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TECHNICAL ADVANCES

Effectiveness of topical use of Lietofix® in wound healing after pilonidalis sinus excision: a multicenter study by the Italian Society of Colorectal Surgery (SICCR)

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Introduction

Pilonidal sinus disease (PSD) is a common inflammation of the sacrococcygeal region (26 pts/100.000 people), mostly affecting younger age and males (a male/female ratio 2:1) [1]. The disease can affect quality of life due to local pain or discomfort and be a significant cost to society due to absence from work before and even after therapy.

Open healing reduces the risk of recurrence by 35% when compared with any closed method [1]. However, open healing is associated with postoperative pain and discomfort and weeks of wound care. Its management is not standardized [2]. Wound dressings impregnated with antimicrobial agents (i.e. silver and alginates or gentamycin collagen sponge) and vacuum-assisted closure (VAC) have been used with controversial benefits. Topical application of hyaluronic acid derivatives and aloe vera have been proved effective in reducing postoperative pain and the burning sensation from surgical and chronic wounds and in accelerating the wound healing process by promoting re-epithelization [3].

Lietofix® (Nathura S.P.A.) is a new hydrophilic cream, the main components of which are hyaluronic acid, sodium alginate, aloe barbadensis gel, glycerin and bovine colostrum. We sought to assess the effectiveness of topical application of this ointment in improving tissue repair and reepithelization and reducing patients' symptoms after pilonidal sinus excision and open wound healing in a randomized comparative study: length and outcomes (pain, wound discharge, discomfort and grade of re-epithelization).

Materials and methods

Consecutive patients with chronic PSD (with a maximum extension of 15 cm length) treated by complete surgical excision of the whole sinus with elliptical incisions as far as the fascia overlaying the sacrum and open healing were recruited from ten Italian Colorectal Units. Exclusion criteria were cancer, human immunodeficiency virus (HIV) infection, diabetes mellitus, pregnancy, Crohn's disease, severe liver disease, known allergy/intolerance to main components or excipients of Lietofix®, recurrent PSD, previous radiation treatment in the sacrococcygeal region and chronic steroid therapy. Smoking and body mass index were not assessed because they do not complicate wound healing or affect long-term recurrence [4].

The preliminary results of this study were presented at the 7th National Congress of the Italian Society of Colorectal Surgery, Rome (Italy), September 30–October 3, and published as abstract on Tech Coloproctol (2017) 21:823–845.

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The study population was randomized into two arms (group A and group B) using a dedicated computer program and each participating center received the randomization list by e-mail. Group A was treated with Lietofix® and group B was treated with application of iodoform dressing (standard treatment). Patients in group A were instructed to apply twice daily (every 12 h) enough ointment to cover the wound surface, previously cleaned with sterile saline solution with a thin coat (about 2 mm). Application was continued for at least 60 days or until complete wound healing, according to the medical advice. Each patient was provided with an amount of the product that would last until the end of the study. Patients in group B were instructed to clean the wound with sterile saline solution and change the iodized dressing twice daily for at least 60 days, or until complete wound healing. No antibiotics were administered in the postoperative period and no restrictions of activity were recommended.

Postoperative assessment was performed at day 3 (T1), day 7 (T2), day 14 (T3), day 21 (T4), day 30 (T5), day 45 (T6) and day 60 (T7). At each follow-up, an independent observer, blinded to the assigned treatment, recorded patients' symptoms (pain, discomfort and wound discharge) using a 0 (no symptoms) to 10 (worst symptos) visual analog scale (VAS), grade of re-epithelization (R0: inflammatory tissue with active secretion and fibrin; R1: granulation tissue formation; R2: partial reepithelization; R3: complete reepithelization) and time to wound healing. All participants gave written informed consent. The study was approved by the ethics committee of each center which participated in the trial.

