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Rev Inves Clin. 2015;67:357-65 ORIGINAL ARTICLE

Randomized Phase II Study of Talc Versus Iodopovidone for the Prevention of Seroma Formation Following Modified Radical Mastectomy

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ABSTRACT

Background: The most common complication following modified radical mastectomy is seroma formation. Numerous approaches have been attempted to prevent this complication, ranging from the use of chemical substances to mechanical means, and none of these have proven to be consistently reliable. **Aim:** The aim of this study was to evaluate the safety and efficacy of talc in preventing postoperative seromas compared with iodine and standard care. **Methods**: Patients with breast cancer undergoing modified radical mastectomy were randomly assigned to one of three study groups: control, subcutaneous talc, or iodine application. The primary endpoint was frequency of seroma formation. Secondary outcomes included wound complications (surgical site infection, flap necrosis, and wound dehiscence), analgesic use, postoperative pain, total drain outputs, and drainage duration. **Results**: Of the 86 patients randomized in the study, 80 were analyzed. After interim analysis, the iodine intervention was discontinued because of increased adverse outcomes (drainage duration and total amount of fluid drained). Talc failed to demonstrate that its application in subcutaneous breast tissue prevents seroma formation (19.4% for talc group vs. 23.3% for control group; p = 0.70). However, patients who developed seroma in the talc group had fewer aspirations per patient seroma and less volume drained when compared with the control group (88.2 ± 73 vs. 158.3 ± 90.5; p = 0.17). **Conclusions**: Subcutaneous talc application was safe in the short term, but there was not sufficient evidence to support its use for seroma prevention following modified radical mastectomy in patients with breast cancer. (REV INVES CLIN. 2015;67:357-65)

Key words: Breast. Cancer. Mastectomy. Seroma. Talc.

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INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of death among women in developed and developing countries worldwide[1]. Currently, in Mexico BC ranks first in frequency and mortality, with a total of 20,444 new cases and 5,680 deaths reported in 2012, with a mortality rate of 31 cases per 100,000 women aged between 50 and 69 years[2]. The majority of women with BC require a surgical procedure for locoregional control of their disease.

The most common complication following modified radical mastectomy (MRM) or axillary lymph node dissection (ALND) is seroma formation, with reported frequency rates ranging between 15 and 90%[3]. Seroma is defined as an abnormal collection of serous fluid and is most commonly localized in the axillary space or under skin flaps after BC surgery. The etiology of this condition remains obscure; however, some authors think that seromas develop from surgical trauma and most likely originate from lymph channel injury[4].

Numerous approaches have been attempted to reduce seroma formation. These approaches range from the use of chemical substances to mechanical means, and none of these methods have proven to be consistently reliable[3]. The most widely employed procedure for reducing seroma formation is the use of closed suction drains. These obliterate dead space and are associated with a lower frequency of surgical site infections (SSI) and wound necrosis[5]. There has been much debate on optimal drain duration: some authors advocate the use of early drain removal, while the majority of surgeons routinely wait until drain volume is < 20-30 ml in 24 hours[6].

At this time, the sole method that has proven effective for preventing seroma formation is mechanical closure of the dead space[4]. Recently, Ten Wolde, et al. stated that fixation of the skin flaps to underlying muscles (quilting) lowers the frequency of seroma and other associated complications but increases operative time[7]. Further studies are needed to provide clear-cut recommendations on the techniques to be used for this purpose and to evaluate the long-term complications associated with these methods. The role of talc in reducing seroma formation has been studied in an animal model but, to our knowledge, no prospective studies have examined the role of talc or of iodopovidone for reducing seroma in patients submitted to MRM.

This study has been designed to evaluate the safety and efficacy in the short term of two approaches in preventing postoperative seromas: talc and iodine vs. standard care.

