, risk of infection was shown to be related more to the duration of drain insertion than the average output per day. This risk of infection is likely due to the communication with skin flora. Therefore, by treating the mastectomy pocket with TXA will provide a dual benefit against infection by both reducing the amount of fluid produced

and by decreasing the duration of drain placement. Intraoperatively, care is taken to deal with all bleeding and achieve hemostasis, however, the risk of hematoma is well described, and prolonged serosanguinous drainage is routinely seen[27]. In addition to hematoma and residual blood requiring operative intervention and increased risk of infection, sustained fluid accumulation in the breast pocket significantly contributes to the most common complication in implant-based breast reconstruction, capsular contracture. Under normal circumstances, the implant is surrounding by a fibrous capsule that remains benign and presents no concerns. However, in response to sustained inflammation from a bacterial biofilm or pro-inflammatory substrates (blood) the capsule can become fibrotic, culminating in capsular contracture that causes significant pain and deformity around the breast implant[7]. In breast reconstruction, capsular contracture affects up to 8.7% of patients with pre-pectoral reconstruction with ADM and up to 13.9% of patients with subpectoral implants[7]. Despite the high incidence of capsular contracture, effective treatment remains elusive with up to 54% of surgically managed capsular contracture cases recurring[28]**.** Therefore, surgeons must adopt surgical techniques to support primary prevention of capsular contracture in order to minimize the extent of this devastating complication in the breast reconstruction population. Studies have demonstrated that TXA administration leads to a systemic decrease in inflammatory mediators and cytokines[14]. Thus topical TXA may not only provide significantly improved serosanguinous output but may also exert its anti-inflammatory effects on the breast capsule, decreasing capsular contracture[13,14].

While topical TXA administration has substantial promise to improve implant-based breast reconstruction outcomes, it is important to note that the topical use is of tranexamic acid still off-label. There currently lacks consensus regarding the optimal TXA concentration in the solution applied, mode of application, or duration of contact. As mentioned, most publications come from joint replacement surgery, where instilling TXA as a bolus into the joint reduces bleeding equivalent to that following intravenous administration. An unexpected finding of a possible negative effect of TXA on leakage of lymph was reported in one randomized clinical trial on topical tranexamic acid in mastectomy wounds[15]. In the subgroup of patients receiving TXA who underwent lymph node clearance, TXA had a less beneficial effect on postoperative fluid production; these patients were later significantly more likely to need seroma aspiration and had an increased seroma volume, although no increase in chronic seroma rates. Tranexamic acid also may have unrecognized cellular antiadhesive properties. TXA inhibits plasminogen, which is ubiquitous in tissue matrix and has numerous functions beyond the cleavage of fibrin[15]. It is possible that TXA may affect wound healing given its anti-inflammatory properties, but this has not been shown in any clinical in-vivo study[15].

In all, topical TXA may play a critical role as an adjunct to intraoperative hemostasis, by minimizing the incidence of postoperative bleeding, seroma, hematoma, infection, and potentially capsular contracture in alloplastic breast procedures. In the present study, we assess its utility and role in this procedure, with the goal of ensuring optimal outcomes for breast reconstruction patients. Patients undergoing bilateral mastectomy with immediate breast reconstruction represent an excellent paired group

with two breasts that are very similar in terms of size, mastectomy technique, skin quality, and reconstruction type.

1.2 STUDY OBJECTIVES:

This study aims to assess whether the use of a 3% topical TXA solution reduces drain output in patients undergoing implant-based breast reconstruction. As a result, the primary clinical outcome is the percentage difference of mean daily drain outputs between the TXA soaked breast and normal saline soaked breast. Secondary objectives include comparing hematoma rate between the groups as well as comparing the frequency of other adverse events including pocket infections, dehiscence, capsular contracture, seroma, and surgical site infections. The overall rationale is to allow surgeons to perform drain-less surgery or decrease the duration of drain use which has been proven to increase morbidity. The reporting of this study adheres to the CONSORT checklist for randomized controlled trials (**APPENDIX A**).

CHAPTER 2: STUDY METHODOLOGY & PROCEDURES

2.1 Trial Design

This trial is a double blinded, paired, placebo-controlled trial design that assessed for the effectiveness of TXA in bilateral implant-based breast reconstruction. The allocation was 1:1 given the sample population having bilateral mastectomies and the fact that each patient is itself a self-control. The included patients underwent bilateral mastectomy and reconstruction, with each breast randomized to the treatment or placebo group by a single reconstructive surgeon. Patients were screened and eligible patients were consented during their pre-operative consultation. Prior to the start of surgery, the non-blinded circulating nurse created both solutions in unmarked bins (Labeled A and B) (one solution 70cc Normal Saline (NS) and 3 Grams of TXA and the other 100cc of NS). The TXA solution is odourless and colourless. Once the case commenced, the scrub nurse and the surgeons were completely blinded. At mastectomy competition, using an online platform (https://www.randomizer.org/) the breasts were randomized in a 1:1 allocation. Baseline demographics and patient-reported outcomes were documented at the time of pre-operative consultation. Patients were followed every week postoperatively for a month, then every month for a year. Upon discirculating from hospital, patients were

taught to mark the daily drain outputs on a standardized JP output sheet which was collected at the time of JP removal. Standard forms can be found in **APPENDIX B/D.**

2.2 Patient Population

2.2.3 Participants and Recruitment:

Patients scheduled for bilateral mastectomies with immediate reconstruction, and a Jackson-Pratt (JP) drain post-operatively, were invited to participate during consultation. Informed consent was obtained from participating patients according to St-Mary's Hospital REB approved consent form. (**Appendix C**).

2.2.4 Randomization Inclusion/Exclusion Criteria:

The inclusion criteria for randomized were:

- All bilateral skin or nipple sparing mastectomies with immediate implant-based reconstruction.
- All bilateral reconstructions (as mentioned above) with the use of drains for measurement.
- Patients will still be included regardless if a sentinel lymph node biopsy or dissection is planned to be performed on one side or another.

The exclusion Criteria to be randomized were:

- Unilateral mastectomy with balancing procedures performed on the contralateral side
- Any reconstruction that does not include drains
- Any unilateral reconstruction
- Any bilateral mastectomy case that doesn’t have immediate reconstruction
- Patients that do not consent for the trial
- Patients under 18 years old
- Known thromboembolic disease or high risk of thromboembolism warranting extra anticoagulation in connection with the procedure
- Pregnant or nursing patient
- Known allergy to TXA
- Intra-operative decision to abort reconstruction of either side due to poorly vascularized flaps or clinical worry

2.3 Study Setting

The study was performed at St Mary’s Hospital & The Jewish General Hospital in Montreal, Quebec, Canada. Here, breast cancer mastectomies with reconstruction are widely performed by four breast surgeons and one plastic surgeon. These cases are commonplace due to the incidence of breast cancer as well as the high volume of genetic cases requiring bilateral risk reducing mastectomies. All data extraction and analysis were performed on site.

2.4 Screening & Enrollment

Patients were explained the study if they qualified by the treating team during their initial consultation in clinic. Traditionally, they are seen twice prior to their surgery (consultation many weeks prior and then final visit two weeks prior to surgery), which is the standard for all patients treated at this institution. The staff surgeon (Dr. Dionisopoulos) was removed from the consenting process to remove pressure on patients from feeling that they have to opt in. Patients identified as interested in participating in the study met with the study coordinator and signed the informed consent. Prior to surgery, the inclusion criteria were again verified. All patients understood that they could retract consent at any point during the outlined process. Success in recruitment is defined as ≥75% of eligible patients asked to be recruited into the study signed consent.

2.5 Trial Interventions

2.5.1 Experimental Group

The intervention in the experimental arm was the breast that was treated with topical TXA (3 grams in 70cc of NS for a total of 100cc). This solution is colourless and odourless. It is prepared by the circulating nurse who is unblinded for the experiment. The TXA and method of administration was approved by Health Canada via a no objection letter (***Ref: HC6-24-c248414*** – APPENDIX C).

