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A Double-Blinded Prospective Randomised Controlled Trial to Assess the Efficacy of Glubran-2 in Reducing Seroma Formation after a Mastectomy with or without Axillary Dissection

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Abstract

Background and Purpose: Seroma formation is a common complication following a mastectomy and axillary surgery. Decreasing the dead space is believed to decrease seroma formation. The aim of this study is to compare the incidence of seroma formation with the use of Glubran-2 versus normal saline during the wound closure in participants undergoing mastectomy with or without axillary dissection. **Methods:** This multicentre, prospective, double-blinded, randomised controlled trial, enrolled women 18 years of age or older with breast cancer, who were underwent total or partial mastectomy, with or without axillary dissection. Participants were randomised to Glubran-2 or Saline arm. The primary outcome was the volume and duration of wound seroma. Secondary outcome was post-operative wound infection. **Results:** A total of 76 women were randomised and there was no loss to follow-up or mortality. The total seroma volume was higher in the Glubran-2 arm. The duration of seroma was higher in the mastectomy and axillary dissection group in the Glubran-2 arm ($P = 0.69$). Elderly and participants with higher BMI had a higher volume of seroma. Post-operative infection rate was higher in the Glubran-2 arm (13.2% vs. 5.6%; $P = 0.26$). There was no statistically significant difference between the groups. **Conclusion:** Our study did not show any benefit with the use of Glubran-2 in mastectomy and axillary surgery in reducing the risk of seroma formation. In elderly and obese participants the use of Glubran-2 showed an increase in seroma formation and post-operative wound infection.

Keywords

Breast Cancer, Mastectomy, Axillary Dissection, Seroma, Glubran, Cyanoacrylate Glue

1. Introduction

Seroma formation is a common complication following a mastectomy and axillary dissection with an incidence reported between 5% and 90% [1]-[7]. Despite most seroma resolve within a few weeks, it often causes patient discomfort and other unnecessary complications such as infection and delayed wound healing. These complications can further delay commencement of adjuvant treatment and can also affect the overall patient recovery [1] [3] [5] [6] [7].

The risk factors for seroma formation include obesity, age, hypertension, breast volume, and use of electro-cautery [2] [8]. Some studies have reported that decreasing the dead space after surgery reduces seroma formation [6] [9] [10]. Several techniques have been trialled including drains, quilting sutures, fibrin glue, tetracycline sclerosing agents, methylprednisolone, and somatostatin analogues to reduce the dead space, volume and duration of seroma [2] [6] [7] [9]-[18]. Although some authors have reported that reducing the dead space minimises volume and duration of seroma, to date there is no general consensus in a single technique to reduce the risk of seroma formation [9] [10] [11].

More recently Glubran-2, which is a synthetic biodegradable cyanoacrylate based glue has been used in a wide number of surgical procedures. Glubran-2 polymerises rapidly on contact and firmly adheres to the tissues. It is reported to have good haemostatic and adhesive properties [18]-[24]. This adhesive property can obliterate the dead space after mastectomy and axillary dissection.

This prospective double-blinded randomised controlled trial compares the incidence of seroma formation with the use of Glubran-2 versus normal saline during the wound closure in participants undergoing total or partial mastectomy with or without axillary dissection.

2. Methods

2.1. Study Design

We conducted a multicentre prospective double-blinded randomised controlled trial involving 76 women. The inclusion criteria were that participants are 18 years of age or older, who had breast cancer of stage 0 to III, and in whom the diagnosis had been confirmed using biopsy (Fine needle or Core-needle biopsy).

The study was conducted across three hospitals in Adelaide, Australia. Human Research Ethics Committee at the three participating hospitals granted ethics approval. Glubran-2 and saline spray was supplied by Matrix Surgical Australia.

Exclusion criteria for the study was neoadjuvant therapy, previous ipsilateral breast cancer, and on immunosuppressive therapy. Post-surgery participants were excluded if they developed post-operative haematoma requiring return to operating theatre for evacuation. Four experienced breast surgeons performed all the procedures.

2.2. Recruitment

The participants were enrolled in the study between the periods of 1st August 2015 till 31st October 2016. The surgeons identified potential participants at the time they were diagnosed at one of the three participating hospitals. Out of 104 patients who were assessed 76 met the inclusion criteria (Flow Diagram). Participants who met the inclusion criteria received a study and participant information sheet. After the selection criteria were satisfied, the consultant surgeon obtained a written informed consent and baseline data.

2.3. Randomisation

Eligible participants were enrolled in the study, with stratification into either Glubran-2 or Saline arms. Randomisation was performed using permuted block randomisation. In each stratum, participants were randomly assigned in a 1:1 ratio to having either Glubran-2 spray (Product A) or saline spray (Product B).

