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Original Research

Is there a role for homeopathy in breast cancer surgery? A first randomized clinical trial on treatment with *Arnica montana* to reduce post-operative seroma and bleeding in patients undergoing total mastectomy

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ABSTRACT

Aim: This study aimed to evaluate the benefits of *Arnica montana* on post-operative blood loss and seroma production in women undergoing unilateral total mastectomy by administering *Arnica Montana 1000 Korsakovian dilution (1000 K)*. **Materials and Methods:** From 2012 to 2014, 53 women were randomly assigned to *A. montana* or placebo and were followed up for 5 days. The main end point was the reduction in blood and serum volumes collected in drainages. Secondary end points were duration of drainage, a self-evaluation of pain, and the presence of bruising or hematomas. **Results:** The per-protocol analysis revealed a lower mean volume of blood and serum collected in drainages with *A. montana* (−94.40 ml; 95% confidence interval [CI]: 22.48-211.28; $P = 0.11$). A regression model including treatment, volume collected in the drainage on the day of surgery, and patient weight showed a statistically significant difference in favor of *A. montana* (−106.28 ml; 95% CI: 9.45-203.11; $P = 0.03$). Volumes collected on the day of surgery and the following days were significantly lower with *A. montana* at days 2 ($P = 0.033$) and 3 ($P = 0.0223$). Secondary end points have not revealed significant differences. **Conclusions:** *A. montana* 1000 K could reduce post-operative blood and seroma collection in women undergoing unilateral total mastectomy. Larger studies are needed with different dilutions of *A. montana* to further validate these data.

KEY WORDS: *Arnica montana*, breast cancer, homeopathy, mastectomy, seroma

INTRODUCTION

Surgery is not free from significant complications, despite advancement in surgical techniques and in perioperative care. One of the major complications, particularly for breast and soft tissues surgery, is post-operative bleeding which represents a critical and, in some cases, lethal risk factor [1,2]. Moreover, post-operative bleeding after breast surgery causes a severe discomfort to the patient, entailing the need for surgical re-intervention and sometimes blood transfusions. Another frequent complication of breast surgery is seroma, which often requires numerous accesses for outpatient drainage, finally resulting in a delay of adjuvant therapy administration and a significant psychological burden [3].

A recent study conducted in the United States has extracted from the 2011 Nationwide Inpatient Sample the hospital discharge rates for primary diagnosis of breast cancer and has selectively identified discharges with post-operative bleeding [3]. Results showed that even if only 2.5% of the discharges had bleeding complications and eventually needed re-operation, globally, bleeding complications extended the length of stay by 1.3 days while increasing hospital costs by $5495 per admission. Moreover, even higher health costs and patients' discomfort are associated with the treatment of chronic or refractory seroma [3].

The risk of blood loss or seroma could be limited by identifying and then correcting potential triggers, but although this topic has

been extensively studied, both hemorrhage and seroma are still largely reported [4,5]. Homeopathy could provide remedies based on compounds with anti-hemorrhagic and anti-inflammatory properties, but their use in diluted homeopathic solutions has been poorly investigated [6-9]. Indeed, some homeopathic remedies have been already evaluated in various surgical settings, however showing controversial effects [10-17]. *Arnica montana* is a plant belonging to the Compositae family and it grows in East and Central Europe [18]. In particular, its anti-inflammatory action is linked to the lactone helenalin that seems to be involved in the inhibition of the pro-inflammatory transcription factor nuclear factor kappa B (NF-κβ) [19-27]. A. *montana* has been recently evaluated in several surgical settings such as esthetic and orthopedic surgeries, but currently, no single study is available in literature on the effects of this homeopathic remedy in breast cancer surgery. In the present study, a homeopathic preparation of A. *montana* 1000 Korsakovian dilution (1000 K) was administered preoperatively and postoperatively in a placebo-controlled, double-blind clinical trial to patients undergoing unilateral total mastectomy, with or without reconstruction, to evaluate any favorable or adverse effect on post-operative blood and seroma collection from surgical drains.