Materials and methods

Between July 2013 and January 2014, a multicenter, randomized, phase II clinical trial was conducted at two tertiary centers in Mexico City. The study was approved by the institutional boards and ethics committees at both medical centers. We included female patients 18-70 years of age with histologically confirmed BC. Neoadjuvant chemotherapy, which included four cycles of 5-fluorouracil, Adriamycin, and cyclophosphamide and 12 paclitaxel applications, was approved for this study. Exclusion criteria included allergy to iodine or to talc powder and if they had received preoperative radiotherapy. Cancer staging was implemented using the American Joint Committee on Cancer (AJCC) system. After providing informed consent, patients with BC undergoing MRM were randomly assigned to one of the study groups by block randomization in 30-patient blocks (Fig. 1). The operation that involved the mastectomy included dissection of cutaneous flaps and of the breast including pectoral fascia. Dissection of the axilla was performed to levels I-II. Axillary content (fat and lymph nodes) and breast tissues were excised *en bloc*. At the end of the surgical procedure, a closed suction drain was placed in the axilla.

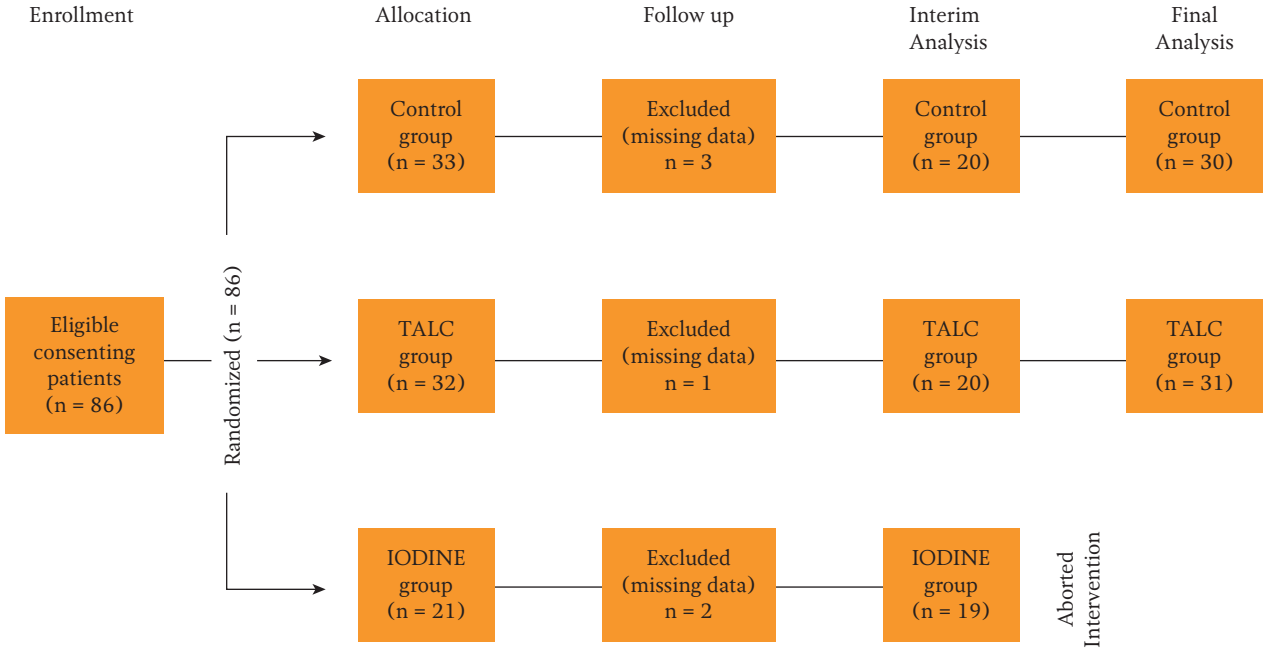
Groups were defined as A, B, and C according to treatment as follows:

– Study group A (control group): MRM was performed with electrocautery dissection.

– Study group B (talc group): At completion of MRM, 5 g of sterile dry talc was applied to the axilla and to the muscle and subcutaneous flaps. The talc was not washed off.

