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Original article

Axillary lymphadenectomy for breast cancer. A randomized controlled trial comparing a bipolar vessel sealing system to the conventional technique

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ABSTRACT

Aim: To compare safety and efficacy of a bipolar vessel sealing system (BVSS) to the conventional technique in axillary node dissection.
Methods: 116 women with breast cancer were randomized to conventional node dissection surgical technique (control; $n = 58$) by scalpel and monopolar cautery or using an electrothermal BVSS (study group; $n = 58$).
Results: The median (range) total volume of fluid collected by drain and aspirations was 305 (30–1420) mL in the study group and 335 (80–1070) mL in the control group ($p = 0.325$). The median (range) total volume of lymph collected by percutaneous aspirations was 207.5 (40–1050) mL in the study group and 505 (270–705) mL in the control group ($p = 0.010$). The incidence of seroma was similar in both groups ($p = 0.845$). The axillary drain was removed earlier in the study group than in controls ($p = 0.046$).
Conclusion: The use of a BVSS offers marginal advantages when compared to the conventional technique.

Introduction

Axillary lymphadenectomy for breast cancer still represents an essential staging procedure, although its application has been markedly reduced by the introduction of the sentinel node biopsy. Lymphorrhea, a persistent clear fluid output from an axillary drainage, is commonly observed after node dissection. This event represents a major risk factor for seroma formation and delays drain removal. Seroma is the most frequent complication following this surgical procedure ranging from 10% to 85%.[1–4] The occurrence of seroma is associated with prolonged in-hospital stay and outpatient management, increasing sanitary costs and patient discomfort.

Several risk factors have been identified for seroma and lymphorrhea: age greater than 60 years,[5] elevated body mass index (BMI),[6] tumor size,[7] neoadjuvant chemotherapy,[8] extent of gland resection,[1,5] number of lymph nodes harvested and their oncologic involvement.[6]

It has been suggested that a more efficient blood and lymph vessels sealing during lymphadenectomy may play a key role in reducing postoperative morbidity.[3] The standard reference technique for axillary dissection comprises the use of sharp dissection, monopolar electrocautery, and vessel ligation. Alternative techniques and new surgical devices have been proposed with the aim of minimizing lymphorrhea, but the results are controversial.[6,7,9–13]

During axillary dissection, vessel sealing, achieved by an electrothermal bipolar system, may offer potential benefits. In fact this device, by combining electrical energy and mechanical pressure, can obtain a permanent vascular and lymph vessels sealing, with a minimal spread of thermal injury to the surrounding tissues.[14–16]

In a nonrandomized trial, the use of such device was shown to be effective in achieving hemostasis and lymphatic sealing during modified radical mastectomy and axillary dissection. The results suggested a significant reduction of drainage output and duration and seroma occurrence when compared with historical controls.[17]

Two prospective randomized trials[18,19] evaluated the potential benefits of the bipolar vessel sealing system on clinical outcome compared to standard technique, with contrasting results.

The aim of this study was to evaluate the safety and the efficacy of the bipolar vessel sealing system in performing axillary dissection and to evaluate its potential role on postoperative outcome.

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Materials and methods

Patient characteristics

Women with documented breast cancer (by histology or cytology) and candidate to elective axillary lymphadenectomy were eligible for the study. The indications to lymphadenectomy were suspected metastatic nodes by clinical exam and ultrasound scanning or cases of positive sentinel node documented by a previous surgical biopsy. Axillary dissection was not associated to breast surgery when previous breast tumor resection was considered adequate (lumpectomy with clear margins).

Preoperative exclusion criteria were: age less than 18 years, previous axillary operations (except for sentinel node biopsy), preoperative radio-chemotherapy, scheduled reconstructive breast operation and denied written informed consent.

The study protocol was approved by the Ethical Committee of our hospital.

The trial was registered at ClinicalTrial.gov with the ID number NCT01286337.

Random assignment

This was a prospective, randomized, open, single center trial. The study was performed at the Department of Surgery, Milano-Bicocca University, San Gerardo Hospital, Monza, Italy.

Patients were randomly assigned to the study group or the control group with a 1:1 ratio according to a list generated by a computer program (based on blocks of 10). Concealment assignment was done by opaque, sealed envelopes that were opened just after the induction of anesthesia by a registered nurse who was not involved in the study.