MATERIALS AND METHODS

Study Design

This randomized, double-blind, placebo-controlled study was carried out between 2012 and 2014 in a single university hospital department (Breast Unit, "Luigi Sacco" University Hospital, Milan, Italy). Fifty-three women affected by breast cancer who were candidates for unilateral total mastectomy, with or without reconstruction, were enrolled in the study. The study was authorized by the Ethical Committee of the same university hospital (Trial Register number: 93/2011, approved by Ethical Committee on February 15, 2012) and was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines. Only patients who had given written informed consent were considered for inclusion. Women were included in the study if they were: (a) aged between 20 and 75 years; (b) hospitalized for unilateral total mastectomy, with or without reconstruction; (c) and subjected to standard treatment, as described in the "concomitant therapies" section. Other variables, such as weight and breast size, were recorded and considered.

Women were excluded from the study if they were: (a) receiving complex surgery such as breast reconstruction by transverse rectus abdominis or latissimus dorsi myocutaneous flaps, or in case of needed axillary dissection; (b) admitted at the emergency department; (c) receiving anticoagulants and antiplatelet treatments; (d) affected by bleeding disorders; (e) patients with liver pathologies or with concomitant severe general diseases; (f) patients receiving drug therapy with aromatase inhibitors or anticancer therapies; (g) patients with a history of stroke or of acute myocardial infarction, <24 months before; (h) patients diagnosed with other concurrent tumors; (i) patients who had participated in other clinical trials in the 3 months prior to the study; (j) and patients with values of prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen outside the normal range of the clinical site (i.e., 0.85-1.18 s for PT, 0.85-1.20 s for PTT, and 170-400 mg/dL for fibrinogen). The day before surgery (day 0), vital signs (blood pressure, heart rate, and blood oxygen saturation) were evaluated, along with any concomitant medication and any adverse event that could have occurred since the screening visit. Moreover, based on the results of blood tests, the eligibility of the patient was re-verified. The enrolled patient was then assigned to a treatment group according to the randomization list.

Randomization was created by the Contract Research Organization (CRO) Opera S.r.l. and generated using the random function (proc plan) of SAS (version 9.4) software. At screening, each patient was assigned to a code composed of the identification number of the clinical site in two digits (e.g., 01) and the identification number of the patient to three digits (e.g., 001-002-003). Time and date of each administration were recorded. The CRO Opera S.r.l held the key to the randomization list in a sealed envelope, which was not opened until the end of the study. The key was used only after freezing of the database and finalization of the statistical analyses.

The patients, according to the randomization list, received sublingually a dose of five drops of A. *montana* 1000 K 3 times a day, or placebo with identical times of administration, from 1st day before the surgery until the 4th day after the surgery (in total 6 days). On the day of surgery (day 1), the previously assigned treatment was continued. All the patients were operated by the same surgical team. During the operation, surgical drains with a caliber of 15 French (equal to 5 mm in diameter) were positioned. Surgeons did not know the allocation of patients in the treatment groups. From the end of surgery and for every 12 h, a control was carried out, the amount of blood and serum volumes collected through drainages was recorded, and for every 24 h, a blood test for the evaluation of the complete blood count (CBC) and the performance of coagulation factors was carried out. In the days following the surgery (days 2-4), the patients continued the previously assigned treatment. Vital signs, any concomitant medication, adverse event, and the presence of bruises or hematomas were monitored. Finally, patients were asked to provide an opinion on the perception of pain after surgery, using a visual analog scale (VAS). Day 5 concluded the study. On this day, the treatment previously assigned was continued, and the liquid collected by drains (if still positioned) was measured. If it was still not possible to remove the drainage, the amount of fluid drained was registered for the last time and, based on other parameters, the date of the possible discharge of the patient was indicatively anticipated. Conversely, if all parameters resulted in the normal range and drains were removed, the patient had the possibility to be discharged before the 5th day; in this case, the patient was not prematurely withdrawn, but she was considered having correctly completed the study.

Endpoints

The principal endpoint of the study was the efficacy of A. *montana* versus placebo in reducing the post-operative blood loss and seroma production in patients undergoing

unilateral total mastectomy, with or without reconstruction. The secondary end points included the following:

- Duration of drainage, which was calculated from day 1 to the day of drainage removal
- Time to reach a collected volume below 10 ml
- Self-evaluation of pain, measured by VAS after surgery
- The average time of hospitalization after surgery, which was measured in days following surgery
- The presence of bruising and hematomas or breast swelling, measured both in terms of presence versus absence and of description or size
- The differences between the volume collected on day 1 and the volume collected in each of the following days
- Possible adverse reactions to treatment.