– Study group C (iodine group): At completion of MRM, a mixture of 15 ml of sterile Iodopovidone

Figure 1. Consort flow diagram of participants.



with 15 ml of sterile saline was applied to the axilla and on the muscle and subcutaneous flaps. After skin closure, the mixture remained for 5-10 min and was drained and disposed of inside the operating room. The solution was not quantified as drain output.

Two transcutaneous flat silicone drains (Biovac™) were inserted into each patient; one was placed in the anterior aspect of the axilla and the other covered the pectoral muscle. All patients were monitored postoperatively for pain, respiratory distress, swelling, and signs of surgical site infection. Patients were admitted to the hospital a few hours prior to surgery and were discharged during the following 24-48 hours. They were instructed to record daily output, limit shoulder movement, and to strip their drains daily to assure patency. Drains were removed when output was < 25 ml in 24 hours. Each patient was seen and monitored for complications weekly at the outpatient clinic of each hospital. Both the patient and the physician who followed up were blinded. The maneuver was not revealed until drainage and suture stitches were removed.

The primary endpoint frequently comprised seroma formation. Seroma was defined as a clinically significant, palpable fluid collection in the axilla or surgical site area after drain removal. Symptomatic seromas were aspirated on an ambulatory basis and the volume was quantified. Number of aspirations per patient seroma (pps) and volume drained per aspiration were also recorded. Secondary outcomes were wound complications (SSI, flap necrosis, and wound dehiscence), analgesic use, postoperative pain (utilizing a visual analog score [VAS]), total drain outputs (in ml), and drainage duration (in days). A SSI was defined according to Centers for Disease Control and Prevention (CDC, 2015) criteria[8].

Statistical analysis

For descriptive analysis, we calculated mean or median, along with standard deviation (SD) or interquartile ranges (IR). Categorical variables were described as proportions. Bivariate analysis was conducted using Student's *t* test, Mann-Whitney *U* test, Analysis of variance (ANOVA) test, Kruskall-Wallis test, Chi-square analysis, and the Fisher exact test. Relative risk (RR) was calculated for various risk factors with corresponding 95% confidence intervals (95% CI) and p values. Any p value ≤ 0.05 or 5% was considered statistically significant.

Statistical analysis was conducted using SPSS ver. 20.0 for IBM.

RESULTS

Of the 86 patients randomized in the study, 80 completed follow-up and were further analyzed (Fig. 1). Six patients were excluded due to missing/incomplete data. The patients' mean age was 49.8 ± 8.9 years, and 63 patients (79%) received neoadjuvant chemotherapy. Of these patients, 14 (17.7%) had a clinical diagnosis of hypertension and six (7.6%) had type 2 diabetes mellitus (DM2). There were no statistical differences in baseline clinical and pathological characteristics between study groups (Table 1). After interim analysis (Table 2), the iodine intervention (Group C) was discontinued because patients under this treatment had increased duration of drainage and total amount of fluid drained from both axillary and pectoral drains.

PRIMARY OUTCOME

Seroma formation and management

The frequency of seroma formation in our study was 21.2% (n = 17). There was no statistical difference in frequency of seroma formation between control and talc groups (23.3 vs. 19.4%; p = 0.70). Twelve of the seromas were aspirated irrespective of the group. Number of aspirations was no different between the study groups (median of 2.2 pps for control group vs. 1.2 pps for talc group; p = 0.87). Volume drained by aspiration (pps) was also quantified, being lower for the talc group when compared with the control group (88.2 ± 73 vs. 158.3 ± 90.5; p = 0.17) (Table 3).

SECONDARY OUTCOMES

Analgesic use and postoperative pain

Each patient's analgesic use was determined for the three days following the surgical procedure. Patients in the Iodine group had substantially more analgesic use compared with other groups (74 vs. 60 and 40%), and there were no differences between the talc and control groups (p = 0.38) (Table 4). Postoperative pain was assessed weekly at clinical visits with VAS ranging from 0-10. The median score for each of the groups was 2.