Procedures

In all patients axillary lymphadenectomy was performed by a standard en-bloc node dissection of level I, II and III. The procedure was carried out by eight members of the surgical staff as we did not have a dedicated breast surgical team.

Patient randomized to the study group were operated without using monopolar electrocautery. During lymphadenectomy, lymph and blood vessels were sealed using an electrothermal bipolar vessel sealing system (Ligasure Precise™; Valleylab, Boulder, Colorado) and limiting as much as possible dissection by scissors or scalpel.

Patients randomized to the conventional treatment (Control group) were operated using scissors/scalpel and monopolar cautery dissection or suture ligation to obtain vessel sealing.

In both groups a close, low-suction, flat, Jackson-Pratt type drain (size 4 × 10 mm, length 110 cm, Redax®, Mirandola, Italy) was placed in the axillary cavity at the end of operation.

At the end of surgery a standard, noncompressive dressing was applied to all patients. No limitation to arm movement was scheduled.

According to protocol, axillary drain had to be removed during in-hospital stay only if the daily output was less than 40 mL in the previous 24 h. This cutoff volume was chosen because it has been recognized as an adequate threshold to minimize the risk of seroma formation.[3]

Antibiotic prophylaxis was prescribed to all patients by a single dose of intravenous cefazolin (2 g) given 30 min before anesthesia induction.

Discharge date was decided by a member of the surgical staff who was not involved in the study, irrespectively of drain removal. In those patients discharged with the drain in place, it was removed during a subsequent office visit when the output was <40 mL/day.

In case of seroma formation (defined as a clinically relevant swelling of the axilla confirmed as fluid collection by a surgeon-performed ultrasound scan) after drain removal, percutaneous aspirations were done every other day until aspirate was less than 10 mL.

Data collection and follow up

In order to reduce possible biases related to the absence of trial blindness, any data collected during hospital stay and postoperative morbidity were recorded by a trained, independent and blind-to-treatment evaluator who classified complications according to a predefined list (Table 1). Patients were followed-up by weekly office visits for a minimum of 30 days after hospital discharge.

Primary and secondary end points

The primary end point was to compare the total volume of fluid collected in the axillary drain by using the two different surgical techniques.

The secondary end points were to compare the time needed to obtain a drain output lower than 40 mL/day by the two different surgical techniques and the incidence of seroma in the two groups.

Efficacy of the experimental technique was judged by the number of lymph nodes harvested and safety by the occurrence of nerve lesions and perioperative blood losses requiring blood transfusion or reintervention.

Statistical methods

A sample size of 56 subjects per study arm was planned to provide a 90% power to detect a 25% reduction of the total volume of fluid drained during the first 4 days after axillary dissection by using a bipolar vessel sealing system when compared to a conventional technique. We anticipated, based on our historical controls, that the average total amount of fluid drained using the conventional technique was 250 mL (standard deviation: 110).

The primary analyses were carried out on an intention-to-treat basis, while the secondary analysis was per-protocol. The latter excluded from both treatment groups patients with protocol violation, that is subjects who had the drain removed when the daily fluid output was greater than 40 mL. An early drain removal affects a correct estimation of postoperative lymphorrhea, as well as may represent a risk factor for seroma formation. Since there was an unbalance between groups in the number of patients undergoing mastectomy, and being this procedure a major risk factor for

Table 1
A priori definition of complications related to axillary lymphadenectomy.

Complication	Definition
Lymphorrea	Persistent daily output of clear fluid > than 40 mL from axillary drain
Seroma	Collection of clear fluid within the axillary cavity after drain removal with a volume > than 10 mL as measured by percutaneous aspiration
Wound infection	Any redness or tenderness of the surgical wound with discharge of pus
Wound dehiscence	Any dehiscence of surgical suture >2 cm
Hemorrhage	Bleeding needing red cell transfusion and/or re-operation
Nerve lesion	Persisting pain and/or mobility defect of shoulder/scapula/arm proven by electromyography

lymphorrhea, we performed also a subgroup analysis including only those subjects.