Sample Size

The appropriate accrual hypothesized for the study was set to 60 patients, with a 1:1 ratio per treatment group (A. *montana* 1000 K vs. placebo). Considering a possible 10% dropout rate, this sample size could allow us to have a final population of 53 women, presenting a mean blood and serum collection of 280 ml in the placebo group and of 200 ml in A. *montana* group (SD 100 ml), considering adequate a statistical power equal to 80%. Finally, 53 women with breast cancer and candidate for unilateral total mastectomy, with or without reconstruction, were enrolled in the study.

Study Treatment

A. *montana* 1000 K was in the form of drops in 30% hydro alcoholic solution, with sublingual absorption. The 1000 K dilution is a very high homeopathic dilution produced according to the French Pharmacopoeia, starting from a mother tincture (complete plant extract) which undergoes 1000 steps of successive dilution and shaking in a 30% water–alcohol solution. The mother tincture of the product used in this study contained a minimum content of 0.04% of sesquiterpenes (expressed as dihydrohelenanin tiglate). According to the Korsakovian dilution method, the same flask was used for the entire preparation: At each step, the flask was emptied of most of the liquid but not dried, and then immediately filled again with the solvent. Because the residual volume after emptying the flask certainly cannot be >10% of the total used in each dilution, the 1000th K dilution is sufficiently high that it certainly does not contain toxic amounts of the plant. The placebo drops were identical in appearance to the active drops, but included only 30% hydro alcoholic solution without any homeopathic dilution. The studied homeopathic treatment and the placebo were manufactured and supplied in strictly identical packaging by Laboratoires Boiron S.r.l. (Segrate, Milan, Italy).

Concomitant Therapies

A standard treatment used in the management of surgical procedures was administered to all the patients enrolled in the study. In particular, it was provided as follows:

- Antibiotic prophylaxis with cefazolin 2 g intravenous (IV) once;
- Antithrombotic prophylaxis using low molecular weight heparin at a dose of 4000 IU 12 h before the surgery;
- Analgesic therapy with paracetamol 1000 mg IV for every 6 h for the first 24 h and tramadol 100 mg IV, if needed.

For patients undergoing reconstruction, morphine 20 mg in continuous infusion with antiemetic medication was administered for the first 48 h.

Statistical Analysis

Interval data were described as the number, mean, and standard deviation (SD). Ordinal data were described as the absolute and relative frequencies with 95% confidence intervals. Comparisons of means were carried out by analysis of variance. The differences in the blood and serum volumes collected by the drainage between A. *montana* and placebo were evaluated with three linear regression models:

- Model 1: Includes the treatment;
- Model 2: Includes the treatment and the volume collected on the day of the intervention;
- Model 3: Includes the treatment, the volume collected on the day of surgery, and patient weight.

Methods of survival analysis (Kaplan–Meier) were used to evaluate the duration of drainage need and time to reach a collected volume below 10 ml. Survival curves were compared using the log-rank test. Quantitative variables were compared using Student's *t*-test for normal distributions. The level of significance was set at 5% ($P = 0.05$). All statistical analyses were carried out using SAS (version 9.4) software.

RESULTS

The 53 women enrolled in the study (26 in the A. *montana* group and 27 in the placebo group) were all included in the intention-to-treat (ITT) population, defined as all patients who took at least one dose of A. *montana* 1000 K or placebo. The per-protocol (PP) population included all women of the ITT dataset, except those women violating the protocol. In particular, in the A. *montana* group, three patients were excluded (two had PT, PTT, and fibrinogen altered values, and one patient received axillary dissection). In the placebo group, seven patients were excluded (five had PT, PTT, and fibrinogen altered values, and two were on aromatase inhibitor or anticoagulant therapy introduced after enrollment). The baseline characteristics of the included patients are described in Table 1. There were no significant differences between treatment groups.

Blood and serum collected by drainages dramatically increased between day 1 and day 2 and then decreased in both treatment groups [Figure 1]. In the PP dataset, the collected volumes were higher in placebo group, but in the ITT dataset, the difference was less noticeable [Figure 1a]. In the PP dataset, the differences between the volume collected on day 1 and the volume collected in each of the following days revealed a difference steadily lower in the A. *montana* group compared to placebo [Figure 1b]. These differences were statistically significantly different between the

two treatment groups on day 2, both in the univariate model ($P = 0.034$) and in the model including treatment and collected volume ($P = 0.033$), and on day 3, only in the latter model ($P = 0.0223$) adjusted for weight and volume to the day of surgery. The difference between the two treatments was not statistically significant on days 4 and 5. Globally, a lower mean volume of blood and serum collected by drainage was observed in A. *montana* group compared to placebo (in PP analysis: 334.35 vs. 428.75 ml, $P = 0.11$) [Tables 2 and 3]. A statistically significant difference was shown in regression model 3 applied on PP dataset, when the estimates were also adjusted for the volume collected from the drainage on day 1 and the weight of the patient [Table 4].