Using permuted block randomisation the participants were randomised into the following three groups: mastectomy without axillary dissection, mastectomy with axillary dissection, and partial mastectomy with axillary dissection. To avoid selection bias, allocation concealment was performed using sequential numbering. The data manager performed the block randomisation and allocation sequence. SPSS software version-24 was used for randomisation and statistical analysis.

2.4. Blinding

Both the investigators and participants were blinded to the content of the spray vials (Glubran-2 and Saline), which were identical in appearance. Prior to wound closure and based on the randomisation the surgical scrub nurse provided the surgeon the product. The participant's number was stored against the product used (Glubran-2 or saline).

2.5. Surgical Technique

Four experienced breast surgeons performed all the procedures. Participants underwent total mastectomy, partial mastectomy and axillary dissection using the standard operative techniques. According to the manufacturer's recommendation, after mastectomy, 1 ml vial containing either Glubran-2 or saline was sprayed to the chest wall. After 10 seconds the skin flap was laid down on the chest wall with compression applied for 90 seconds. This procedure was repeated for the lower flap. In participants who underwent axillary dissection, 1 ml

of either Glubran-2 or saline was sprayed over the axillary fossa. One suction drain was placed in all participants who underwent total mastectomy and axillary dissection. After spraying the product the surgeon waited for 30 seconds before placing the drain in order to avoid adherence of the drain to the tissue. The drain was routinely removed on the second post-operative day and the participants were discharged home.

2.6. Study Outcomes

2.6.1. Primary Outcomes

The primary outcome was the volume and duration of wound seroma requiring aspiration. A seroma in this study is defined as a postoperative fluid collection on clinical examination. The aspiration frequency, volume and duration of seroma were collected in the participant's medical records by the surgeon and the breast care nurse.

2.6.2. Secondary Outcome

Post-operative wound infection.

2.7. Follow-Up

All participants were followed-up until the seroma resolved. Any loss to follow-up was recorded for statistical analysis.

2.8. Data Management

Data was recorded on a case report form (CRF). All participants were de-identified using a coded patient number in their CRF. Preoperatively all records that contain participants names or other identifying information were stored separately from the study records. The intervention arm was revealed to the clinicians post-surgery during the participant follow-up.

2.9. Statistical Analysis

Statistical analysis was performed using chi square tests for categorical variables and Mann-Whitney U tests for continuous variables. $P < 0.05$ was considered evidence of statistical significance. A sample size of 102 participants was estimated to demonstrate a statistically significant difference with a power of 90%. SPSS software version-24 was used for all statistical analysis.

3. Results

A total of 74 participants were recruited in this trial. After randomisation 38 and 36 participants were allocated to Glubran-2 and Saline arm respectively. There was no loss to follow-up or mortality (**Figure 1**). The enrolled participant's age and BMI were equally distributed amongst the three groups. The median age was 62.5 and 65 in the Glubran-2 and Saline arms respectively. The mean BMI was 27.8 in the Glubran-2 group and 28 in the Saline group (**Table 1**).