Continuous data were described by median and range, categorical data by the percentages of subjects falling in each category. Comparisons were performed by the nonparametric Wilcoxon test for continuous variables and chi-square test for discrete variables. The proportion of patients with drain removed over time and the proportion of patients who reached 40 mL of daily output and had the drainage removed in time were described by the Kaplan–Meier estimate and compared by the log-rank test.

Results

Fig. 1 shows the trial profile according to the CONSORT statement.[20] One hundred and forty-two patients were eligible for the study. Due to exclusion criteria, 116 subjects were randomized, 58 into the experimental group and 58 in the control group. Primary analysis was by intention-to-treat. In 17/58 (29%) patients of study group and in 18/58 (31%) controls, we recorded an accidental removal of the drain before the daily output was less than 40 mL/day with a violation of the study protocol. The remaining 41 patients in the experimental group and 40 patients in the control group were analyzed as per-protocol.

The two groups were well matched for baseline and pathology characteristics except for the number of patients who underwent mastectomy that was higher in the control group (Table 2). The two different techniques were similar in terms of lymph nodes harvested (median 15 vs. 16 in the control and in study group respectively, $p = 0.282$) and operative time (median 90 min in both groups, $p = 0.470$). As for safety outcome, no intra- and postoperative hemorrhage, nerve damage, and wound dehiscence was observed in both treatment groups.

Post-operative outcome variables are reported in Table 3. The median (range) total volume of drainage was 205 (20–600) mL in the study group and 248 (20–545) mL in the control group ($p = 0.403$) according to per-protocol analysis. In a subgroup analysis including only patients who underwent mastectomy the median (range) total volume of drainage was 280 (70–540) mL in the study group and 260 (40–545) mL in the control group ($p = 0.848$). No significant difference between the two techniques was also observed in the intention-to-treat analysis. Evaluating the axillary output as the overall collected fluid by axillary drain and by percutaneous aspirations, no difference was observed between the two groups according to intention-to-treat analysis (median volume of 305 mL in the study group vs. 335 mL in the control group, respectively. $p = 0.325$).

One out of 58 (1.7%) patient in control group and 2/58 (3.4%) patients in study group were discharged with drainage in place.

Per-protocol analysis showed a similar incidence of seroma in the two groups: 24.4% (10/41) in the study group and 22.5% (9/40) in controls ($p = 0.845$). In a subgroup analysis including only patients who underwent mastectomy, seroma rate was 0% (0/9) in the study group and 21.1% (4/19) in controls ($p = 0.137$).

The median number of aspirations per patient was 4 in both groups. The median (range) total volume of lymph collected by percutaneous aspirations was 275 (40–1050) mL in the study group and 505 (130–890) mL in the control group ($p = 0.226$). This difference reached statistical significance in the per-protocol analysis: 207.5 (40–1050) mL vs. 505 (270–705) mL, in study group and in controls respectively ($p = 0.010$).