After completion of mastectomy, Pectoralis I & II blocks were performed using long acting anesthetic with epinephrine[29]. Additionally, the sites where the JP drains were placed were infiltrated similarly with long acting local anesthesia with epinephrine. Breast pocket sutures were placed only if required at the lateral chest and inframammary crease using heavy absorbable vicryl (Johnson & Johnson, New Jersey, United States) sutures. Care was always taken to avoid suturing into the pectoralis muscle which could increase postoperative drain output or bleeding if ruptured. Then a JP drain was placed at the previously infiltrated sites on each side of the chest. Once placed and sutured into place, hemostasis was achieved using electrocautery. At this time, a randomized sponge (TXA soaked solution or NS) was placed to contact the entirety of the surgical breast surface. Any residual solution was placed into the breast and left closed for five minutes (timed). No TXA was administered intravenously. No NSAIDS or any pharmacologic agent is administered in the postoperative period to possibly enhance the risk of bleeding given their anti-platelet effects. At termination of the five minutes, 100cc of 10% povidone-iodine, triple antibiotic (1 Gram of cefazolin, 80mg of gentamicin and 50 000 IU of bacitracin), and NS (500cc) solution was irrigated into the breast pocket prior to a no-touch implant placement[30]. Additionally, as will be mentioned in the discussion, all adjunctive procedures (axillary lymph node dissection/biopsy) were performed through separate axillary incisions and do not communicate with the breast pocket.

2. 5. 2 Control Group

Breasts in the control group received standard perioperative care as listed in the above section. At completion of the standard steps, a sponge soaked with normal saline was placed instead of tranexamic acid. This was determined by simple randomization as previously described.

2.6 Randomization:

Each breast underwent simple randomization to either receive TXA (3 grams of TXA in 70cc of NS – 100cc total) or saline alone group (Placebo, 100cc of NS alone). The surgeon (blinded) was handed a solution (either TXA or saline) to soak the mastectomy pocket for five minutes by the scrub nurse who is was also blinded. The solutions are identical (clear, without odour). Only post-operatively, the breast will be labeled for data collection by the circulating nurse who prepared the solutions. The solutions were prepared pre-operatively by the circulating nurse in plastics (Either labeled A or B). The breasts were randomized using an online randomization software. Both breasts will be soaked in the respective solution for a total of five minutes.

2.6.1 Randomization type

Using a 1:1 allocation, each breast of the individual patient was randomized to A or B using an online randomization software.

2.6.2 Randomisation: allocation concealment mechanism

The TXA solution is prepared by the circulating nurse in plastics prior to starting the case. It is odourless, colourless and identical in appearance to the 100cc of Normal Saline as placebo. The TXA solution is created with 3G of TXA (30cc) and 70cc NS. The entire surgical procedure and postoperative care is identical, and the treating team remains blinded throughout.

2.7 Outcomes & Data Collection

2.7.1 Baseline Demographics and Surgical Details.

Standardized forms for the initial consultation, operative procedure, and follow-up visits were created to assist with consistency in reporting patient demographics, surgical details and postoperative visits. These forms were inserted after completion into the patient's chart to be able to be accessed for data collection. These forms can be seen in the **APPENDIX E**.

2.7.2 Primary Clinical Outcome

The primary clinical outcome of the study was the amount of daily JP output. Since the cases are all bilateral, mastectomy specimens and extent of dissection was very similar and as such should at baseline have similar JP outputs. These outputs were measured by the patient and recorded as cc/day on a dedicated JP sheet (**APPENDIX B**).

2.7.3 Secondary Clinical Outcomes:

- *Days to JP removal:* At our institution JP drains are removed when the daily output is less than 25cc/day for at least three consecutive days[8]. As a secondary outcome, we examined if TXA would decrease the length of JP insertion.

- *Complications:* All complications were recorded. Acute complications occur within the first two weeks, with sub-acute or late complications occurring after. Minor complications are defined as any intervention not requiring general anesthesia or re-admission to hospital. These include cellulitis, epidermolysis, dehiscence, and minor bruising. Significant capsular contracture was defined as a Baker-Spear grade three or four[7]. This clinically this is represented by a breast that is firm, appears abnormal and may be painful.

2.8 Frequency and Duration of Follow-up

All breast reconstruction patients are followed longitudinally given the high percentage of revisions required and continually surveillance by the oncologic surgeons. In this study, patients are seen weekly postoperatively for one month and then every month thereafter for three months, then every six months.

2.9 Bias & Blinding

2.9.1 Selection Bias

As mentioned previously, the randomization was performed using an online randomization software. Given that each patient represents their own control, selection bias is minimized.

2.9.2 Attrition Bias:

Every patient is seen and followed up at the same time intervals. Given that the study mainly focuses on JP outputs, patients must be followed at the clinic to remove drains which are sutured into place. This helps to prevent attrition bias.

2.9.3 Blinding

Surgeons and nursing staff assisting in the procedure were blinded throughout the entire operative intervention. The circulating nurse (not involved in the procedure) made the solution preoperatively, so they were not blinded to what are the contents of solutions “A” and “B”. The circulating nurse performs the randomization but is also blind to which solution is which.

Postoperatively, the breasts are labeled (A or B), and blinding were be maintained until data analysis. Drain outputs were measured daily by the patient and removed when they are below a standard output of less than 25cc/day for three consecutive days. The blinding/masking remained until data collection, even though once drains were removed no other intervention or change in clinical course was able to be performed. For data collection, the circulating nurse who created the solutions contacted the head of the trial (Dr. Tyler Safran) who will mark the breasts for data collection.

2.9.4 Contamination

The biggest issue encountered in the study is the lack of drain output reporting and inability to ensure accuracy of measurements even if all patients received JP form. To combat this issue, a standardized form was created for JP output reporting was given to all patients and they underwent drain teaching prior to leaving the hospital. The same nursing team, as well as the Plastic Surgery team rounding would go over the emptying and documenting protocol. The patient would empty and mark the output under supervision once before leaving hospital. At the first postoperative visit, the JP sheet was verified and any and all questions regarding the process were answered. Success was defined as >70% of enrolled patients measuring drains.

2.10 Sample Size

The study size was been estimated to be 82 included breasts (41 TXA group and 41 NS group). This has been calculated using a power of 80% and an alpha of 5%. To come to this calculation, the mean JP outputs were taken from the literature[15,23]. Additionally, another randomized control trial with a similar methodology found there to be 39% reduction in drain outputs[15,23]. We hypothesize a smaller % reduction of 20% to more realistically design our study. A 20% decrease still represents a very large change from baseline. To recruit these patients, a six-month inclusion period was anticipated.

2.11 Statistical Analysis

This study utilized SPSS (IBM, Armonk, New York) for all statistical calculations. Each group was compared to the contralateral for daily drain outputs. For the duration of drains an independent t-test will also be used. Additionally, independent t-tests were used for incidence of complications and duration of drains, as well as odds ratio calculations for all the complications. Descriptive statistics were calculated for demographics.

2.12 Ethics

Institutional review board (IRB) approval was obtained via St-Mary's Hospital (Montreal, Quebec) before the start of recruitment SMHC-20-16 . Additionally, a Health Canada no objection letter was received for the use of Tranexamic Acid in this context (**HC6-24-c248414).**

2.13 Funding

This study was performed without any external funding. The budget was covered by the department of Plastic Surgery at the Jewish General Hospital and St Mary's. Dr. Tyler Safran executed the study for completion his master's degree in Experimental Surgery. The TXA medication itself is a part of the surgical cardex at our institution. The secretary (Sura Appel) assisted in the consenting process and organization of the trial and received no additional fees.

CHAPTER 3: STUDY RESULTS

3.1 Patient Demographics:

All patients were recruited during a six-month period from January 2021 until June 2021 at the Jewish General Hospital plastic surgery clinic where all the patients are seen for their preoperative consultation. Amongst all participants, the mean age of the patients was 48 (RANGE: 30 – 70) with an average BMI of 24.2 (RANGE: 19.5 – 28.7). All patients were non-smokers, however this is not a strict exclusion criteria for inclusion. One patient (1.9%) had a prior lumpectomy to her breast with subsequent radiation therapy. No included patient had any significant co-morbidity including diabetes or was on immunosuppressant medication.