Wound complications

The overall frequency of wound complications other than seroma (SSI, flap necrosis, and wound dehiscence) was 14.7% (n = 11). Two patients (7.1%) each from both the control and the talc groups developed SSI and were treated with antibiotics. One patient each from the talc (3.6%) and the iodine group (5.3%) were diagnosed with flap necrosis during clinical follow-up, and two patients each of the talc (7.1%) and the iodine groups (10.5%) had wound dehiscences that were managed on an outpatient basis. The wound dehiscence of one patient in the talc group was associated with direct blunt trauma during the week following the surgical procedure (Tables 2 and 4).

Drain removal and total volume drained

Total amount of pectoral drain days for the control, talc, and iodine groups were 8 ± 4.5, 7.5 ± 7, and 10 ± 5 days, respectively, with a total pectoral drain volume of 388 ± 302.3, 404 ± 528.3, and 620.3 ± 315.2 ml, respectively. Statistical differences were only found for pectoral drain volume when comparing the iodine with the control group (p = 0.02). Total amount of axillary drain days for the control, talc, and iodine groups were 12.5 ± 6. 5, 11.3 ± 6.1, and 18.5 ± 5.3 days, respectively, with total axillary drain volume of 847 ± 353.58, 640 ± 1,031, and 1,421.7 ± 625.4 ml, respectively. No statistical differences were found when comparing the talc and control groups for both axillary drain days (p = 0.10) or drain volume (p = 0.35). When comparing the iodine and the control group, statistical differences were observed for total axillary drain volume (p < 0.01) and axillary drain duration (p < 0.01) (Fig. 2).

DISCUSSION

Breast cancer has become the leading cause of cancer-related death in Mexican women since 2006, and only 10% of all cases are detected at an early stage[9,10]. The majority of these women require radical surgical procedures for local disease control. Seroma formation is the most common complication following BC surgery, and this increases morbidity by raising the risk of other surgical site complications, such as SSI (OR: 1.65; 95% CI: 1.28-2.12)[11], skin flap necrosis,

Table 1. Baseline clinical and pathological characteristics of the participants according to study group

Characteristics	Control (n = 30)	Talc (n = 31)	Iodine (n = 19)	P value
Age	48.9 ± 9.0	50.0 ± 9.6	50.9 ± 8.0	p = 0.74
Weight (kg)	67.1 ± 11.6	68.4 ± 10.7	67.6 ± 9.6	p = 0.89
Height (m)	1.53 ± 0.07	1.54 ± 0.05	1.52 ± 0.05	p = 0.55
BMI	28.7 ± 5.3	28.9 ± 4.7	29.3 ± 4.1	p = 0.91
Hypertension - n (%)				p = 0.61
Yes	5 (17)	7 (23)	2 (11)	
No	25 (83)	24 (77)	17 (89)	
Diabetes - n (%)				p = 0.23
Yes	2 (7)	1 (3)	3 (16)	
No	28 (93)	30 (97)	16 (84)	
Clinical stage - n (%)				p = 0.12
Stage II	10 (33)	13 (42)	3 (16)	
Stage III	18 (60)	18 (58)	14 (74)	
Stage IV	2 (7)	0 (0)	2 (10)	
Breast vol. (cc)*	1,731.4 ± 740	1,912.5 ± 1329.5	1,996 ± 744	p = 0.11
Total LN	13.5 ± 7.3*	16 ± 6.3*	15.3 ± 4.4	p = 0.63
SBR*	8 ± 2	7 ± 2	7 ± 2	p = 0.94
Histologic type - n (%)				p = 0.67
IDC	27 (90)	29 (94)	17 (89)	
Other	3 (10)	2 (6)	2 (11)	
HR status - n (%)				p = 0.60
Positive	22 (83)	25 (81)	13 (68)	
Negative	8 (27)	6 (19)	6 (32)	
Ki-67 status - n (%)				p = 0.53
< 14 %	10 (33)	14 (45)	9 (47)	
≥ 14 %	20 (67)	17 (55)	10 (53)	
Her-2/neu status - n (%)				p = 0.19
Positive	11 (37)	5 (16)	5 (26)	
Negative	19 (63)	26 (84)	14 (74)	

BMI: body mass index; LN: lymph nodes; SBR: Scarff-Bloom-Richardson system; IDC: invasive ductal carcinoma; HR: hormone receptor; vol.: volume.
*Median ± interquartile range, the other variables are expressed as mean ± standard deviation.