During the 5 days of the study, the drainage was removed in 36 patients, equally distributed in the two groups. The analysis of time of drain removal revealed no difference between the two groups of patients both in the ITT dataset (log-rank test $P = 0.7287$) and in the PP dataset (log-rank test $P = 0.8653$), although in A. *montana* group, drainage was apparently removed earlier [Figure 2a]. The analysis of the time up to collected volume below 10 ml neither revealed difference between the two treatments in the ITT analysis (log-rank test $P = 0.8653$) nor in the PP analysis (log-rank test $P = 0.6138$), but showing a better performance of the patients treated with A. *montana* in the latter [Figure 2b].

The presence of bruising and hematomas or breast swelling did not differ significantly by treatment group, $P = 0.67$ and $P = 0.57$, respectively. Even the perception of pain, measured by VAS, showed no statistically significant differences between the two treatment groups ($P > 0.05$). All the recorded adverse events were not severe (e.g., rush, headache, nausea), not correlated with the A. *montana* treatment, and completely recovered at the end of the study. Moreover, they were equally distributed between the two groups: Five patients experienced at least an adverse event in the A. *montana* group versus four in the placebo group.

Table 1: Baseline characteristics of the ITT population

Characteristics	Statistics	Placebo (*N*=27)	*Arnica* (*N*=26)
Age	Mean±SD	56.59±12.65	55.77±11.41
	Median	52.28	53.60
	Min-Max	33.91-75.42	38.15-73.22
Race	Asian (%)	-	1 (3.8)
	Caucasian (%)	27 (100)	25 (96.2)
Height	Mean±SD	160.96 (4.74)	162.46 (7.27)
	Median	162	160.50
	Min-Max	150-70	150-178
Weight	Mean±SD	64.19±13.05	66.95±13.17
	Median	60.40	62.90
	Min-Max	48.00-104.50	50.10-96.30
BMI	Mean±SD	24.74±4.71	25.33±4.59
	Median	24.34	22.81
	Min-Max	18.25-40.82	20.04-38.58
Systolic blood pressure (mmHg)	Mean±SD	119.74±17.90	120.00±15.30
	Median	120.00	120.00
	Min-Max	85.00-150.00	100.00-160.00
Diastolic blood pressure (mmHg)	Mean±SD	73.52±11.99	75.19±7.41
	Median	70.00	80.00
	Min-Max	50.00-100.00	60.00-90.00
Heart rate (beats/min)	Mean±SD	73.78±8.45	74.88±11.67
	Median	74.00	75.00
	Min-Max	60.00-88.00	50.00-102.00

SD: Standard deviation, ITT: Intention-to-treat

DISCUSSION

In this study, which to our knowledge is the first to test the effect of A. *montana* in breast cancer surgery, we have measured

Table 2: Mean daily volume and total volume in the two treatment groups for the ITT dataset

Treatment	ITT dataset				95% CI
	Day	Patients (*N*)	Volume Mean (ml)	SD	
A. montana 1000 K *N*=26	1	26	39.42	40.68	23.79-55.06
	2	26	124.42	49.94	105.23-143.62
	3	26	98.08	57.08	76.14-120.02
	4	25	70.20	65.54	44.51-95.89
	5	20	55.00	97.73	12.17-97.83
	Total	26	371.73	239.97	279.49-463.97
Placebo *N*=27	1	27	37.78	30.21	26.38-49.17
	2	27	133.15	82.38	102.07-164.22
	3	27	107.41	70.39	80.86-133.96
	4	26	71.15	59.02	48.47-93.84
	5	21	49.52	60.09	23.82-75.23
	Total	27	385.37	235.36	296.59-474.15

SD: Standard deviation, ITT: Intention-to-treat, *A. montana*: *Arnica montana*, CI: Confidence interval

Table 3: Mean daily volume and total volume in the two treatment groups for the PP dataset