3.2 Surgical Details:

All included patients underwent bilateral mastectomies with immediate implant-based breast reconstruction. All patients underwent Nipple Sparing Mastectomy (n=53). No skin sparing mastectomies were performed. Thirty patients (56.6%) underwent prophylactic mastectomies for a genetic mutation, whereas 23 patients (43.4%) were diagnosed with unilateral active cancer and underwent adjunctive sentinel lymph node biopsies as a result. One breast (1.9%) was previously radiated after lumpectomy.

3.3 Feasibility Outcomes

3.3.1: Eligibility & Recruitment Outcomes:

Fifty-eight patients seen in consultation were deemed eligible to participate in the trial based on the abovementioned eligibility, inclusion and exclusion criteria. These patients were explained the trial at the time of preoperative consultation and were given the option to participate. Of the 58 patients that were deemed eligible to participate, 53 (90%) had consented to be a part of the clinical trial. No patient, once recruited, was removed, left, or became ineligible. This was deemed successful having been including >75% of screened patients.

3.3.2 Retention:

Once consented, all 53 patients were successfully recruited into the study and each breast was randomized. After randomization, 30 patients (56.6%) were randomized to receive TXA in their right breast and 23 patients (43.4%) to receive TXA in their left breast. No patient was lost to follow up. Drain data was only usable in 43 patients (81.1%) of patients for a variety of factors, given that only complete data sheets were included for statistical accuracy. These included inaccurate use of the provided drain sheet (n=6), forgot to list everyday their outputs (n=3), lost their drain sheet (n=1). Data on complications, follow up and surgical details was obtained for all patients.

3.4: Surgical Outcomes

In terms of surgical outcomes, 53 patients all underwent nipple-sparing mastectomies with immediate reconstruction. No reconstruction was performed with acellular dermal matrix or any dermal substitute. Additionally, all cases successfully underwent reconstruction after mastectomy completion. Twenty-three patients (43.4%) underwent a sentinel lymph node biopsy that was performed through a separate incision. Of these twenty-three, 10 (43.5%) had the SLNBs performed on the TXA treated side and 13 (56.5%) on the placebo. Twenty-two (41.5%) of patients underwent a skin-reduction (wise) mastectomy and the remainder (58.5%) through an infero-lateral incision. In all patients, identical implants were used on either side of the reconstruction (Mean size: 355.7cc). Mean follow up time is 69.8 weeks.

Table 1: Patient and Surgical Demographics

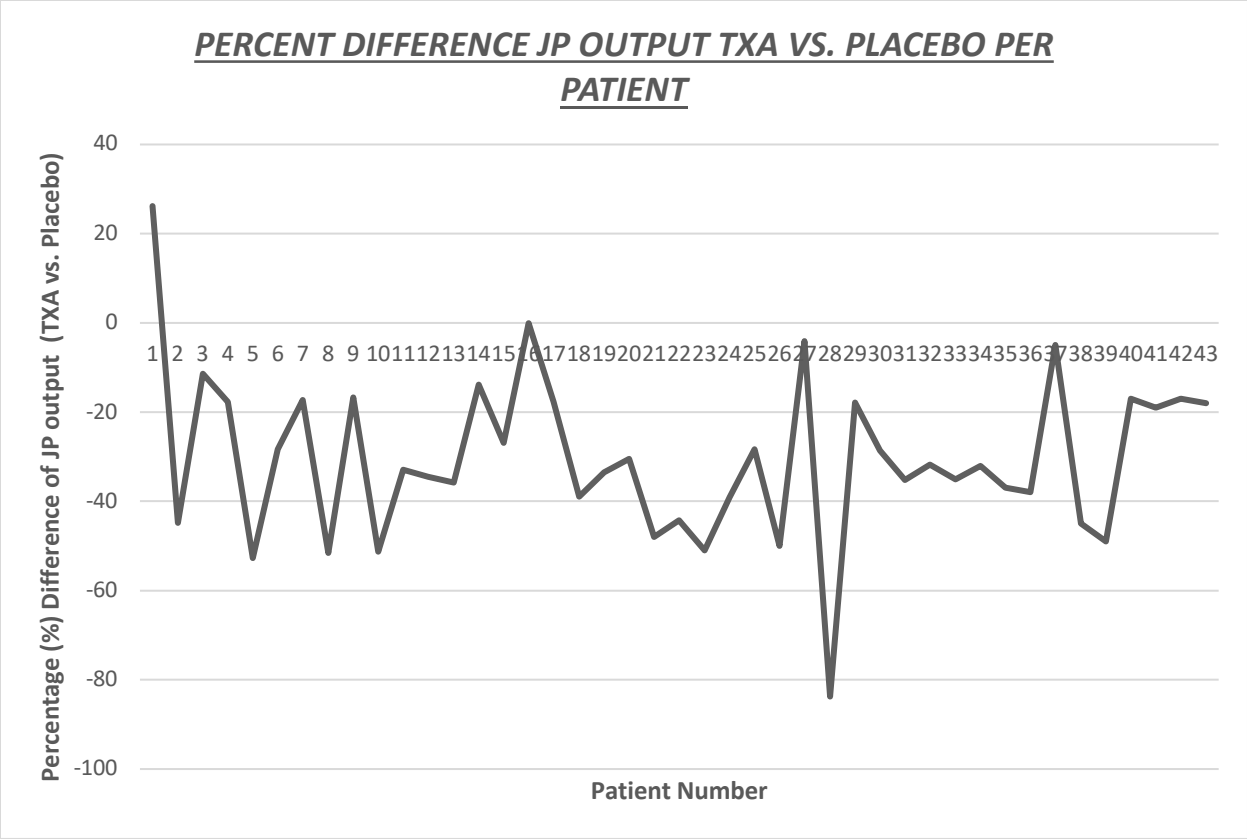
Number of Patients	53
Number of Breasts	106
Age (RANGE)	48 (30-70)
BMI (RANGE)	24.2 (19.5 – 28.7)
Prophylactic (%)	30 (56.6)
Active Cancer (%)	23 (43.4)
Prior Lumpectomy	1
SLNB	23
Inferolateral Incision (%)	31 (58.5)
Wise Pattern (%)	22 (41.5)
Mean Implant Size, cc	355.7

3.5: Primary Clinical Outcome

3.5.1 Percentage difference drain output

The primary clinical outcome measured was the percentage difference in JP drain output between the TXA and placebo treated breasts. After analysis of 53 patients, drain data was deemed usable in 43 (81.1%) of patients. The mean percentage difference was calculated to be TXA resulted in an average percent difference of 30.5% (RANGE: -83.6% - 26.6%). Only one patient (2.3%) had 26.20% more drainage on the TXA treated breast. All other patients reported less drainage on the side treated with TXA.