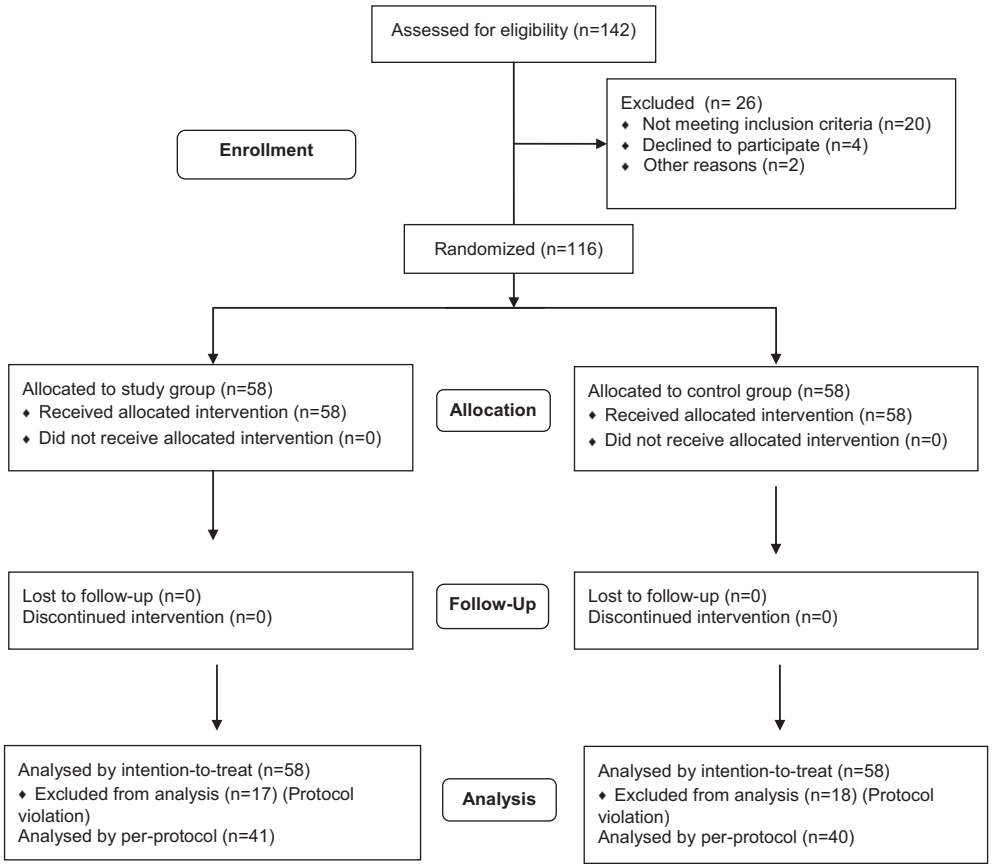

Fig. 1. Study diagram according to the CONSORT statement.

Table 2
Baseline, pathology and operation characteristics according to treatment group and type of analysis.

		Intention-to-treat		Per-protocol	
		Study ($n = 58$)	Control ($n = 58$)	Study ($n = 41$)	Control ($n = 40$)
Age – median [range], yr		65 [36–84]	69 [39–87]	64 [36–84]	70 [39–87]
Body mass index – median [range], Kg/m^2		25.7 [16.2–43.4]	25.4 [15.1–43.0]	25.4 [16.2–35.5]	25.5 [15.1–43.0]
Associated surgical procedures – no. (%)	None	18 (31.0)	7 (12.1)	11(26.8)	3 (7.5)
	Lumpectomy, external sectors	22 (37.9)	21 (36.2)	17 (41.5)	15 (37.5)
	Lumpectomy, internal sectors	5 (8.6)	6 (10.3)	4 (9.8)	3 (7.5)
	Mastectomy	13 (22.4)	24 (41.4)	9 (22.0)	19 (47.5)
Tumor dimension – no. (%)	pT1	34 (58.6)	34 (58.6)	23 (56.1)	22 (55.0)
	pT2	23 (39.7)	21 (36.2)	17 (41.5)	16 (40.0)
	pT3	1 (1.7)	3 (5.2)	1 (2.4)	2 (5.0)
Tumor histology – no. (%)	Ductal	40 (69)	38 (65.5)	30(73.2)	29(72.5)
	Lobular	9 (15.5)	13 (22.4)	7 (17.1)	5 (12.5)
	Other	9 (15.5)	7 (12.1)	4 (9.7)	6 (15)
Patients with clinically positive nodes – no. (%)		23 (39.7)	28 (48.3)	17(41.5)	21(52.5)
Patients with positive sentinel node biopsy – no. (%)		35 (60.3)	30 (51.7)	24 (58.5)	19 (47.5)
Lymph nodes harvested –median [range]		16 [6–26]	15 [5–36]	16 [7–26]	15 [5–36]
Patients with positive nodes confirmed by pathology– no. (%)		33 (56.9)	29 (50.9)	21(51.2)	21(52.5)
Number of positive nodes per patient – median [range]		5 [1–16]	5 [1–20]	6 [1–16]	5 [1–20]
Operative time – median range], min.		93 [50–170]	90 [50–155]	90 [50–170]	90 [50–150]

No differences between the two groups in terms of wound infection rate and length of hospital stay were observed.

A significant earlier drainage removal was observed in the study group when compared with controls, in both intention-to-treat analysis and per-protocol analysis (Fig. 2).

The median time needed to reach 40 mL of daily output from the drain showed a significant faster decrease of lymphorrhea over time in the study group than in controls (median day 3 days vs. 4 days respectively; $p = 0.03$) (Fig. 3). No differences were observed in the subgroup of patients who underwent mastectomy (median day 4 in both groups; $p = 0.425$).