Treatment	PP dataset				95% CI
	Day	Patients (n)	Volume mean (ml)	SD	
A. montana 1000 K *N*=23	1	23	42.17	40.42	24.70-59.65
	2	23	119.78	45.11	100.27-139.29
	3	23	91.09	50.99	69.04-113.14
	4	22	57.73	35.81	41.85-73.61
	5	18	33.33	37.10	14.88-51.78
	Total	23	334.35	164.64	263.15-405.55
Placebo *N*=20	1	20	43.50	28.43	30.20-56.80
	2	20	154.50	77.15	118.39-190.61
	3	20	127.00	66.34	95.95-158.05
	4	20	67.50	45.67	46.13-88.87
	5	16	45.31	52.87	17.14-73.48
	Total	20	428.75	214.32	328.44-529.06

SD: Standard deviation, *A. montana*: *Arnica montana*, CI: Confidence interval, PP: Per-protocol

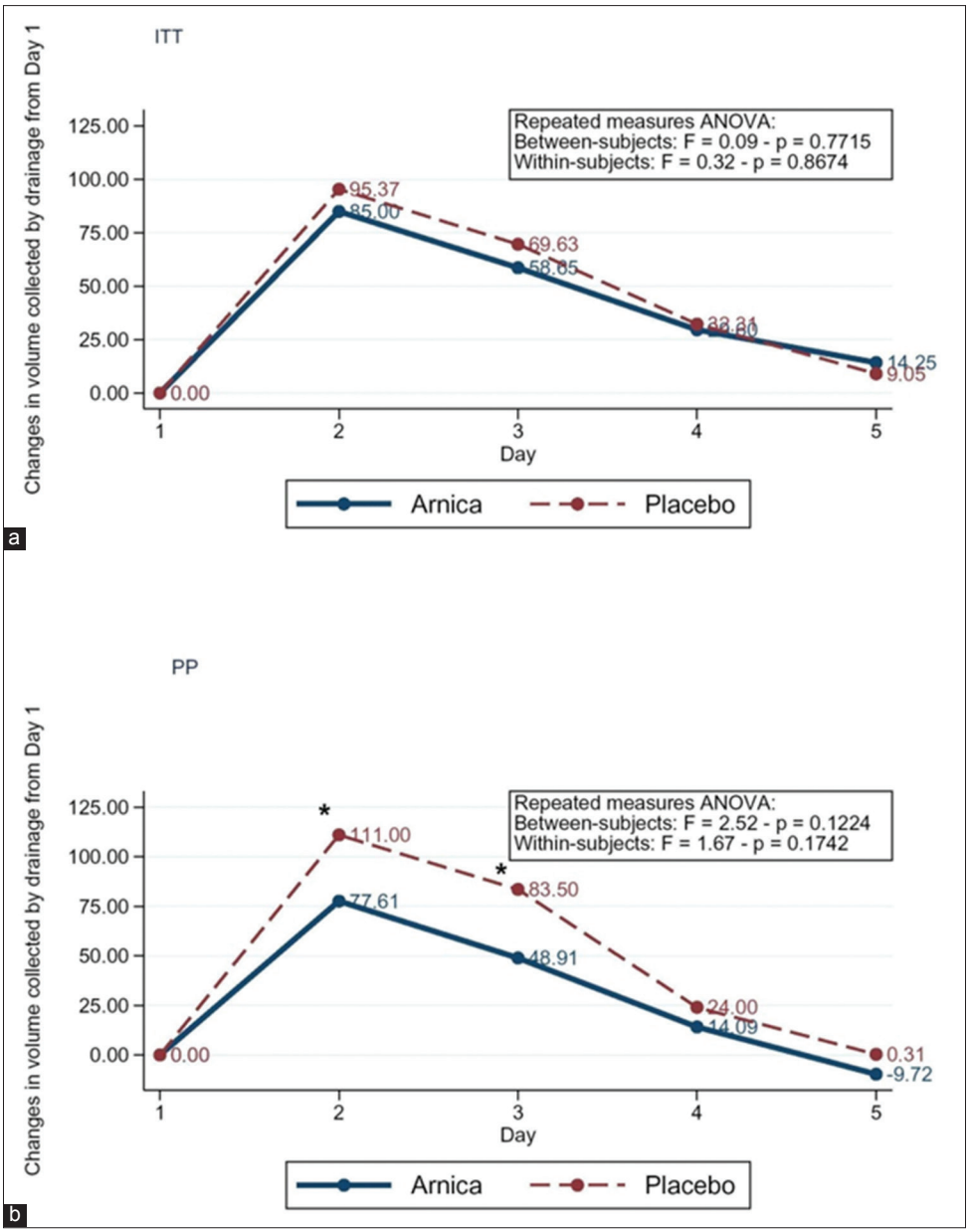

Figure 1: Changes in volume collected by drainage from day 1 to each following day per treatment: (a) Intention-to-treat population and (b) per-protocol population; *P < 0.05