Statistical analysis

The Skewness and Kurtosis test was used to evaluate the normality of continuous variables and, when possible, for those not normally distributed, a normalization model was set using the square root function. To calculate the sample size, a significance level (α) was set at 0.05 and power was set at 80%. Assuming an expected prevalence of patients with complete re-epithelialization (45 days after surgery/T6) of 70% in Lietofix group (group A) vs 50% in standard treatment group (group B), the subjects to be recruited were 186, of which 93 (50%) belonging to group A and 93 (50%) to group B. Assuming that 10% of the patients would be lost at the follow-up, the final sample size consisted of 205 patients, 103 (50.2%) belonging to group A and 102 (49.8%) to group B. The patients were assigned to one of the two treatment arms using a random method, making the two groups homogeneous by age and sex. The Student's *t* test for independent samples (parametric) was used to compare normally or normalized continuous variables between groups and the Wilcoxon rank test (nonparametric) to compare the not normalizable continuous variables. The Friedman test (nonparametric) was used to compare continuous variables between whole time series, while categorical variables were compared by the Chi-square test and Fisher's exact test. Correlation between age, type of treatment (group A or B), wound size and outcomes (pain, wound discharge, discomfort and grade of reepithelization) at day 3 (T1) and day 7 (T2) was performed by the Spearman's rank correlation test (Spearman's rho, confidence intervals—95% CI). The association between re-epithelization at T6 (YES/NO) and re-epithelization at T1, age, sex, type of treatment (group A or B), and wound length was assessed by univariate log-binomial regression analysis. The relative risk (RR) values were estimated, with 95% CI; the *z* score test was performed. Subsequently, a multivariate log-binomial regression model was created, using as determinant the type of treatment (group A or B) adjusted for the variables associated with the outcome in the univariate log-binomial regression. The adjusted RR (aRR) values were calculated, with 95% CI and the *z* score test was performed. A p value ≤ 0.05 was considered significant.

Results

From April 2016 to December 2017, 205 patients were recruited from 10 centers in Italy and randomized into two groups (Fig. 1). Nineteen patients in group B were excluded because they declined Lietofix, leaving 186 patients (124 males, 66.7%; mean age 25.3 ± 10.2 years, range 15–64 years) 103 (55.4%) in group A (Lietofix) and 83 (44.6%) in group B (standard treatment group). The two groups were comparable for demographic data (group A: 60.2% males and group B: 74.7% males) and age (group A: 24.0 ± 10.2 years; range 15–59 vs. group B: 25.6 ± 10.2 years; range 15–64; $P = 0.329$). Overall, the mean length of the open wound was 6.4 ± 2.6 (range 2.0–14.5) cm, without a statistically significant difference between group A (6.7 ± 2.5; range 2.0–3.0 cm) and group B (6.2 ± 2.7; range 2.0–14.5 cm) ($p = 0.181$). Patients with complete re-epithelization (R3) (1 patient at T4, 11 patients at T5 and 59 patients at T6) were excluded from the analysis of pain, wound discharge and discomfort at the subsequent follow-up visits. Seven patients were lost to follow-up and were included in the analysis until their last follow-up. At T6, 181 patients (97.3%) (group A 99/181, 54.7% and group B 82/181, 45.3%) and at T7 (last follow-up), 179 patients (96.2%) (group A 98/179, 54.7% and group B 81/179, 45.3%) were included in the analysis of grade of re-epithelization (Fig. 1). No serious adverse events were reported in either group.