A quantitative description of fluid collected by percutaneous aspirations during different office visits is depicted in Fig. 4 in the per-protocol population. We observed a progressive reduction of the median volume of aspirates over time in the study group, while in the control group the volume remained quite constant. This difference reached significance at the second ambulatory visit ($p = 0.027$).

Discussion

The necessity to perform axillary lymphadenectomy during breast cancer surgery is strikingly reduced after the introduction of the sentinel node biopsy. Nevertheless, radical node dissection still has precise indications and represents a key clinical problem for the associated postoperative morbidity. In particular, lymphorrhea with subsequent delayed drain removal, seroma, hematoma, wound infection, bleeding and nerve lesion, may lead to patient discomfort, longer in-hospital stay, prolonged outpatient treatment, and increased costs.

Aetiology of seroma formation is still poorly understood and controversial, appearing to be a multifactorial event. Several factors seem to be involved, such as acute inflammatory exudates from surgical trauma and tissue damage, lymph leakage from interrupted lymphatic channels and the size of dead space after wound closure.

Several clinical trials addressed the problem of morbidity related to axillary dissection. Alternative technical and pharmacological options have been proposed to improve the standard procedure to lessen lymph output and seroma formation with inconsistent results. By comparing the use of scalpel alone to monopolar electrocautery, the latter seemed to be more effective in achieving hemostasis, but it resulted in increased seroma formation and other wound complications (i.e. necrosis and infections) due to the spread of thermal injury to the near tissues.[21,22] After radical mastectomy, the closure of dead space by suturing skin flaps to the underlying muscle was reported to be effective in reducing the incidence of seroma.[23–25] The administration of tranexamic acid significantly decreased drainage volume in patients who underwent axillary dissection during breast-cancer surgery.[26] Contrasting results were reported on the possible role of fibrin sealant and sclerotherapy in reducing morbidity after axillary dissection.[27,28]

Table 3
Post-operative outcome parameters according to treatment group and type of analysis.

	Intention-to-treat		p-value	Per-protocol		p-value
	Study ($n = 58$)	Control ($n = 58$)		Study ($n = 41$)	Control ($n = 40$)	
Drainage volume, median [range], mL	265 [30–600]	260 [30–600]	0.500	205 [20–600]	248 [20–545]	0.403
Seroma, no. (%)	18 (31)	15 (25.9)	0.537	10 (24.4)	9 (22.5)	0.845
Number of aspirations per patient, no. (%)	$n = 18$ pts	$n = 15$ pts		$n = 10$ pts	$n = 9$ pts	
≤3	4 (22.2)	5 (33.3)	0.767	4 (40)	3 (33.3)	0.192
4–6	10 (55.6)	7 (46.7)		5 (50)	5 (55.6)	
≥7	4 (22.2)	3 (20)		1 (10)	1 (11.1)	
Total volume aspirated, median [range], mL	275 [40–1050]	505 [130–890]	0.226	207.5 [40–1050]	505 [270–705]	0.010
Overall amount of fluid collected by drain and aspirations, median [range], mL	305 [30–1420]	335 [80–1070]	0.325	240 [30–1360]	270 [80–920]	0.136
Wound infection, no. (%)	4 (6.9)	1 (1.7)	0.170	3 (3.7)	0 (0)	0.081
Length of postoperative stay, median [range], days	4 [2–5]	4 [1–5]	0.189	4 [2–5]	4 [1–5]	0.103