Figure 1: Percentage Difference JP output TXA vs. Placebo

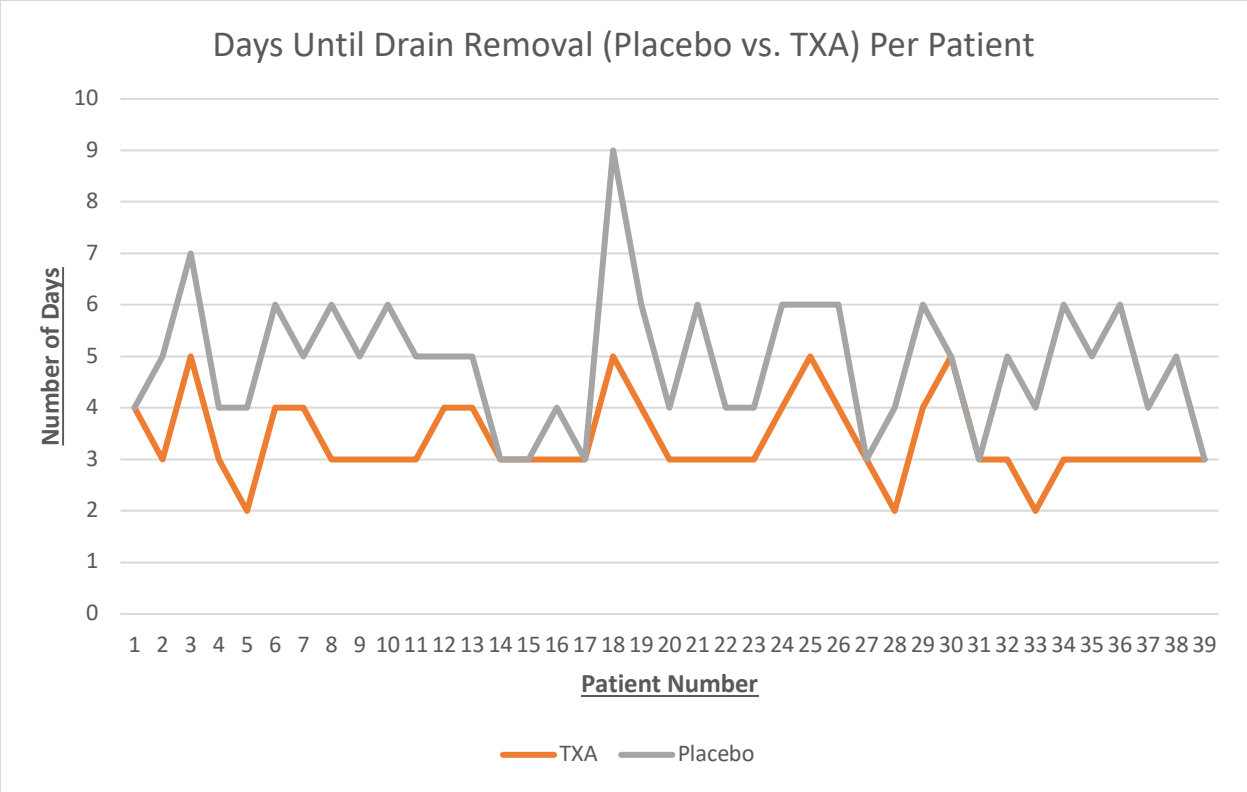


3.6 SECONDARY OUTCOMES:

3.6.1 Days until drain removal:

As mentioned in the methods, drains were eligible to be removed when the output was less than 25cc for two consecutive days. Drains on the TXA treated breast were eligible for removal an average of 1.4 (RANGE: 0-4) days sooner than placebo.

Figure 2: Days Difference until JP removal TXA vs. Control



3.6.2 Surgical Complications:

In terms of all complications, the TXA treated group had two complications (3.57%) versus 13 in the placebo group (28.3%) (Odds Ratio: 0.0993, p= 0.0032). Specifically, for operative hematomas, the TXA group had none (0%) versus three in the placebo group (5.7%) (Odds Ratio: 0.1348, P=0.18). Although patients are followed at different time points, at the time of analysis, severe capsular contracture was seen in seven breasts in the placebo group compared to one in the TXA treated group. Not all patients have had sufficient long term follow up to definitively state whether any late complications have occurred. Two of the cases (28.6%) of significant capsular contracture in the placebo

group, however, underwent post-mastectomy radiation therapy which could have contributed to the onset of capsular contracture. No significantly capsular contracture was present in bilateral breasts. No minor complications occurred in this cohort. Five of the complications (29.4%) occurred on the side that a sentinel lymph node biopsy was performed, however, it is always completed through a separate incision.

Table 2: Surgical Complications

Complications	TXA Group, N (%)	Control Group, N (%)	P-Value
Hematoma	0 (0.0)	3 (5.7)	0.24
Seroma	1 (1.9)	1 (1.9)	1.00
Pocket Infection	1 (1.9)	4 (7.5)	0.36
Capsular Contracture (Baker/Spear 3-4)	1 (1.9)	7 (13.2)	0.06
Mastectomy Skin Flap Necrosis	0 (0.0)	0 (0.0)	1.00
Minor Complications	0 (0.0)	0 (0.0)	1.00

CHAPTER 4: DISCUSSION

This paired, double-blinded, randomized placebo-controlled trial demonstrates that the use of topical TXA in immediate breast reconstruction decreases JP drain outputs, decreases overall complications, and decreases the time until drain removal. Over 100,000 women undergo implant-based breast reconstruction annually in the United States. It follows that efforts to improve surgical outcomes stand to benefit a substantial number of women, underscoring the potential widespread impact of the findings of this

study. As mentioned in the introduction, TXA represents a safe, low-cost, and effective modality to help improve outcomes in breast cancer reconstruction.

4.1: Trial Novelty

The impact of tranexamic acid on drain outputs post oncologic breast surgery has been shown in previous trials[31]. This, however, is the first trial that demonstrated and investigated its effectiveness in topical form and alloplastic breast reconstruction. Moreover, this is the only trial that was designed with each patient's breast having its own control and that is both randomized and prospective in nature. It is well known that drain outputs vary heavily on many patient and surgical factors such as mastectomy weight, patient's BMI, breast/adipose tissue ratio, use of electrocautery, and use of ADM[32,33]. By creating a matched trial, these factors are all controlled, and each breast is compared to its contralateral side that is similar in volume and tissue composition. Previous work in plastic surgery has shown that TXA may be effective in intravenous form in preventing hematomas in breast reconstruction, however this was shown in a small and retrospective study[34]. Aside from breast surgery, TXA has been shown to decrease JP outputs in facelift surgery and abdominoplasty[35]. Those surgeries, however, are performed with excision and re-arrangement of tissues only, whereas this study also examines the effects of TXA on a prosthetic device and the relationship with the dissected tissues.

In 1994, the first randomized controlled trial examining TXA on mastectomy and lumpectomy was performed[36]. They found that the IV dosing of 1 gram of TXA three times per day was associated with a significant decrease in postoperative drainage. Following suit, multiple other trials using TXA on breast surgery were performed, all concluding that it is effective. One RCT examined how topical TXA (25 mg/ml) would affect drain output in mastectomies without reconstruction[15]. As shown previously, they found that TXA significantly reduced mean drain production at 24 hours. Additionally, they found that one patient in the TXA group had early hematoma compared with seven in the placebo group (OR 0.13 (95% CI: [0.02 to 1.07]); $P = 0{\cdot}057$)[15]. These findings are indeed similar to the ones presented in this trial. Interestingly, the authors found that TXA was less effective in the subgroup of patients who underwent axillary dissection (AND), but not for those who underwent SLNB. This is likely due to the increased seroma potential and lymphatic drainage, but no patient in the current study underwent an ALND. Additionally, in all cases, the axillary procedures are always performed through a separate incision and maintain a tissue wall between the breast cavity and axillary space. One study examined how IV and PO TXA affected postoperative ALND drainage and found that TXA patients had significantly lower axillary drainage (440 ml vs 715.5 ml, P = .003) with earlier removal of the drain (8 vs 11 days, P = .046), seroma formation (19.1% vs 32.6%, P = .13) and wound-related infections (4.3% vs 8.7%, P = .43)[37]. Although administered IV, this is in contrast to the previous study that hypothesized the TXA could cause prolonged healing of lymphatic tissue via its antifibrinolytic activity. In the current study, however, there was a relatively equal distribution of patients who received TXA and had SLNB, with 43.5% (n=10) having had the SLNBs performed on the TXA treated side and 56.5% (n=13) on

the placebo). Moreover, only in one case (no SLNB performed) did the TXA treated side drain more. Lastly, in patients who undergo AND, they are often left with a separate JP drain and this could have had an effect on results. No patient was left with a drain after undergoing SLNB in this cohort.