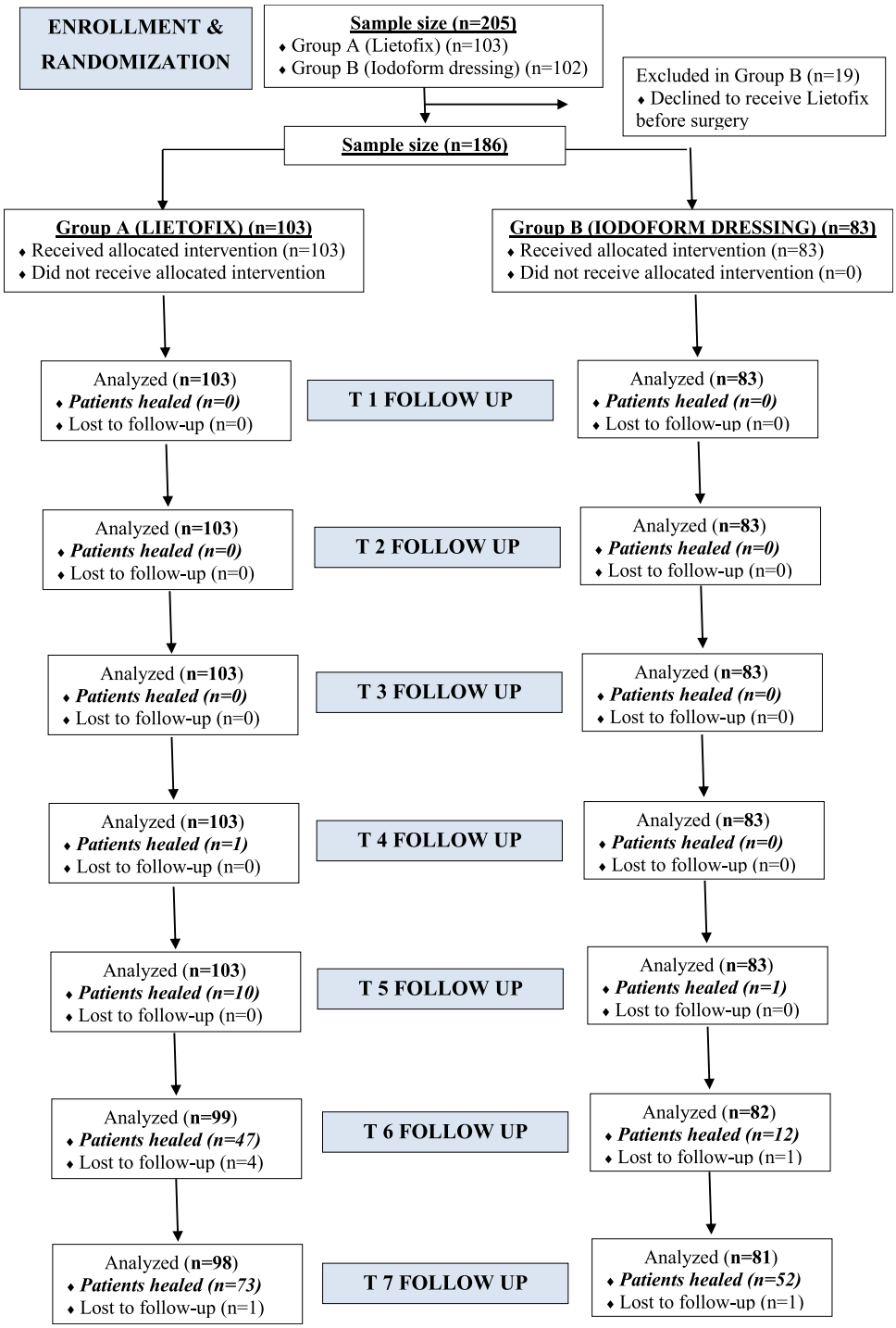

Fig. 1 Flow chart of the cohort

Analysis of outcomes

Lietofix patients had significantly less postoperative pain at T1 (group A 4.6 ± 2.1 and group B 5.3 ± 2.8, $P = 0.047$) and T2 follow-up visits (group A 3.8 ± 2.0 and group B 4.8 ± 2.9, $p = 0.007$). This difference became not significant after 14 days (T3) from surgery (Table 1). Similarly, they reported a significantly lower level of discomfort at T1 (group A 4.6 ± 2.2 and group B 5.8 ± 2.8, $p = 0.002$) and T2 follow-up visits (group A 4.0 ± 2.0 and group B 5.0 ± 2.8, $p = 0.008$). This difference became not significant after 14 days (T3) from surgery (Table 2). Wound discharge was significantly reduced at each follow-up visit until 21 days after surgery (T4: group A 2.9 ± 1.7 and group B 3.9 ± 2.0, $p < 0.001$). This difference became not significant after 30 days (T5) from surgery (Table 3). Figure 2 reports median, IQR range