Table 2. Interim analysis: Primary and main secondary outcomes

Endpoint	Control (n = 20)	Talc (n = 20)	Iodine (n = 19)	P value
Seroma formation - n (%)	6 (30)	4 (20)	4 (21.1)	p = 0.80
SSI - n (%)	1 (5)	0 (0)	1 (5.3)	p = 0.77
Flap necrosis - n (%)	0 (0)	1 (5)	1 (5.3)	p = 0.77
Wound dehiscence - n (%)	0 (0)	2 (10)	2 (11)	p = 0.45
Drain replacement - n (%)	1 (5)	0 (0)	1 (5.3)	p = 0.77
Analgesic use - n (%)				
Yes	12 (60)	10 (50)	14 (74)	p = 0.32
No	8 (40)	10 (50)	5 (26)	
Postoperative pain (VAS)†	2 ± 0	2 ± 2	2 ± 0	p = 0.02
Pectoral drain (days)†	8 ± 3.75*	7 ± 7*	10 ± 5*	p = 0.04
Pectoral drain (total ml)	345 ± 363.5*	466 ± 589*	620.3 ± 315.2	p = 0.08
Axillary drain (days)†	12.5 ± 6.5*	11.3 ± 6.1	18.5 ± 5.3	p < 0.01
Axillary drain (total ml)†	847 ± 353.58*	640 ± 1031*	1,421.7 ± 625.4	p < 0.01

SSI: surgical site infection; PPS: per patient seroma; VAS: visual analog score.
*Median ± interquartile range, the rest of the variables are expressed as mean ± standard deviation.
†p < 0.05 for comparisons between groups.

Table 3. Primary outcome and management according to study group

Endpoint	Control (n = 30)	Talc (n = 31)	P value
Seroma formation - n (%)	7 (23.3)	6 (19.4)	p = 0.70
Seroma management - n (%)			
Expectant	1 (14)		p = 0.87
Aspiration	6 (86)	6 (100)	
Aspirations (pps)	2.2 ± 1.2*	1 ± 1*	p = 0.16
	Range (1-4)	Range (1-2)	
Volume Drained by Puncture (pps)	158.3 ± 90.5	88.2 ± 73	p = 0.17
	Range (35-265)	Range (15-200)	
Drain replacement - n (%)	1 (3.6)	0 (0)	p = 0.49

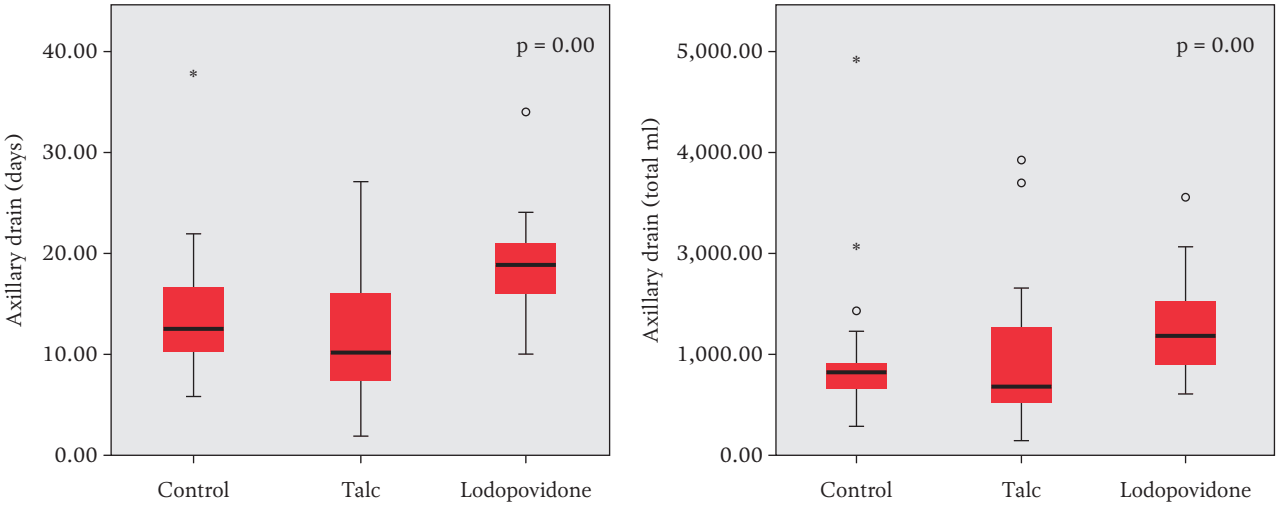
PPS: per patient seroma.
*Median ± interquartile range, other variables expressed as mean ± standard deviation.