Currently, in the plastic surgery literature, there is no RCT that examines topical TXA on breast surgery with implants. One study in breast reduction surgery found a 39% reduction in drain fluid when TXA was used topically in breast reductions[23]. Mastectomies, however, include much more aggressive dissection with transection of the major arterial supply to the breast skin[23]. Today, most plastic surgeons don't utilize drains after reduction mammaplasty, but it is globally agreed that drains are placed after alloplastic breast reconstruction due to the risk of implant pocket infection, biofilm, and prolonged drainage. One single-center, retrospective study examined topical TXA's effect in implant-based breast reconstruction. Patients who received topical TXA were significantly less likely to develop postoperative seromas (n = 28, 7.5%) than patients who did not receive TXA (n = 35, 12.5%) (P = 0.032). Furthermore, patients who received TXA also had their surgical drains removed significantly earlier (12.3 ± 4.3 days) than the patients who had not received topical TXA (13.1± 4.9 days) (P = 0.024). The rate of developing a hematoma among patients who received TXA (n = 3, 0.8%) was not significantly different than the control group (n = 5, 1.8%) (P = 0.256)[25]. This article, however, didn't control for mastectomy type, patient demographics, and reconstructive factors. These results are all similarly represented in the present trial. In the present study, although the difference in

hematoma rates were not statistically significant, there was a decrease between the groups. Hematomas are complication, albeit not as frequent as others, but may confer considerable morbidity necessitating surgical drainage and may also affect future results of the reconstruction. Another group examined how IV TXA affected implant-based breast reconstruction and found that patients who received TXA were less likely to develop hematomas (n = 1; 0.46%) than controls (n = 19; 2.9%)[24]. In addition, the rate of seroma in the tranexamic acid group was lower (*n* = 5 (2.3%)) than in the group that did not receive tranexamic acid (*n* = 28 (4.3%)), although this was not statistically significant (*p* = 0.093)[24].

Aside from breast surgery, there is literature showing a benefit of topical TXA in a variety of procedures. One procedure found to benefit greatly from the addition of TXA has been liposuction[38,39]. Multiple studies have shown a decrease in postoperative ecchymosis and drain output when TXA was either injected into the surgical site or administered intravenously. In facial surgery, one systematic review found that TXA was associated with a decrease in drain outputs and less ecchymosis in rhinoplasty, blepharoplasty, and facelift procedures[40]. In all, TXA likely represents a safe and effective adjunct to plastic surgical procedures, however until now has not been shown in a paired, double-blinded randomized controlled trial.

4.2 Mechanism of Effect

This study demonstrated that TXA was able to decrease overall drain output which includes residual bleeding immediately postoperatively but then transitions to serous fluid over the course of JP insertion. Seroma or serous fluid is hypothesized to stem primarily from the inflammatory reaction following surgically induced trauma, which increases in response to fibrinolytic activity in serum and lymph[41]. Compared to mastectomy without reconstruction, any prosthetic device insertion has been shown to decrease the incidence of seroma likely due to the dead space being obliterated by the implant[41]. Moreover, one prospective trial found that women undergoing immediate breast reconstruction may decrease the risk of lymphedema compared to non-reconstructed patients[42]. This trial, however, aims to view TXA's effect on decreasing additional serous and sanguineous drainage in reconstructed patients. Seroma fluid has been also said to increase with the use of excessive electrocauterization, increase in friable adipose in the pocket, larger pockets, and higher BMI[32]. Interestingly, some adjunctive medications have been shown to decrease seroma formation in animal models, including Fibrin glue, light-activated fibrin sealant, and transdermal photo-polymerized adhesive. Topical hemostatic agents range from physical agents to biologically active agents, however, all differ from TXA in their effect and mechanism of action.

Oxidized regenerated cellulose (Surgicel) is one physical agent that gets resorbed by 14 days. Additionally, it has been shown to have bactericidal activity due to its acidic Ph, which has also been shown to inhibit proteases and elastase in chronic wounds[43]. Unfortunately, any residual product in the wound has been associated with infection,

scarring, and adhesion formation, which would be extremely detrimental in the alloplastic reconstructed breast. In one study, unabsorbed oxidized regenerated cellulose was identified as a risk factor for pelvic abscesses and was found in the pelvis more than one year after it was placed[44]. Gelatin matrices, with or without topical thrombin additives, are effective at stropping bleeding but need to be removed completely to avoid any infection, granuloma, and fibrosis formation. Additionally, there is the added potential for traumatic disruption of the clot if the sponge is removed[45].

Biologically active agents include TXA, but also include thrombin and fibrin sealants. One systematic review of outcomes using fibrin sealant demonstrated that breast RCTs (n=1277 patients) (not limited to mastectomy or reconstruction) had a non-significant reduced risk of developing seroma than the control group (OR 0.84, 95% CI (0.64 to 1.11), $p = 0.26$)[46]. One RCT examined the use of hemoblast (Biom'Up, Paris, France) which is a topical spray comprised of porcine collagen, chondroitin sulfate, and thrombin. They found that compared to placebo, the use of hemoblast resulted in decreased incidence of seroma, hematoma, and return to OR, especially in the mastectomy group. They record an 8.7% seroma rate and 0% return to OR rate in the hemoblast group (n = 23), as compared to 17.4% seroma and 13% return to OR rate in the non-hemostatic agent group (n = 23). These were without statistical significance, but the authors believed this to be attributed to smaller sample size. Additionally, JP drain duration was statistically significantly decreased in the hemoblast group as compared to the non-hemostatic agent group among oncoplastic (5 vs 11.4 days, $P < .01$), mastectomy (12.7 vs 30.4 days, $P <$

.01), and expander exchange (2 vs 14.8 days, $P < .01$) operations[47]. One study examined the effect of fibrin spray and topical thrombin on capsule formation in rabbits. While the fibrin spray exhibited lower rates of capsular contracture, decreased capsular thickness, and intracapsular pressures compared to placebo, topical thrombin did not exhibit such large differences. The authors of this study attribute these findings to the fact that thrombin requires active bleeding to activate, which in a normal mastectomy should be completely devoid of active bleeding prior to insertion of the implant. Additionally, the anti-inflammatory properties of the fibrin spray are more likely the culprit in the decreased capsule formation. In all, TXA in comparison has been shown to exhibit not only anti-inflammatory but platelet stabilizing properties[48]. In all, hemostatic agents are primarily employed to help achieve hemostasis, and the use of each category is usually guided by the amount and rate of bleeding in the surgical field. For the purpose of breast reconstruction with implants, TXA is extremely well suited.

Tranexamic acid is hypothesized to decrease serous output by decreasing residual blood in the pocket through its clot-stabilizing properties and through its anti-inflammatory properties[13]. By decreasing the conversion of plasminogen to plasmin, TXA prevents the fibrin degradation. Plasminogen binds not only to fibrin, causing fibrinolysis, but also to receptors on cells involved in the inflammation process, such as monocytes, macrophages, neutrophils, endothelial cells, and platelets[49]. As such, existing blood clots are stabilized by stabilizing the fibrin matrix and even improve platelet function[50]. This is why the TXA is placed after meticulous hemostasis is achieved and clots and platelet

plugs have formed on prior surgical bleeding sites. This, as mentioned, differs from other hemostatic products which require active bleeding to be activated. Additionally, postoperatively, any residual blood is very inflammatory and has high oncotic pressure. Both these factors lead to increased serous production into the breast cavity which increases JP outputs. Residual blood in the breast pocket has been shown to very high in pro-inflammatory cytokines. The residual blood is hypothesized to stem acutely from surgical dissection, dislodging of clots postoperatively, or in rare cases after erosion of vessels from persistent inflammation and capsule formation[51].