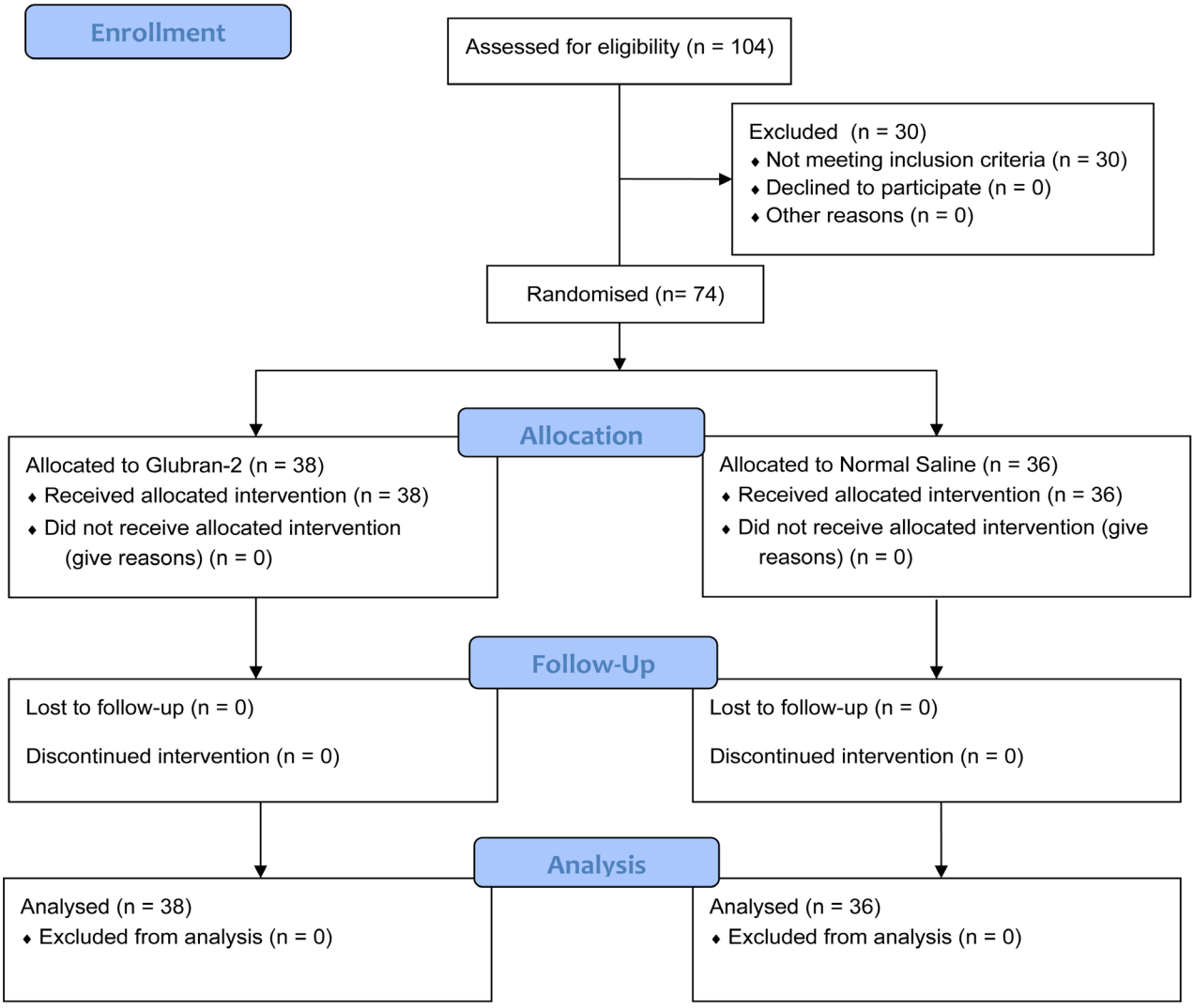

Figure 1. The randomised controlled trial.

Table 1. Patient baseline characteristics.

Characteristics	Glubran-2 (n = 38)	Saline (n = 36)	*P*-value
Age-year (Median)	62.5 (38)	65.0 (36)	0.493
Median age in each group (n)			
- <50 years	48.0 (6)	44.5 (10)	0.608
- 50 - 60 years	51.5 (8)	58.0 (3)	0.061
- 60 - 70 years	63.0 (11)	65.0 (12)	0.100
- >70 years	75.0 (13)	77.0 (11)	0.414
Treatment Group			0.961
- Total Mastectomy	16 (42.1%)	14 (38.9%)	
- Total Mastectomy and Axilla Dissection	16 (42.1%)	16 (44.4%)	
- Partial Mastectomy and Axilla Dissection	6 (15.8%)	6 (16.7%)	
BMI (Mean)	27.8 [25.8 - 29.8] (32)	28.0 [25.5 - 30.5] (25)	0.899
Mean [95% CI] BMI in each group (n)			
- Normal (<25.0)	22.7 [21.8 - 23.7] (13)	22.2 [20.5 - 23.9] (9)	0.486
- Overweight (25.0 - 29.9)	27.8 [26.7 - 28.8] (10)	27.0 [25.5 - 28.5] (7)	0.326
- Obese (≥30.0)	35.1 [32.1 - 38.1] (9)	34.6 [31.8 - 37.3] (9)	0.769

Overall the participants in the Glubran-2 arm showed a higher total volume of seroma. The mastectomy group in the Glubran-2 arm had a higher volume (1203 versus 766 mls, $P = 0.288$) and longer duration for seroma resolution (55 versus 35.5 days, $P = 0.07$) (Table 2).

In the Glubran-2 arm, participants over 70 years of age who underwent total mastectomy showed more than double the volume of seroma when compared to the saline arm (1692 versus 804 mls, $P = 0.324$). Participants between the age of 50 - 60 who underwent total mastectomy and axillary dissection in the Glubran-2 arm showed a significantly higher volume of seroma (5820 versus 2438 mls, $P = 0.171$). Elderly participants over the age of 70 in the saline arm showed a higher volume (4,047 versus 2086 mls, $P = 0.244$). In the Glubran-2 arm and partial mastectomy group, participants between the ages of 60 - 70 had higher volume of seroma (973 versus 275 mls, $P = 0.234$) (Table 3).