Table 4. Secondary outcomes according to study group

Endpoint	Control (n = 30)	Talc (n = 31)	P value
SSI - n (%)	2 (6.7)	2 (6.5)	p = 0.99
Flap necrosis - n (%)	0 (0)	1 (3.2)	p = 0.51
Wound dehiscence - n (%)	0 (0)	2 (6.5)	p = 0.49
Analgesic use			p = 0.38
Yes	14 (46.7)	11 (35.5)	
No	16 (53.3)	20 (64.5)	
Postoperative pain (VAS)†	2 ± 0*	2 ± 2*	p = 0.01
Pectoral drain (days)	8.5 ± 4.5*	7.5 ± 7*	p = 0.09
Pectoral drain (total ml)	388 ± 302.3*	404 ± 528.3*	p = 0.79
Axillary drain (days)	12.5 ± 7.5*	11.7 ± 5.8	p = 0.10
Axillary drain (total ml)	871 ± 445.25*	713.5 ± 701*	p = 0.35

VAS: visual analog score.
*Median ± interquartile range, all others are expressed as mean ± standard deviation.
†p < 0.05 for comparisons between groups.

Figure 2. Comparison of total axillary drain volume and drainage duration between study groups (interim analysis).



and wound dehiscence. In our setting, seroma has not been related with an increased risk of other major wound complications, but prolonged use of drains has been shown to be a risk factor for SSI[12]. Additionally, seromas increase patient discomfort and psychological distress and may delay the initiation of adjuvant treatment.

The formation of axillary dead space following BC surgery is the tipping point for seroma formation. The frequency of seroma formation varies considerably among studies; in our study, the frequency was 21.2%. The lack of an objective and uniform definition of seroma contributes significantly to this large variation in frequency rates. The definition of seroma in this study was clinical, and all symptomatic seromas were treated at the outpatient clinic.

Breast cancer surgeries are clean procedures, in which low rates of infection are expected; however, individual studies have reported higher infection rates[13-17]. Radical procedures and preoperative radiation tend to increase SSI and other wound complications. In our study, the SSI rate was 6.3%, lower compared with the mean cumulative frequency reported yearly at our institution. This may be explained by not including patients with preoperative radiation and due to the Hawthorne (observer) effect. In this study, seroma formation and DM2 increased the risk of developing an SSI.

The pathogenesis of seroma formation is not fully understood, but increased body mass index (BMI), hypertension, electrocautery[4] use, and the extent of the surgical procedure (ALND vs. MRM) have all been associated with an increased risk for this complication[3,18,19]. Hypertension (RR: 0.99; 95% CI: 0.3-3.0; p = 0.99), BMI ≥ 25 kg/m^2 (RR: 2.02; 95% CI: 0.51-8.0; p = 0.31), and DM2 (RR: 1.62; 95% CI: 0.47-5.48; p = 0.43) were not associated with greater seroma formation in our study. However, it is noteworthy that 88.2% of patients who developed seroma were overweight or obese.