As mentioned previously, TXA has been shown to demonstrate a variety of anti-inflammatory properties. One of the most common complications in Implant based breast reconstruction is capsular contracture (excessive periprosthetic scarring). This is hypothesized to arise from either a subclinical bacterial contamination of the implant surface or a persistent inflammatory reaction[7]. Interestingly, the secondary outcome examining complications found that the breasts treated with TXA had significantly less capsular contracture and complications overall. Any implant placed in the body elicits an inflammatory foreign body reaction. In the case of breast implants, this reaction leads to the formation of a fibrous capsule surrounding the device[7]. Optimally, the implant capsule remains benign and presents no concerns. However, in response to sustained inflammation (via blood or sub-clinical bacterial infection), the capsule may become fibrotic, culminating in capsular contracture that causes significant pain and deformity around the breast implant[7]. This deformity, in alloplastic breast reconstruction has been

described to occur in up to 14% of patients and is considered to be the most common complication after implant-based breast reconstruction. This complication, if deemed significant as per grading scales, requires a surgical intervention to break up the capsule (capsulotomy) or remove it (capsulectomy) and possibly exchange the implant[7]. That intervention is not only costly to the hospital system, but also requires patients to undergo another postoperative rehabilitation. This study demonstrated that the TXA treated breasts exhibited less significant capsular contracture (7 in placebo group vs. 1 in TXA). This effect can be a response to the decrease inflammation from the TXA itself, or the decrease in fluid that is both inflammatory and excellent nidus for infection. The non-significance of this difference, albeit approaching significance, is likely due to the small sample size.

This anti-inflammatory effect of TXA was demonstrated in one RCT in patients undergoing total knee arthroplasty[52]. When comparing IV TXA to placebo, there was decreased peri-operative blood loss, transfusion rates, and dynamic pain[52]. Interestingly, when analyzed they found decreased systemic levels of FDP, D-dimer, CRP, and IL-6 as well[52]. Clinically, studies in plastic surgery have found that TXA administration improves ecchymosis and other inflammatory responses[35]. The anti-inflammatory properties of TXA originate by blocking plasmin activation of the complement cascade[35]. Studies have shown that TXA led to less upregulation of proinflammatory genes and increase in anti-inflammatory genes[13,14]. In this study it was noted subjectively that breasts treated with TXA exhibited

less ecchymosis on initial follow up. TXA is now used by the senior surgeon in a variety of procedures.

4.3 Historic Use & Dosing

Historically there are three antifibrinolytic drugs that have been used: TXA, E-Aminocaproic Acid and Aprotinin[53]. Although all three have demonstrated reduced bleeding and transfusions previously. Aprotinin, a nonspecific serine protease, was withdrawn in 2008 from the market after the Blood Conservation Using Antifibrinolytic Randomized Trial demonstrated increased systematic risks from its use[54].

The CRASH series of trials demonstrated that TXA significantly reduced head-injury related deaths after traumatic brain injury[55]. Moreover, to date, no study in the plastic surgery literature has demonstrated any adverse event related directly to the use of TXA. IV administration, however, has been shown previously to possibly be linked with the incidence of seizures[56]. Topical administration avoids this issue by providing a high-concentration to the surgical site without major systemic absorption. One meta-analysis demonstrated that in 29 trials, topical TXA reduced blood loss by 29% and the risk of blood transfusion by 45%[57]. These findings were then reiterated in another meta-analysis of 67 RCTs[16].

In a recent systematic review on TXA in plastic surgery, they reviewed the possible dosing for topical administration[35]. In one double-blind randomized controlled trial, high-dose (3 g) topical tranexamic acid has higher potency in reducing blood loss after total knee arthroplasty compared with low dose (500 mg)[21]. It showed a reduction of 43% without any significant complications[21]. Additionally, the US department of Veterans Affairs released dosing guidelines for topical irrigation, including 3 grams in a 70cc dilution for a total of 100cc[58]. Since, it has become almost standard of care to utilize any route of TXA in a variety of orthopedic surgery techniques. Also, in the orthopedic literature, TXA's effect on chondrocytes was examined in order to characterize its effect on adjacent tissues[59]. It was determined that chondrocyte toxicity increased with both concentration and exposure with a 20-25mg/ml dose being the threshold, however the cells were exposed for over 48 hours[59]. Another study demonstrated that re-epithelialization was completely absent in wounds chronically exposed to topical TXA in concentrations of 25 mg/ml or above, and at 50–100 mg/ml induced epidermolysis of normal epithelium, possibly by a non-toxic mechanism[60]. Wound re-epithelialization was slightly delayed, but not impaired, by limited exposure to 100 mg/ml or chronic exposure to 25 mg/ml[60]. In this trial, the concentration used was 3000mg/100ml for limited exposure, which avoids the possible side effect profile seen in this trial. Additionally, in practice, the chronic exposure can be avoided by letting TXA solution soak for five minutes and then employing the betadine or triple antibiotic wash to remove any residual solution.

In terms of systemic absorption, one study of patients undergoing abdominoplasty compared topical moistening the wound surface, retrograde infusion of a bolus through the wound and IV infusion[61]. Either of the topical methods results in a mean maximum systemic level of 5 μg/mL, which is below the 10-μg/ mL limit considered to cause any systemic antifibrinolytic effect[61].

4.4 CONFOUNDERS:

While the study described herein was optimized as much as possible, we recognize that there exist a variety of possible confounding factors found in the trial. Firstly, the hand dominance of the patient could theoretically influence drain output given increase in movement and use, however we did not examine this finding nor has it been described in literature. It is hypothesized that increase activity on one side versus the other may predispose the patient for increased drain output given the activation of the adjacent musculature. Secondly, pre-operative radiation may also have influence on postoperative drain output, but this was only seen in one individual breast and as such we believe that it will have a negligible impact on our results. Lastly, we cannot control for any variability in activity, trauma, or wound care between patients that occurs at home. For instance, concerning JP management, it is hypothesized that by consistently ensuring negative suction on the JP bulb, it would promote more drainage from the breast and could possibly distort numbers compared to the contralateral side. This difference, if arose, would likely be due variations on how frequently patients empty their JP bulbs. Additionally, it is important to standardize the teaching that each patient receives. Differences in how the

JP is squeezed and how often it is emptied has also been shown to differ in suction potential[62]. With incremental filling of the suction bulb, there is a decrease in suction. Patients may be more liberal with activities or sleeping habits which may have influence on drain outputs. The study also is designed to have patients record their own drain outputs. This process can be both cumbersome and may not be fully taken serious by the patients themselves. Although there is a demonstrable difference in JP quantities and complications, it is still a possible confounder that must be taken into account.

4.5 FUTURE DIRECTIONS & CLINICAL IMPLICATIONS

This study successfully demonstrates that soaking the mastectomy pocket with topical TXA in alloplastic breast reconstruction primarily reduces JP drain output and decreases overall complications. Although topical TXA is more costly than its IV formulation (based on increase dosage requirements), it still represents a safe and effective mechanism to decrease postoperative bleeding, drain output and possibly capsular contracture[63]. This study could have large implications and topical TXA may become a gold standard in all alloplastic breast procedures. In terms of future directions, these patients will continue to be followed and another study examining the chronic or long-term complications will be performed to better elicit the long-term effects of TXA on the breast. It is hypothesized that the TXA treated side will persistently exhibit less capsular contracture compared to the contralateral breast given the less inflammatory milieu. Additionally, future histological studies examining the effect of TXA on capsule formation should be performed. In patients that undergo revision surgery for a variety of reasons can have biopsies

specimens of their capsules taken, stained for inflammatory markers and compared grossly to the contralateral breast. This analysis would allow for histological and biochemical evidence of anti-inflammatory effects of TXA. Studies examining the effect of topical TXA on the perfusion of the mastectomy flaps should be performed. Although TXA is not a procoagulant and has not been shown to affect perfusion of the mastectomy flaps, it would be helpful to demonstrate that, through perfusion imaging, it would not have any effect on perfusion. Lastly, one device that is hypothesized to decrease capsular contracture is an Acellular Dermal Matrix. This cadaveric dermis is expensive, may increase the risk of seroma and pocket infection, and have received recent warnings from the FDA for its possible risk of complications[18,64]. TXA may be one of the adjuncts that can help replace the need for regenerative tissue matrices by eliminating the culprit in the first place. It represents a cheap, safe, and effective method at preventing complications. Based on the results of this study, TXA may become part of the gold standard of care in any alloplastic procedure. It can be argued, however, that in most centers the gold standard of alloplastic reconstruction is a two-staged reconstruction with the use of ADM. For this study to be generalizable, it should be performed in a variety of alloplastic techniques, not just limited to direct-to-implant prepectoral breast reconstruction.