All obese (BMI > 30) participants in the Glubran-2 arm except partial mastectomy group showed a higher total volume of seroma. There was no statistical significant difference between the groups (Table 4).

Overall the post-operative wound infection rate was higher in the Glubran-2 arm (13.2% versus 5.6%, $P = 0.262$) (Table 5).

Two participants who underwent total mastectomy in the Glubran-2 arm experienced persistently high volume bloodstained seroma for over two months, which required wound exploration and debridement. Intraoperative findings showed a cavity lined with bleeding hypergranulation tissue. The histology revealed intense foreign body reaction.

Table 2. Post-operative seroma outcomes.

Characteristics	Glubran-2 (n = 38)	Saline (n = 36)	*P*-value
Inpatient Seroma Drainage-mls (mean)			
- Total Mastectomy	157	285	0.291
- Total Mastectomy and Axillary dissection	383	380	0.971
- Partial Mastectomy and Axillary dissection	227	205	0.806
Total Seroma Drainage-mls (mean)			
- Total Mastectomy	1203	766	0.288
- Total Mastectomy and Axillary dissection	2916	2905	0.991
- Partial Mastectomy and Axillary dissection	729	676	0.849
Duration of Seroma-days (median)			
- Total Mastectomy	55.0	35.5	0.070
- Total Mastectomy and Axillary dissection	61.5	62.0	0.696
- Partial Mastectomy and Axillary dissection	28.0	25.5	0.240

Table 3. Post-operative seroma outcomes as per age.

Characteristics	Glubran-2 (n = 38)	Saline (n = 36)	*P*-value
Inpatient Seroma Drainage-mls (mean)			
Total Mastectomy (n)	157 (16)	285 (14)	0.291
- <50 years	113 (3)	260 (2)	0.141
- 50 - 60 years	173 (3)	-	-
- 60 - 70 years	278 (3)	347 (7)	0.864
- >70 years	117 (7)	208 (5)	0.310
Total Mastectomy + Axillary Dissection (n)	383 (16)	380 (16)	0.971
- <50 years	303 (3)	290 (6)	0.934
- 50 - 60 years	628 (2)	190 (1)	0.381
- 60 - 70 years	474 (5)	500 (4)	0.869
- >70 years	265 (6)	430 (5)	0.202
Partial Mastectomy + Axillary Dissection (n)	227 (6)	205 (6)	0.806
- <50 years	-	135 (2)	-
- 50 - 60 years	197 (3)	404 (2)	0.144
- 60 - 70 years	257 (3)	130 (1)	0.569
- >70 years	-	20 (1)	-
Total Seroma Drainage-mls (mean)			
Total Mastectomy (n)	1203 (16)	766 (14)	0.288
- <50 years	727 (3)	285 (2)	0.437
- 50 - 60 years	1031 (3)	-	-
- 60 - 70 years	710 (3)	876 (7)	0.796
- >70 years	1692 (7)	804 (5)	0.324
Total Mastectomy + Axillary Dissection (n)	2916 (16)	2905 (16)	0.991
- <50 years	807 (3)	2658 (6)	0.323
- 50 - 60 years	1313 (2)	540 (1)	0.439
- 60 - 70 years	5820 (5)	2438 (4)	0.171
- >70 years	2086 (6)	4047 (5)	0.244
Partial Mastectomy + Axillary Dissection (n)	729 (6)	676 (6)	0.849
- <50 years	-	363 (2)	-
- 50 - 60 years	485 (3)	819 (2)	0.469
- 60 - 70 years	973 (3)	275 (1)	0.234
- >70 years	-	1415 (1)	-

Table 4. Post-operative seroma outcomes as per BMI.

