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Safety and Biochemical Impact of Cyanoacrylate-Based Sealant GLUBRAN® 2 on Postoperative Drainage Fluids after Breast Surgery: A Randomized Controlled Trial

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Abstract

Seroma and lymphocele often occur amongst patients after breast surgery and axillary lymphadenectomy, increasing postoperative morbidity and delaying adjuvant therapy. Cyanoacrylate-based sealants, such as Glubran® 2, have been proposed to reduce seroma formation, though evidence remains inconsistent. In order to evaluate the effect on human body fluids, drainage fluids were collected from 80 patients (38 treated with Glubran® 2 and 42 controls) on the day of drain removal (15 days post-surgery). All biochemical and cytological parameters analyzed showed no statistically significant differences between the Glubran® 2 and control groups. Interleukin-6 concentrations were elevated in both groups, exceeding normal reference values, indicating a sustained local inflammatory response. Glubran® 2 appears to be safe for use in breast of postoperative drainage fluids. The persistent inflammatory profile suggests that seroma formation is primarily driven by surgical trauma rather than the sealant's presence.

Keywords: Breast cancer; Seroma; Cyanoacrylate glue; Glubran® 2; Drainage

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Abbreviations

LDH: Lactate Dehydrogenase; IL-6: Interleukin 6

Seroma and lymphocele often occur amongst patients after breast surgery and axillary lymphadenectomy. The incidence of seroma is high and variable from different institution and ranges from 5% up to 90% [1-5]. The presence of a seroma increases the number of results in discomfort and stress for most of the patients by increasing the number of outpatient visits and by delaying the initiation of chemotherapy and radiotherapy. A late start of chemotherapy beyond three months after surgery has been shown to determine inferior survival and tumor control amongst breast cancer patients [6]. Electrocautery, overweight and large breasts are risk factors for seroma formation. In the daily clinical practice, surgeons try to reduce the incidence of seroma through different techniques, although none of those have demonstrated the expected results [5]. Nowadays, sealant either synthetic or biologic glues have been suggested to attempt the reduction of seroma after breast surgery, although different results have been published in the current literature [7-10]. One of the widely used glue is the cyanoacrylate-based glue renowned for adhesive and hemostatic properties called Glubran® 2.

Glubran® 2 is a synthetic sealant, cyanoacrylate based (N-Butyl-2-CyanoAcrylate+Metacryloxi sulfolane) widely used by surgeons in different fields [7,11-13]. Once applied, the glue polymerizes and creates a protective film that complies the surgical bed. Lymphatic vessels are supposed to be sealed by the glue, thus limiting seroma and lymphocele incidence. We recently published results from the GLUBREAST Trial (ISRCTN43919783), a prospective, single-center, randomized, controlled trial that explored the effect of Glubran® 2 in reducing seroma after axillary dissection [7]. The GLUBREAST Trial was launched in 2018 and ended in 2022. Older patients produced higher volume of seroma per day (β 0.30; 95% CI: 0.00–0.60). Higher daily drained seroma amount

Table 1: Population characteristics.

	Whole cohort (n=80)	Glubran® cohort (n=38)	Control cohort (n=42)	p
Age (years)	67.31±12.27	65.98±12.48	68.53±12.08	ns
Stage I A (%)	10 (12,5)	6 (15,8)	4 (9,5)	ns
Stage II A (%)	21 (26,3)	10 (26,3)	11 (26,2)	
Stage II B (%)	20 (25,0)	7 (18,4)	13 (31,0)	
Stage III A (%)	16 (20,0)	10 (26,3)	6 (14,3)	
Stage III B (%)	4 (5,0)	1 (2,6)	3 (7,1)	
Stage III C (%)	6 (7,5)	2 (5,3)	4 (9,5)	
Stage IV (%)	3 (3,8)	2 (5,3)	1 (2,4)	
Invasive Ductal Carcinoma (%)	68 (85)	35 (92,1)	33 (78,6)	ns
Invasive Lobular Carcinoma (%)	12 (15)	3 (7,9)	9 (21,4)	
Lymph Node Ratio	0.15 (0.00 – 0.32)	0.17 (0.04 – 0.38)	0.14 (0.00 – 0.25)	ns

Continuous parametric variable is reported as mean ± standard deviation and non-parametric variable is reported as median and interquartile range. Differences between two groups were assessed using Student's t test, Mann–Whitney or Chi-Square test as appropriate.

Table 2: Drainage liquid composition differences.