Table 1 Mean, standard deviation and ranges of postoperative pain in the two treatment groups at each follow-up visit

Follow-up	Group A	Group B	Total	*z*	*p*
T1 (3 days)	4.6 ± 2.1 (0.0–10.0)	5.3 ± 2.8 (0.0–10.0)	4.9 ± 2.5 (0.0–10.0)	2.0	0.047
T2 (7 days)	3.8 ± 2.0 (0.0–8.0)	4.8 ± 2.9 (0.0–10.0)	4.2 ± 2.5 (0.0–10.0)	2.7	0.007
T3 (14 days)	2.8 ± 1.7 (0.0–8.0)	3.3 ± 2.5 (0.0–10.0)	3.0 ± 2.1 (0.0–10.0)	1.3	0.198
T4 (21 days)	1.7 ± 1.5 (0.0–7.0)	2.0 ± 2.2 (0.0–8.0)	1.8 ± 1.8 (0.0–8.0)	0.4	0.701
T5 (30 days)	1.1 ± 1.2 (0.0–6.0)	1.1 ± 1.6 (0.0–6.0)	1.1 ± 1.4 (0.0–6.0)	1.5	0.132
T6 (45 days)	0.6 ± 0.8 (0.0–3.0)	0.6 ± 1.3 (0.0–6.0)	0.6 ± 1.1 (0.0–6.0)	1.9	0.056
T7 (60 days)	0.2 ± 0.5 (0.0–2.0)	0.1 ± 0.4 (0.0–3.0)	0.1 ± 0.5 (0.0–3.0)	1.5	0.141

Table 2 Mean, standard deviation and ranges of level of discomfort in the two treatment groups at each follow-up visit

Follow-up	Group A	Group B	Total	*z*	*p*
T1 (3 days)	4.6 ± 2.2 (0.0–10.0)	5.8 ± 2.8 (0.0–10.0)	5.2 ± 2.6 (0.0–10.0)	3.2	0.002
T2 (7 days)	4.0 ± 2.0 (0.0–8.0)	5.0 ± 2.8 (0.0–10.0)	4.4 ± 2.4 (0.0–10.0)	2.6	0.008
T3 (14 days)	3.1 ± 1.9 (0.0–9.0)	3.7 ± 2.4 (0.0–9.0)	3.4 ± 2.2 (0.0–9.0)	1.8	0.070
T4 (21 days)	2.1 ± 1.5 (0.0–7.0)	2.7 ± 2.1 (0.0–8.0)	2.4 ± 1.8 (0.0–8.0)	2.1	0.038
T5 (30 days)	1.5 ± 1.2 (0.0–6.0)	1.7 ± 1.6 (0.0–5.0)	1.6 ± 1.4 (0.0–6.0)	0.5	0.631
T6 (45 days)	0.7 ± 0.7 (0.0–3.0)	0.8 ± 1.3 (0.0–6.0)	0.7 ± 1.0 (0.0–6.0)	1.9	0.055
T7 (60 days)	0.2 ± 0.4 (0.0–3.0)	0.3 ± 0.9 (0.0–6.0)	0.2 ± 0.7 (0.0–6.0)	0.9	0.355

Table 3 Mean, standard deviation and ranges of wound discharge in the two treatment groups at each follow-up visit