the efficacy of the homeopathic treatment versus placebo in reducing the post-operative bleeding and seroma production in patients subjected to total mastectomy. The difference in the volume of blood and serum collected by drainages between the group of women treated with A. *montana* and those treated with placebo was statistically significant in the PP dataset, but only in the model which included, in addition to the type of treatment, the volume collected on the day of surgery, and the weight of the patient. Thus, we determine that these two additional variables have a considerable effect on the efficacy of the treatment, and further studies are needed to investigate their specific contributions. In general, the other data obtained, such as a slightly earlier removal of the drainage and a faster reduction in the volume of blood and serum collected in the drainage, were not statistically significant and only suggested a slight advantage in the post-operative recovery process of patients treated with A. *montana*. The variability is similar in the two groups and it appears not due to different responses to the drug tested. The high Korsakovian dilution used in this study compared to other studies could explain the failure to reach the threshold of significance despite the fact that the differences are quantitatively small but noticeable [6,11]. This high Korsakovian dilution was chosen to surely avoid any toxicity from A. *montana* extract, to administer a harmless experimental treatment.

Overall, the efficacy of homeopathic treatments in surgical settings is still controversial. In obstetrics, evaluating the effect of A. *montana* and *Bellis perennis* on blood loss, Oberbaum *et al.* found that the mean hemoglobin levels remained the same

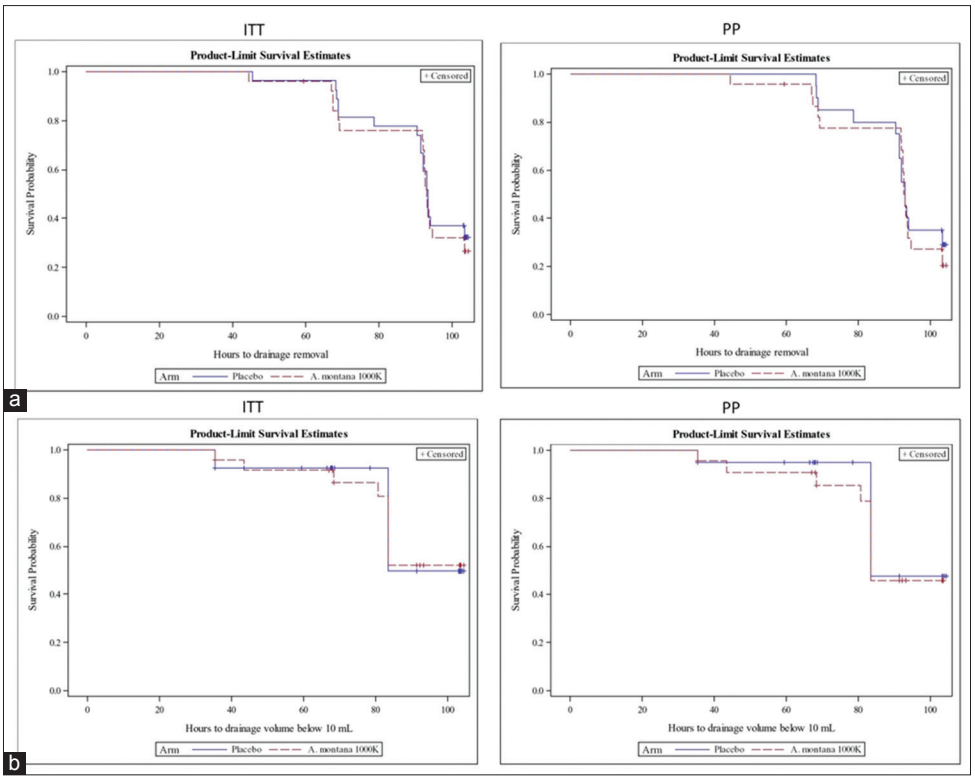

Figure 2: Duration of drainage (a) and time to drainage volume below 10 mL (b) per treatment (intention-to-treat and per-protocol datasets)

Table 4: Estimates of the mean difference in total volume collected by drainage during the study between the two treatment groups (*Arnica*–Placebo) by dataset