	Whole cohort (n=80)	Glubran® 2 group (n=38)	Control group (n=42)	p
Glucose (mg/dL)	57.30±37.14	58.31±38.40	56.33±36.37	ns
Creatinine (mg/dL)	0.76 (0.68 – 0.86)	0.74 (0.69 – 0.88)	0.78 (0.65 – 0.90)	ns
Total Proteins (g/dL)	3.49±0.67	3.51±0.66	3.46±0.68	ns
Albumin (g/dL)	2.2 (2.0 – 2.6)	2.39 (2.14 – 2.70)	2.18 (2.00 – 2.50)	ns
Interleukin-6 (pg/mL)	4542.00 (1933.00 – 15764.00)	4663.00 (2068.00 – 15384.00)	4337.00 (1737.25 – 18077.25)	ns
LDH (U/L)	559 (357 – 839)	559.5 (366.5 – 813.5)	557.5 (354.5 – 959.5)	ns
Total Cholesterol (mg/dL)	66.21±20.00	65.94±19.59	66.45±20.60	ns
HDL Cholesterol (mg/dL)	23.3(18.6 – 26.9)	22.8 (19.4 – 27.4)	23.9 (16.9 – 26.9)	ns
LDL Cholesterol (mg/dL)	28.9 (21.7 – 35.95)	29.4 (23.0 – 38.4)	27.2 (17.5 – 34.8)	ns
Triglycerides (mg/dL)	86.1 (49.5 – 194.75)	80.50 (50.25 – 202.00)	86.60 (47.75 – 188.25)	ns
Red Blood Cells (/µL)	5135.00 (1603.75 – 12286.00)	7774.00 (1212.00 – 13527.75)	4220.00 (1795.25 – 11863.75)	ns
Leukocytes (/µL)	187.00 (58.50 – 604.25)	147.50 (58.50 – 1171.25)	245.00 (56.75 – 503.50)	ns
Epithelial Cells (/µL)	98.50 (28.25 – 197.00)	105.00 (51.50 – 248.50)	72.50 (23.00 – 169.25)	ns
Bacteria (/µL)	72.50 (25.00 – 268.50)	72.50 (28.75 – 324.75)	72.50 (21.50 – 197.50)	ns

correlated with 5-U increase in body mass index (BMI) amongst patients after breast-conserving surgery (β 5.0; 95% CI: 0.62–9.4), compared to those who had mastectomy (β 2.5; 95% CI: −3.6–8.6). Not statistically significant differences among the study groups were reported in terms of drained seroma volume, however 5% of patients enrolled in the Experimental Arm recovered earlier between the fourth and the fifth outpatient visits (p=0.069 and p=0.072, respectively) [7]. During follow- up, we looked carefully to the safety of the product and searched for any eventual adverse events by asking patients whether they experienced symptoms that could be correlated the use of the glue, such as fever, itching, allergies, pain or infection. We did not find statistical differences amongst the group having the glue applied and the control group in terms of adverse effects. In order to evaluate the effect of cyanoacrylate-based glue on human body fluids composition, such as lymphocele and seroma, we collected drainage fluid from 80 patients (38 Glubran® 2 and 42 controls) within the suction drainage, on the day that was removed (fifteen days after radical modified mastectomy or breast-conserving surgery). Cells count (red blood cells, leukocytes, epithelial cells, bacteria) were performed on drainage samples using the UF-4000 citofluorimeter (Dasit), whereas biochemical parameters (glucose, creatinine, total proteins, albumin, interleukin-6, lactate dehydrogenase (LDH), total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) were evaluated on drainage samples after centrifugation using the Cobas 6000 system (Roche). Samples were processed immediately for cytologic assessment and then centrifuged and stored at −80 °C until testing for biochemical analysis. Parametric continuous variables were calculated by mean ± Standard Deviation. Non-parametric continuous variable was evaluated by median and interquartile range. Categorical variables were calculated by counts and percentages. Student's t test or Mann-Whitney test were applied to detect differences between groups normally distributed with homogeneity of variance, whereas Chi Square test was used for categorical variables by SPSS 28.0 software (SPSS, Chicago, IL, USA).

No significant differences were reported in age and clinical variables, confirming that the two cohorts were correctly matched at baseline (Table 1).

All biochemical parameters evaluated yielded no significant differences between groups (Table 2). Notably, interleukin 6 (IL-6) values were notably above the upper reference limit (7.0 pg/mL).

In this study, we explored the possible biochemical and

cytological changes in drainage fluids collected from patients treated with Glubran® 2 after breast surgery. Despite the theoretical rationale supporting the sealant's ability to limit lymphatic leakage and thus reduce seroma formation, our data did not demonstrate significant differences in biochemical composition or cell counts between the experimental and control groups. These findings suggest that the application of Glubran® 2 does not alter the inflammatory or metabolic profile of drainage fluids. The elevated IL-6 concentrations observed in both groups indicate a persistent local inflammatory response, likely reflecting the normal tissue reaction to surgical trauma rather than a specific effect of the glue. In conclusion, this study highlights that cyanoacrylate-based sealants, although safe for use in breast surgery, do not induce any significant biochemical or cytological changes in postoperative drainage fluids.

Declarations

Ethics approval and consent to participate: This study involving humans was approved by National Cancer Institute Ethical Committee on March14th 2018 with the following number: 12/18. The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Availability of data and materials

The datasets generated and analysed during the current study are available in the Zenodo repository, https://zenodo.org/records/13150809.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EE conceived the idea, co-wrote the paper and collected samples. RdF co-wrote the paper and performed statistical analyses. CS collected samples, created the dataset and followed up patients. SA, DG, and LR performed sample analyses. EC supervised and reviewed the manuscript writing. RdG designed the study, collected data and supervised the manuscript writing. All authors read and approved the final manuscript.

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