Follow-up	Group A	Group B	Total	*z*	*p*
T1 (3 days)	5.5 ± 2.1 (1.0–10.0)	7.1 ± 2.1 (1.0–10.0)	6.2 ± 2.3 (1.0–10.0)	5.1	0.001
T2 (7 days)	4.9 ± 2.3 (1.0–10.0)	6.3 ± 2.4 (0.0–10.0)	5.5 ± 2.4 (0.0–10.0)	4.3	0.001
T3 (14 days)	3.8 ± 1.8 (0.0–10.0)	5.1 ± 2.1 (0.0–10.0)	4.4 ± 2.1 (0.0–10.0)	4.6	0.001
T4 (21 days)	2.9 ± 1.7 (0.0–8.0)	3.9 ± 2.0 (0.0–8.0)	3.4 ± 1.9 (0.0–8.0)	4.0	0.001
T5 (30 days)	2.0 ± 1.6 (0.0–8.0)	2.3 ± 1.6 (0.0–6.0)	2.1 ± 1.6 (0.0–8.0)	1.9	0.051
T6 (45 days)	1.1 ± 1.2 (0.0–8.0)	1.3 ± 1.2 (0.0–6.0)	1.2 ± 1.2 (0.0–8.0)	1.4	0.174
T7 (60 days)	0.4 ± 1.0 (0.0–8.0)	0.4 ± 0.8 (0.0–3.0)	0.4 ± 1.2 (0.0–8.0)	0.3	0.756

and range of these three symptoms (pain, discomfort and discharge) in the two groups of patients at each follow-up visit. The Friedman test showed a statistically significant difference of the variables pain, discomfort and discharge for the entire duration of the ($p < 0.001$), in patients in group A ($p < 0.001$) and in patients in group B ($p < 0.001$).

The grade of re-epithelization was significantly improved at each follow-up visit from 7 days (T2: group A 0.6 ± 0.5 and group B 0.3 ± 0.5, $p < 0.001$) to 45 days after surgery (T6: group A 2.5 ± 0.5 and group B 2.1 ± 0.5, $p < 0.001$) (Table 4). Complete wound healing (R3) was confirmed in 11 patients (11/186, 5.9%) at 30 days after surgery and in 59 patients (11/186, 32.6%) at 45 days after surgery, with a significant difference between the two groups (T5: group A 10/103pts., 9.7% vs. group B 1/83 pts., 1.2% $p = 0.024$; T6: group A 47/99 pts., 47.5% vs. group B 12/82 pts., 14.6%; $p < 0.001$) (Table 5). At the last follow-up (60 days), 125 patients (69.8%) were healed (R3) (group A 73/98 pts., 74.5% vs. group B 52/81 pts., 64.2%; $p = 0.135$) (Table 5). In 54 patients, there was still only partial re-epithelization of the open wound at T7. These patients were followed until complete healing but were not included in the final analysis.

On postoperative day 7, Spearman analysis demonstrated a significant correlation between type of treatment and pain ($\rho = 0.2$; 95% CI 0.1–0.3; $p = 0.007$) or level of discomfort ($\rho = 0.2$; 95% CI = 0.1–0.3; $p = 0.008$). At the same follow-up (T2), wound discharge and grade of reepithelization were significantly correlated to wound length ($\rho = 0.3$; 95% CI 0.2–0.5; $p < 0.001$; $\rho = -0.2$; 95% CI −0.3 to −0.1; $p = 0.036$, respectively) and type of treatment ($\rho = 0.3$; 95% CI 0.2–0.4; $p < 0.001$; $\rho = -0.3$; 95% CI −0.4 to −0.2; $p < 0.001$, respectively).

Univariate regression analysis showed a statistically significant association between re-epithelization at T6 and the type of treatment in group B vs. group A (RR 0.3; 95% CI 0.2–0.5; z 4.1; $p < 0.001$) and in sex (RR 0.6; 95%CI 0.4–0.9; $z = 2.6$; $p = 0.008$). No other associations were found ($p > 0.05$).