4.6 LIMITATIONS:

4.6.1 Data Quality:

This study is not without limitations. One of the major limitations of the primary clinical outcome we assessed was the patient derived data reliability given that patients were given a drain output sheet and asked to write down their outputs. Unfortunately, drain data was only usable in 43 patients (81.1%) of patients for a variety of factors as mentioned in the results. These included inaccurate use of the provided drain sheet (n=6), inaccurate reporting (n=3), lost their drain sheet (n=1). The investigators repeatedly reminded patients to keep track of their outputs and each patient received teaching prior to discirculating from hospital, but this was not always the case. In contrast, secondary outcomes were less subject to this limitation given that they were objective measures taken from the patients' chart and from follow-up visits.

4.6.2 Surgical Technique

Although the reconstructive procedure was indeed performed by a single reconstructive surgeon, the mastectomies were performed by a variety of general surgeons. Variations in plane, mastectomy technique and experience of the oncologic surgeon could bias many factors. Moreover, each side of the patient represents an individual breast with some variation and can be subject to technical variation. Thin flaps can lead to increased complications including flap necrosis[64]. Any vascular insult to the flaps can also lead to issues longer term, including capsular contracture and increase risk of infection. Variations in mastectomy flap are mitigated by the fact that each patient (two breasts) is operated on by the same oncologic surgeon. Lastly, although each breast undergoes meticulous hemostasis, it is impossible to ensure that every single possible vessel is

cauterized in the breast, balancing the possible residual thermal damage. Some vessels, given the epinephrine from the blocks, can be constricted and may only bleed postoperatively.

5.0 Conclusion

In conclusion, this paired, double blind, randomized controlled trial has shown that topical soaking of TXA into the mastectomy pocket prior to implant insertion leads to significantly decreased JP output, decrease in JP insertion length and decreased complications. This medication represents a cost-effective, safe, and effective adjunct that should be used in all alloplastic breast reconstructions. Future studies will continue to examine the long-term effects of TXA on outcomes and the breast capsule.

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APPENDICES

APPENDIX A

/CONSORT 2010 checklist of information to include when reporting a randomised trial*

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	9
	2b	Specific objectives or hypotheses	17
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	17
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	18
Participants	4a	Eligibility criteria for participants	19
	4b	Settings and locations where the data were collected	20
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	21
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	22
	6b	Any changes to trial outcomes after the trial commenced, with reasons	22
Sample size	7a	How sample size was determined	27
	7b	When applicable, explanation of any interim analyses and stopping guidelines	24
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	24
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	24
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	25
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	25
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	26
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	26
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	27
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	29
	13b	For each group, losses and exclusions after randomisation, together with reasons	30
Recruitment	14a	Dates defining the periods of recruitment and follow-up	31
	14b	Why the trial ended or was stopped	33
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	29
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	32
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	33
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	31
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	33
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	35
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	36
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	38
Other information			
Registration	23	Registration number and name of trial registry	60
Protocol	24	Where the full trial protocol can be accessed, if available	60
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

APPENDIX B

Hôpital général juif
Jewish General Hospital

Jackson-Pratt (JP) Drain Output Sheet

Group:_____. Surgery date: _____. ADM:_____.

Date.	Time	JP Outputs		Date.	Time	JP Outputs		Date.	Time	JP Outputs	

APPENDIX C

INFORMATION AND CONSENT FORM

Title of the research project:	Effects of Topical Tranexamic Acid in Immediate Prepectoral Breast Reconstruction: A Paired, Double-Blind, Randomized Control Trial
Principal investigator:	Tassos Dionisopoulos MD FRCSC
Co-researcher(s):	Tyler Safran MD
Member(s) of research staff:	Joshua Vorstenbosch MD PHD FRCSC
Sponsor or granting agency:	Not funded
Protocol number:	*SMHC-20-16*

1. Introduction

We invite you to participate in a research project. However, before agreeing to participate in this project and signing this information and consent form, please take the time to read, understand and carefully consider the following information.

This form may contain words you do not understand. We invite you to ask any questions that you may have to the researcher in circulating of this project or to a member of its research staff and to ask them to explain anything that is not clear.

2. Nature and objectives of the research project

You are being asked to consent to participate in a research study that will investigate the use of tranexamic acid (TXA) as a topical (applied directly to the body after surgery) solution in your breast reconstruction surgery. Our study goal is to make breast cancer surgery safer and improve outcomes for all patients.

TXA is a medication used to treat or prevent excessive blood loss. Normally, TXA is taken orally (by mouth) or intravenously (in a vein) but we want to see how effective it is when applied directly to the body (topically). In other studies, when TXA alone was used to treat mastectomy patients there were significantly fewer bleeding complications.

Our overall goal is to see if TXA administered topically will offer a better alternative to the present standard of care (saline).Currently, we clean out the breast pocket after the mastectomy with saltwater (normal saline) after making sure that all bleeding is stopped. This study would soak tranexamic acid (TXA) in one breast pocket, in hopes that it will improve clot formation and preservation as well as to make sure no bleeding happens after the surgery. The other breast would be soaked with only saltwater (normal saline) as a comparison.

It is the standard of care to use Jackson Pratt drains to collect bodily fluid from the surgical site. These drains can be bothersome and represent a risk of infection should they be kept in place for too long. We will look primarily at the output of your Jackson Pratt (JP) drains that will be placed during the surgery to reduce fluid collection and also look at how your recovery proceeds. We are hoping to show that using TXA will both reduce the length of time that these drains are kept in place and lower the rate of bleeding after surgery. We hope that the use of TXA could decrease the need for further surgeries, bleeding and drain output, thus reducing the need for drains or the duration they are kept in for. 100ml of saltwater will be placed in one breast and 100cc of TXA solution (30cc TXA (3Grams) with 70cc of salt water).

We plan to recruit 50 participants, women, aged above 18 years old for this research project.

3. Conduct of the research project

3.1 Location of the research project, duration and number of visits

This research project will take place at St. Mary's Hospital Center. Your participation in this project will last 24 months and will include 12 visits that will coincide with your regular follow up visits. Therefore, should you choose to participate, there will be no difference from your regular standard of care follow up appointments.

3.2 Nature of your participation

You are having surgery on both of your breasts. Should you agree to participate in this study, one breast will be randomized to receive topical tranexamic acid (TXA), while the other will receive normal saltwater solution (also known as saline). The saline solution is the standard of care, meaning all patients have the saline solution applied after this type of surgery.

Apart from the use of the TXA solution, your surgery will be conducted in exactly the same manner as it would if you did not participate in the research study. Only the operating room nurse will know which breast gets which solution. You will not know, nor will your surgeon know until the beginning of data analysis.

We will be evaluating three main outcomes:

(1) The output of your drains which you will be recording as you part of your normal process of emptying them regularly both after the surgery and the day they are removed.

(2) Any occurrence of complications.

(3) The results of your surgery follow-ups at 1 month, 6 months, 1 year intervals and up to five years if this is deemed necessary.

Your medical records will be consulted, and information may be collected for your research file in order to measure the above outcomes (see section 8: Confidentiality).

4. Disadvantages associated with the research project

There are no disadvantages to participation.

5. Risks associated with the research project

The research team believes that participating in this research project carries little risk to you, however there may be unknown risks associated with the use of TXA topically.

Orthopedic, dental and trauma literature indicate here already are a large number of patients who have had TXA applied topically (in solution) in They all have shown good results without any increased risk of complications.

The overall complications of breast reconstruction surgery, aside from bleeding include: Seroma (fluid collection), infection, poor scarring, and implant issues. The risk of these occurring is the same regardless of participation.