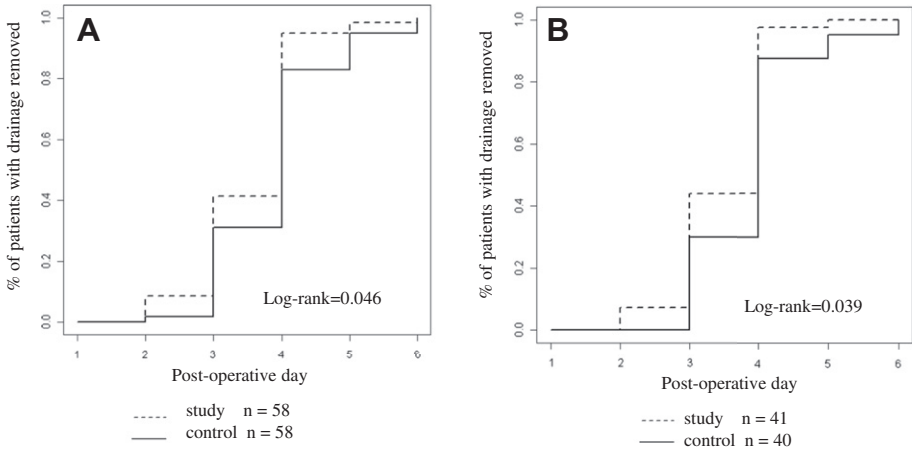

Fig. 2. Cumulative percentage of patients with the drainage removed over time. Panel A: Intention-to-treat analysis and Panel B: Per-protocol analysis.

External compression dressing, traditionally used to obliterate axillary dead space, was shown to increase postoperative morbidity and seroma rate.[29,30]

The impact of different new surgical devices, such as the harmonic scalpel and the electrothermal bipolar vessel sealing system, in affecting postoperative morbidity has been also investigated. In fact, optimal blood and lymph vessel fusion might represent a key factor for better outcome. At the same time, the reduced thermal spread to surrounding tissues obtained by the use of these devices represents another strong rationale for a positive effect on morbidity following lymphadenectomy.

In a non-randomized trial[31] a harmonic scalpel used during radical mastectomy resulted in reduced blood loss and duration of drainage as compared to monopolar electrocautery, while no significant difference was observed in seroma rate. Lumachi et al., in two randomized studies, observed a positive effect of ultrasound scissors in reducing the total amount of lymph output and incidence of seroma following axillary dissection.[6,7] On the contrary, Galatius et al.[12] reported no differences in terms of surgical outcome comparing ultrasonic dissection to standard technique in performing modified radical mastectomy. However, in this study ultrasound scalpel was not used during axillary dissection and the drain was removed regardless of drainage volume.

The electrothermal bipolar vessel sealing system combines electrical energy and mechanical pressure to obtain a permanent vascular and lymph vessels fusion and sealing with a minimal spread of thermal injury (up to 1 mm) to the surrounding tissues.[14,15] This permanent fusion is achieved by melting the collagen and elastin in the vessel walls. This device may seal vessels up to 7 mm in diameter or tissue bundles. These peculiarities represent the rationale for a possible positive effect following axillary node dissection. Yet, the use of a bipolar vessel sealing system for axillary dissection has not been intensively investigated and the results are sparse.[17–19]

The results of our trial on safety and efficacy confirmed previous observations.[17–19] The device did not affect the number of lymph nodes harvested and its use was not associated with clinically relevant bleeding or nerve damage.

In subjects undergoing radical mastectomy and lymphadenectomy, Manouras and colleagues,[17] in a non-randomized trial,

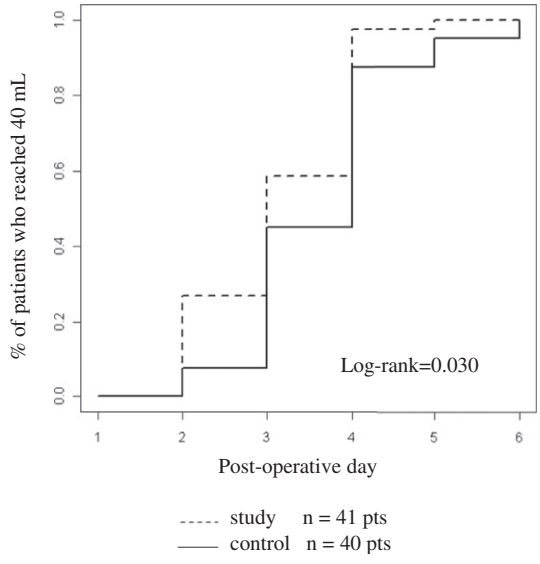

Fig. 3. Cumulative percentage of patients who reached 40 mL of daily drain output (per-protocol analysis).