Characteristics	Glubran 2 (n = 38)	Saline (n = 36)	*P*-value
Inpatient Seroma Drainage-mls (mean)			
Total Mastectomy (BMI)			
- Normal (<25.0)	94 (6)	100 (5)	0.909
- Overweight (25.0 - 29.9)	230 (4)	657 (3)	0.430
- Obese (≥30.0)	172 (6)	260 (4)	0.311
Total Mastectomy + Axillary Dissection (BMI)			
- Normal (<25.0)	277 (8)	302 (6)	0.837
- Overweight (25.0 - 29.9)	540 (4)	470 (3)	0.725
- Obese (≥30.0)	438 (4)	392 (6)	0.749
Partial Mastectomy + Axillary Dissection (BMI)			
- Normal (<25.0)	157 (3)	187 (3)	0.625
- Overweight (25.0 - 29.9)	297 (3)	70 (2)	0.112
- Obese (≥30.0)	-	528 (1)	-
Total Seroma Drainage-mls (mean)			
Total Mastectomy (BMI)			
- Normal (<25.0)	407 (6)	216 (5)	0.365
- Overweight (25.0 - 29.9)	1132 (4)	1400 (3)	0.736
- Obese (≥30.0)	2046 (6)	1016 (3)	0.304
Total Mastectomy + Axillary Dissection (BMI)			
- Normal (<25.0)	1349 (8)	798 (6)	0.303
- Overweight (25.0 - 29.9)	2942 (4)	4451 (3)	0.400
- Obese (≥30.0)	6024 (4)	3629 (6)	0.358
Partial Mastectomy + Axillary Dissection (BMI)			
- Normal (<25.0)	563 (3)	387 (3)	0.243
- Overweight (25.0 - 29.9)	895 (3)	768 (2)	0.843
- Obese (≥30.0)	-	1358 (1)	-

Table 5. Post-operative infection requiring antibiotics.

Characteristics	Glubran2 (n = 38)	Saline (n = 36)	*P*-value
Total (n_1/n) (%)	5/38 (13.2%)	2/36 (5.6%)	0.262
-Total Mastectomy (n_1/n) (%)	2/16 (12.5%)	0/14 (0%)	0.170
-Total Mastectomy + Axillary Dissection (n_1/n) (%)	2/16 (12.5%)	1/16 (6.2%)	0.541
-Partial Mastectomy + Axillary Dissection (n_1/n) (%)	1/6 (16.7%)	1/6 (16.7%)	1.0

4. Discussion

Seroma formation and its complications can have a significant impact on the patients overall recovery [1] [3] [5] [6] [7]. Seroma can lead to prolonged hospital

stay, increased frequency of clinic visits for aspirations, increased risks of wound infection and delayed wound healing. This can increase the patients overall morbidity and delay their adjuvant treatment. This can lead to unnecessary additional financial burden to the healthcare system [1] [3] [7] [14] [15] [16] [17] [18].

Several techniques such as suturing the flaps, prolonged use of drains, and pressure dressing have not shown any benefit in reducing seroma formation [2] [3] [6]-[11]. Pharmaceutical agents such as fibrin glue, light activated fibrin sealant, tetracycline, somatostatin analogues, corticosteroids, and sclerosing agents have been trialled but failed to demonstrate any convincing benefit in reducing seroma formation [2] [6]-[15]. Quilting sutures have been shown to have some benefit in reducing seroma formation, volume and length of drainage time but can cause significant pain and discomfort [16] [17] [18]. Despite all these techniques and agents there is no efficient single solution to tackle this common complication.

To the best of our knowledge there are no previous randomised trials published in mastectomy or axillary surgery investigating the efficacy of Glubran-2 in seroma formation. Although the use of Glubran-2 as an adjunct in other areas such as pelvic lymphadenectomy showed reduced lymph production, there was no such benefit shown in our study [24]. The findings of this study were that the use of Glubran-2 did not reduce the risk, volume or duration of seroma. In fact the use of Glubran-2 can increase the volume of seroma, particularly in elderly and overweight participants. Participants in the Glubran-2 arm also showed increased rate of post-operative wound infection. However there was no statistically significant difference between the Glubran-2 and saline group. Therefore it is difficult to draw a definitive conclusion.

In 2017, the estimated incidence of breast cancer diagnosis in Australia is approximately 17,000 [25]. Approximately 30% - 40% of those diagnosed are treated with a mastectomy [26]. Each vial of Glubran-2 cost approximately AUD $300.00. Participants undergoing mastectomy alone require one vial and mastectomy and axillary dissection require 2 vials of Glubran-2. This can lead to significant additional cost to our healthcare system. As our study did not find any positive benefit in reducing seroma formation, use of Glubran-2 in mastectomy and axillary surgery may not be beneficial. In fact its use may increase the overall cost of the surgery without any potential benefit to the patient outcome.

5. Conclusion

In conclusion, this double-blinded randomised controlled trial did not show any benefit with the use of Glubran-2 in mastectomy and axillary surgery in reducing the risk of seroma formation. In some patient groups the use of Glubran-2 showed increase in seroma formation. But there was no statistically significant difference to generalise the findings of this study. Being a pilot study the main limitation is the sample size. Therefore the findings are underpowered. However, this study can work as a platform for future research using a larger sample

size to further assess the impact of Glubran-2 on seroma formation after mastectomy and axillary surgery.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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