Multivariate analysis confirmed the association of the outcome with the type of treatment (group B vs. group A:

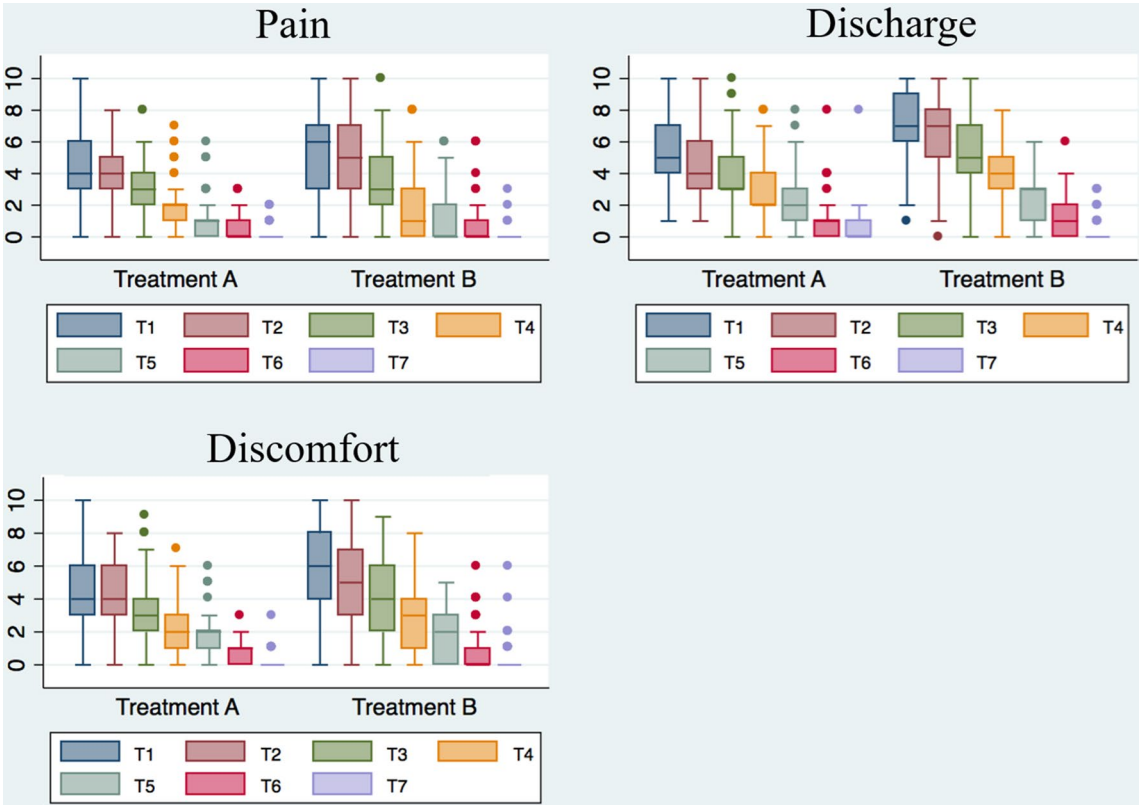

Fig. 2 Mean, IQR range and ranges of the three symptoms (postoperative pain, level of discomfort and wound discharge) in the two treatment groups (treatment A received Lietofix) at each follow-up visit

Table 4 Mean, standard deviation and ranges of grade of reepithelization in the two treatment groups at each follow-up visit