Although not proven in any clinical studies, there may be a risk of decreased wound healing in patients receiving high dose tranexamic acid for longer periods of time. You will only receive TXA once, at the time of your surgery.

6. Benefits associated with the research project

You will receive no personal benefit from your participation in this research project. However, we hope the results obtained will contribute to the advancement of scientific knowledge in this area of research.

7. Voluntary participation and possibility of withdrawal

Your participation in this research project is voluntary. You are therefore free to refuse to participate. You can also withdraw from this project at any time. You do not have to give reasons. You need only to inform the research team.

Your decision not to participate in or withdraw from this research project will not affect the quality of care and services to which you are entitled or your relationship with the teams providing them.

The researcher in circulating of the research project, the St. Mary's Hospital Center Research Ethics Committee may terminate your participation, without your consent. This can happen if new discoveries or information indicate that your participation in the project is no longer in your interest, if you do not follow the instructions of the research project, or if there are administrative reasons for abandoning the project.

If you withdraw from the project or are withdrawn from the project, the information and materials already collected under this project will nevertheless be retained, analyzed or used to ensure the integrity of the project.

Any new knowledge gained during the course of the project that could have an impact on your decision to continue to participate in this project will be communicated to you quickly.

8. Confidentiality

During your participation in this research project, the researcher in circulating of this project, as well as the members of its research staff will gather, in a research file, the information concerning you and necessary to meet the scientific objectives of this research project.

This research file includes the following: information about your past and present health status, your lifestyle, and the results of all tests, examinations and procedures that will be performed. Additionally, surgical details, any complications, re-operations and drain outputs will be included. Your file also includes the following personal information: your name, gender, date of birth and ethnicity.

All information collected will remain confidential to the extent permitted by law. In order to preserve your identity and the confidentiality of this information, you will only be identified by a code number.The key code linking your name to your data will be kept by the researchers in circulating of the study in a password-protected document. Only the principal investigator and authorized members of the research team will have access to this key.

To ensure safety, a copy of the information and consent form will be added to your medical record. Therefore, any person or company that has access to your medical record will also have access to this information.

These research data will be kept for a maximum period of 25 years after the end of the study by the researcher responsible for this research project. Research data may be published or scientifically discussed, but it will not be possible to identify you from the data alone.

For purposes of surveillance, control, protection, security, your research folder will be accessible by a person mandated by regulatory agencies, by the institution or by the St. Mary's Hospital Center Research Ethics Committee. These individuals and organizations adhere to a privacy policy.

You have the right to consult your research file to verify the information collected and to have it corrected if necessary. However, access to certain information before the end of the study could require that you are removed from the project in order to preserve its integrity.

9. Possibility of marketing

Research results resulting from your participation may lead to the creation of commercial products. However, you will not receive any financial benefit.

10. Financing of the research project

This project is self-financed by the division of Plastic Surgery at St-Mary's Hospital.

11. Compensation

You will not receive financial compensation for participating in this research study.

12. In case of harm

Should you suffer harm of any kind following administration of the study drug, or following any other procedure related to the research study, you will receive the appropriate care and services required by your state of health.

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the researcher in circulating of this research study or the institution, of their civil and professional responsibilities.

13. Identification of contacts

If you have questions or experience problems in connection with the research project or if you want to be removed from participation, you can contact the researcher in circulating of the research project or a member of the research staff at the following number: *514-734-9969*

14. Complaints

For questions about your rights as a participant in this research project or if you have any complaints or comments, you can contact the Commissioner for Complaints and Quality Services CIUSSS de l'Ouest-de-l'Île-de-Montréal at 1-844-630-5125 or by email at commissariat.plaintes.comtl@ssss.gouv.qc.ca.

15. Declaration of interests

The principal investigator states that he has no personal interest that could conflict with his role as a researcher.

16. Monitoring of the ethical aspects of the research project

The St. Mary's Hospital Center Research Ethics Committee approved the research project and assures monitoring.

17. Secondary Endpoints:

This consent also includes access to your chart and operative course for further analysis and possible evaluation. All confidentiality and terms still apply.

Declaration of Consent

Title of research project:	**Effects of Topical Tranexamic Acid in Immediate Prepectoral Breast Reconstruction: A Paired, Double-Blind, Randomized Control Trial**

Future research projects (secondary use)

Do you agree that your research data be used by the researcher in circulating of the main research project to carry out other research projects in the same research area? This secondary use will comply with the data use conditions mentioned in the Informed Consent Form, including section 8 on confidentiality and destruction date requirements. Only research projects that have obtained ethics approval will be allowed to use your data for secondary use.

☐Yes ☐No

Participant's consent

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

I authorize the research study team to have access to my medical record for the purposes of this study.

Name and signature of participant Date

Signature of the person who obtained the consent (if different from the Principal investigator)

I explained to the participant the research project and this information and consent form and I answered the questions s/he asked me.

Name and signature of the person obtaining consent Date

Signature and commitment of the Principal investigator

I undertake, together with the research team, to respect what was agreed upon in the information and consent form, and to give a signed and dated copy of this form to the research participant.]

Name and signature of the Principal investigator Date

APPENDIX D

CONSULTATION
JGH Breast Reconstruction

1) Age

2) Referring physician Dr. Anderson Dr. Basik Dr. Boileau
Dr. Brabant Dr. Wong Dr. Prakash

3) Reason for referral

4) Past medical history (please list) Prior radiation to chest? Yes No

5) Past surgical history (please list) a) Prior lumpectomy? Yes No

b) Other breast surgery? Yes No

6) Smoking history (PPD-years) Actively smoking? Yes No

7) Family history (FHx) BRCA carrier 1 2 OTHER:

8) Indication for surgery Cancer Prophylaxis

9) Reason if prophylaxis BRCA Strong FHx

Other (please indicate)

10) Neoadjuvant Chemotherapy Radiation therapy Hormonal therapy

11) Pathology on biopsy DCIS LCIS Carcinoma Other

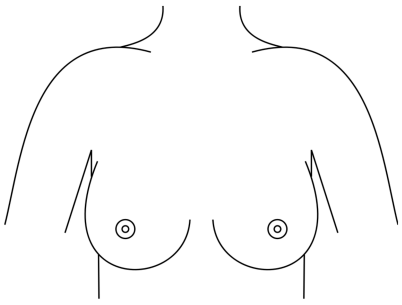
12) Acceptable for immediate reconstruction? Yes No

13) Surgical plan (indicate plan for cancer-affected and contralateral breast)

Cancer

Right or Left

☐ NSM
☐ SSM
☐ Oncoplastic



Contralateral

Right or Left

☐ NSM
☐ SSM
☐ Oncoplastic
☐ Augmentation
☐ Reduction
☐ Mastopexy
☐ No surgery

OPERATIVE NOTE
JGH Breast Reconstruction Database

1) OR date (yy/mm/dd)

2) General Surgeon Dr. Anderson, Dr. Basik, Dr. Boileau, Dr. Brabant, Dr. Wong, Dr. Prakash

3) Site JGH, St-Mary's

4) Reconstruction type Immediate, Delayed

5) Cancer location Right breast, Left breast

	Cancer side	**Contralateral side**
6) Mastectomy type	NSM SSM Oncoplastic mastectomy Oncoplastic lumpectomy	NSM SSM Oncoplastic mastectomy Augmentation Reduction Mastopexy No surgery
7) Incision	Lateral breast IMF Wise pattern	Lateral breast IMF Wise pattern
8) Free-nipple graft	Yes No	Yes No
8) Sentinel lymph node	Yes No	
If YES	Positive Negative	
9) Skin flap thickness	Thin Medium Thick	Thin Medium Thick
10) Specimen weight (g)		
11) Skin flap concerns	Yes No	Yes No
If YES	Cautery burn Erythema Nipple congestion Other:	Cautery burn Erythema Nipple congestion Other:

12) Implant sticker (place on back)

13) ADM sticker (place on back)

14) Nitro paste Yes No