Tissue dissecting devices, such as scalpel, electrocautery, ultrasonic dissector, the electrothermal bipolar vessel-sealing system, and argon diathermy, exert an influence on operating time, blood loss, and seroma formation. There is evidence that ultrasonic dissection decreases operating time, blood loss, and overall complications in BC surgery when compared with electrocautery[20,21]. However, these devices significantly increase hospital costs and are not universally available. Electrocautery use comprises the mainstay device for tissue dissection in Mexico[22]. A group in Turkey demonstrated how the use of this device induces greater tissue damage and acute inflammatory response by measuring tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) from drain samples[21].

Numerous approaches to obliterate dead space have been attempted previously with inconsistent results. The most successful approaches in reducing axillary dead space following BC surgery to date have been mechanical techniques that involve flap fixation. Halsted first described these in 1913, and several recent randomized clinical trials have demonstrated promising results, mainly reductions in seroma formation and drainage duration[7,23-26]. These techniques, however, increase postoperative pain and operating time. Long-term complications also require assessment, particularly chronic pain and shoulder mobility. Larger prospective randomized trials are needed to further evaluate these techniques.

Techniques involving chemical agents have also been evaluated with inconsistent results[5]. Iodopovidone is an effective agent that is currently used for producing chemical pleurodesis in many low-income countries worldwide (it is commonly used in our institution for this purpose)[27]. This antiseptic has gained popularity because it is safe, low-priced, and nearly universally available. Its mechanism of action remains unknown; however, Agarwal, et al. think it has to do with low pH solutions (pH 2.97) and proinflammatory properties[28]. Recently, Agarwal, et al. compared iodopovidone pleurodesis with that of cosmetic talc (5 g) and found them equally safe and effective[29]. To our knowledge, iodopovidone has never been used for the prevention of seroma formation in humans; however, it has been employed safely and successfully as a sclerosing agent for percutaneous treatment of post-mastectomy chronic seroma and pelvic lymphocele[30,31]. In the present study, this intervention did not prevent seroma formation and led to increased drainage duration and total volume drained for both axillary and pectoral drains when compared with talc and standard treatment. It is possible that the manner in which we applied iodopovidone in subcutaneous breast tissue during the trial was not the ideal technique for seroma prevention, and this should be

further assessed. The serous surface of the pleura may be significantly more susceptible to iodopovidone's proinflammatory properties compared with subcutaneous breast tissue. This inflammation could have a harmful effect on breast tissue, possibly increasing serous fluid/lymph secretion.

Talc poundage is safe and considered the most effective sclerosant for pleurodesis in patients with malignant pleural effusion[32-34]. This agent induces intense pleurisy, causing both pleura to seal, preventing the accumulation of fluid in this virtual space[35]. Klima, et al. found that the application of subcutaneous talc after axillary dissection decreased both drain duration and volume, as well as prevented seroma formation in a porcine model[36]. The authors demonstrated that this method was safe after histological and laboratory evaluation of these pigs[36]. Subcutaneous talc has also been successfully utilized in patients with large ventral-hernia repairs, with earlier drain removal and fewer wound complications[37].

We were not able to demonstrate that talc application in subcutaneous breast tissue prevents seroma formation in humans. Patients who developed seroma in the talc group in our study had fewer aspirations per patient seroma (pps) and less volume drained when compared with the control group. We also observed a trend toward decreased drainage duration and the amount drained for the axillary drain when compared with the control group; however, we do not think this is clinically relevant.

The patients in this study were followed prospectively for at least 30 days, and had similar outcomes among study groups; however, our study had some limitations. Although meticulous observations were conducted, different surgeons operated on the patients, and the iodine group was interrupted after the inclusion of 21 patients due to increased adverse outcomes. Also, although all patients received standard oncological treatment, we do not know whether one of the maneuvers could have had any impact on long-term survival.

In conclusion, subcutaneous talc application is safe in the short term, but there is not sufficient evidence to support its use for seroma prevention following MRM in patients with BC. To our knowledge, neither subcutaneous talc nor iodine has ever been used for seroma prevention following MRM in humans. We believe our results could be limited by our study power, and larger trials are needed to further explore subcutaneous talc application following axillary dissection.

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