Dataset	Model[1]	Variables	Parameter estimate[2]	95% CI	*t*-value	*P* value
ITT	1	Treatment	−13.64	−138.51-111.23	−0.22	0.83
	2	Treatment	−18.85	−129.87-92.17	−0.34	0.73
	3	Treatment	−28.69	−138.27-80.89	−0.53	0.60
PP	1	Treatment	−94.40	−211.28-22.48	−1.63	0.11
	2	Treatment	−90.28	−186.71-6.14	−1.89	0.07
	3	Treatment	−106.28	−203.11-−9.45	−2.22	0.03*

[1]Regression models are as follows: (1) Model 1: Treatment only, (2) Model 2: Treatment and volume collected on the day of the intervention, (3) Model 3: Treatment, volume collected the day of surgery, and patient's weight, [2]Mean difference in volume (mL) collected by drainage during the study between *Arnica* and placebo groups (*Arnica*–Placebo). *$P<0.05$. CI: Confidence interval, PP: Per-protocol, ITT: Intention-to-treat

after the administration of the homeopathic treatment whereas the levels decreased significantly in the placebo group (12.7 versus 11.6; $P < 0.05$) [17]. A systematic review has analyzed A. *montana* in eight randomized controlled trials (RCTs) from 1966 to 1997 [10]. Two of the included trials, one on the effect of A. *montana* on the delayed onset of muscle soreness (DOMS) and the other on the prevention of post-operative complications, showed a statistically significant result in favor of the homeopathic treatment. The other six trials did not demonstrate statistically significant differences, but some of these trials were not considered qualitatively adequate for a proper meta-analysis [10]. Other RCTs had conflictual data. Only one of the three RCTs on DOMS and none of the two on surgical patients showed statistically significant between-group differences, in particular, on the recovery after total abdominal hysterectomy and on the stripping of varicose veins [13,28-32]. In a double-blind, placebo-controlled clinical study involving patients undergoing prolonged venous perfusion, A. *montana* reduced pain symptoms, hyperemia, edema, and formation of hematomas [33]. A. *montana* treatment also slightly increased a number of coagulation factors and platelet aggregation.

In vitro studies are more promising. In fact, different authors have shown that helenalin, the most active component of A. *montana*, not only blocks the transcriptional NF-κB in T-cells, B-cells, and epithelial cells, but it also inhibits human neutrophil migration and chemotaxis and the activities of 5-lipoxygenase and leukotriene C4 synthase [34]. All these mechanisms are known to be associated with the induction of pain and inflammation, as observed in animal models of inflammatory pain [34,35]. However, these studies were conducted with pure helenalin rather than with plant extract and with much higher doses than those used here. A recent work carried out on human macrophage cells differentiated with interleukin-4 demonstrated that homeopathic doses of A. *montana* stimulate the expression of genes involved in the repair of connective tissue and, in particular, fibronectin [36]. Given the importance of this protein to the adhesion, proliferation, and movement of cells (both epithelial and connective), this could be a further target at the cellular level of this plant's action.

Undoubtedly, one as yet unsolved problem of homeopathy concerns the mechanism of action of dilutions so high that

the presumed active substances are often not detectable in molecular terms. Many laboratory studies that use homeopathic dilutions report dose-response curves that are non-linear and sometimes pseudo-sinusoidal, with peaks occurring at different dilutions, alternating with other inactive doses [37-39]. In relatively recent times, evidence has been found, especially in physicochemical studies, pointing to the presence of nanoparticles even in extremely high dilutions, or the formation of coherence domains among the molecules of the water–alcohol solvent, as predicted by quantum electrodynamics [40,41]. Although these findings fall outside the scope of the present work, if consolidated by further experimental studies, they might furnish a basis of plausibility to this complementary pharmacological approach.

The main limitations of the study were the relatively small sample, the analysis of post-operative recovery, which was limited only to 5 days, and the use of a high Korsakovian dilution which could have negatively impacted on the statistical significance of our findings. Observational studies with different Korsakovian dilutions could be useful to highlight any significant effect of *A. montana* and further validate these findings.

CONCLUSIONS

The scientific community often claims that homeopathy effects are not supported by rigorous clinical trials. This study, although reporting statistical significance only for some specific data settings, suggests a reduction in post-operative blood loss and seroma production in a group of women who underwent breast cancer surgery and treated with A. *montana* 1000 K.

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