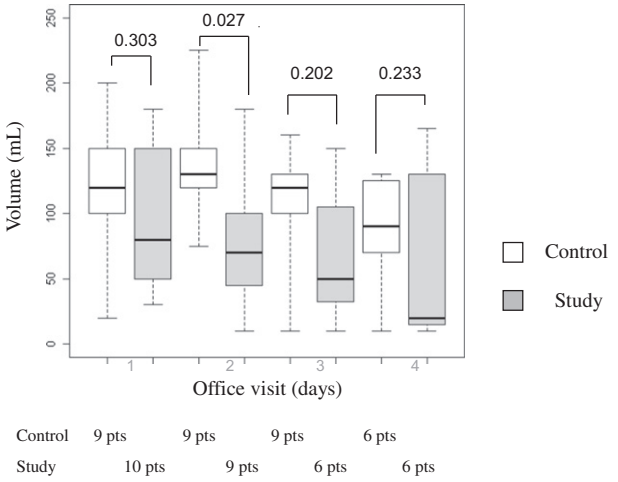

Fig. 4. Distribution of the volume of percutaneous aspirations during out-patient visits in subjects who developed seroma (per-protocol analysis). Boxplot legend: upper horizontal line of box: 75th percentile, lower horizontal line of box: 25th percentile, horizontal bar within box: median value and vertical dotted line: minimum–maximum value.

reported that by using a bipolar vessel sealing system the average axillary output was 155 mL and the mean drainage duration was 2.7 days, less than what usually reported in the literature. Moreover, they did not experience postoperative seroma, hematoma or wound infection. Similarly to what reported by a previous randomized trial,[18] we did not observed a reduction in rate of seroma and wound infection in patients treated using the bipolar vessel sealing system. According to the per-protocol analysis, we observed a clear trend, which did not reach statistical significance, toward to a lesser incidence of seroma formation in the subgroup of patients who underwent mastectomy, confirming results by others.[17]

Although not statistically significant, a higher incidence of wound infections has been observed in the study group compared to controls. A confirmation of this trend will need larger series.

The discrepancy of the present data with other experiences[17] could be explained by several factors. The most important is the limitation and the potential interpretation bias of nonrandomized trials overestimating positive results of treatments when compared with controls.[32] Another possible reason is that the lack of a dedicated surgical team in this study might result in a lower accuracy in the use of this device.

Like others,[18,19] we could not confirm any significant advantage of a bipolar vessel sealing system in terms of drainage volume when compared to the conventional technique even in the subgroup of patients undergoing mastectomy. No difference was found even evaluating the axillary output as the sum of fluid drained until drain removal and the volume aspirated percutaneously.

In our study the exact timing of drain removal was not defined *a priori*, being the only indication an output of less than 40 mL. This threshold was chosen because when the drain is removed with less than 40 mL the incidence of seroma is minimized.[3] Therefore, the potential impact of the tested device on the reduction of lymphorrhea was investigated in a per-protocol-analysis on the time required to reach 40 mL of daily output. This type of analysis excludes from both groups patients with protocol violation, that is subjects who had the drain removed when the daily fluid output was greater than 40 mL. An early drain removal affects a correct estimate of postoperative lymphorrhea, as well as it may represent a risk factor for seroma formation. By this secondary analysis our data suggest a significant faster decrease of axillary fluid production over time in the study group compared to controls. This result may be interpreted as the possibility to remove the drain one day before in the studied patients, as observed in a previous randomized trial.[19]

A conceivable explanation may be linked to the reduced inflammatory exudation obtained by the lower thermal spread to tissues of the bipolar sealing system when compared to monopolar electrocautery. The significative reduction in volume of lymph aspirated percutaneously observed in study group when compared to controls further supports this hypothesis.

Another reason for the earlier drain removal and lower volume of lymph aspirated percutaneously might be attributed to the higher number of mastectomy patients in the control groups.

The marginal impact of the bipolar vessel sealing system on postoperative outcome may confirm the multifactorial pathophysiology of seroma formation.[33,34] In such scenery, it is reasonable that lymphorrhea and seroma can not be completely controlled by a technical device.

Conclusion

We confirm that the use of a bipolar vessel sealing system in performing axillary node dissection for breast cancer is safe and feasible. In the per-protocol analysis, which mimic an ideal and strict application of this device, there were significant benefits in terms of earlier drain removal and reduction of lymph aspirated percutaneosly.

Ethical approval

The research protocol was approved by the local ethical committee.

Conflict of interest statement

The authors declare no conflict of interest.

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