Follow-up	Group A	Group B	Total	Z	*p*
T1 (3 days)	0.04 ± 0.19 (0.00–1.00)	0.05 ± 0.22 (0.00–1.00)	0.04 ± 0.20 (0.00–1.00)	0.3	0.755
T2 (7 days)	0.6 ± 0.5 (0.0–2.0)	0.3 ± 0.5 (0.0–1.0)	0.5 ± 0.5 (0.0–2.0)	4.2	0.001
T3 (14 days)	1.2 ± 0.6 (0.0–2.0)	0.9 ± 0.5 (0.0–2.0)	1.0 ± 0.6 (0.0–2.0)	3.7	0.002
T4 (21 days)	1.6 ± 0.5 (0.0–3.0)	1.3 ± 0.5 (0.0–2.0)	1.5 ± 0.6 (0.0–3.0)	3.6	0.001
T5 (30 days)	2.0 ± 0.4 (1.0–3.0)	1.8 ± 0.4 (1.0–3.0)	1.9 ± 0.4 (1.0–3.0)	3.2	0.001
T6 (45 days)	2.5 ± 0.5 (1.0–3.0)	2.1 ± 0.5 (0.0–3.0)	2.3 ± 0.5 (0.0–3.0)	4.9	0.001
T7 (60 days)	2.7 ± 0.4 (2.0–3.0)	2.6 ± 0.6 (0.0–3.0)	2.7 ± 0.5 (0.0–3.0)	1.5	0.125

Table 5 Complete reepithelization in the two treatment groups at each follow-up visit

Follow-up	Group A (103 pts.)		Group B (83 pts.)		Total		χ^2	*p*
	n	%	*n*	%	*n*	%		
T1 (3 days)	0	0.0	0	0.0	0	0.0	–	–
T2 (7 days)	0	0.0	0	0.0	0	0.0	–	–
T3 (14 days)	0	0.0	0	0.0	0	0.0	–	–
T4 (21 days)	1	1.0	0	0.0	1	0.5	0.8	1.000
T5 (30 days)	10	9.7	1	1.2	11	5.9	6.0	0.024
T6 (45 days)[a]	47	47.5	12	14.6	59	32.6	22.0	0.000
T7 (60 days)[b]	73	74.5	52	64.2	125	69.8	2.2	0.135

[a]181 patients (97.3%) (group A 99/181: 54.7% and group B 82/181: 45.3%)

[b]179 patients (96.2%) (group A 98/179: 54.7% and group B 81/179: 45.3%)

aRR 0.3; 95% CI 0.2–0.6; $z = 3.9$; $p < 0.001$) and sex (aRR 0.66; 95%CI 0.45–0.96; $z = 2.6$; $p = 0.032$).

Discussion

The aim of this multicenter, randomized study was to assess whether the topical application of a new ointment (Lietofix®, Nathura S.P.A.) on the open wound after pilonidal sinus excision promotes tissue repair and re-epithelization and reduce patients' symptoms, compared to standard treatment. Our results demonstrated that Lietofix patients had significantly less postoperative pain and discomfort at short-term follow-up (T2, 7 days), when the inflammatory reaction was maximal. At > 2 weeks after surgery, when the inflammation was reduced, the advantage of the ointment on pain and discomfort vs. standard treatment became not significant. Application of Lietofix significantly reduced wound discharge in the medium term (T4, 21 days) and improved re-epithelization and complete healing in the long term (T6, 45 days). When the open wound was almost closed (T7, 60 days), no difference on grade of re-epithelization or number of patients completely healed was found between the two groups. Interestingly, at post-operative day 7, the type of treatment was significantly correlated to all outcomes (pain, discomfort, wound discharge and grade of re-epithelization). At the same follow-up (T2), wound discharge and grade of re-epithelization were significantly correlated to wound length.

One limitation of this study is that patients were not blinded to treatment. However, this was an "effectiveness" study, with all outcomes registered by a blinded examiner at each follow-up and the statistical analysis performed by a statistician blinded to the two arms of the trial. Another limitation was the lack of data on recurrence rate. Indeed, the primary aim of this trial was to compare the effectiveness of Lietofix® versus standard treatment on patients' symptoms and wound healing. Assessment of recurrence would require a longer period of observation [5].

Conclusions

After pilonidal sinus excision and lay-open, Lietofix® effectively improved patients' symptoms in the short term (postoperative pain and discomfort), reducing wound discharge in the medium term and promoting healing and grade of reepithelization in the long term.

Data availability The datasets analysed during the current study are available from the corresponding author on reasonable request

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committee of each center which participated in the trial.

Informed consent All participants gave written informed consent.

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