Hypericum and neem oil for dehisced post-surgical wounds: a randomised, controlled, single-blinded phase III study

Objective: To evaluate the clinical efficacy of a hypericum and neem oil dressing, Primary Wound Dressing [ONE] (1PWD) (Kerecis AG, Switzerland), in a patient population with dehiscence of surgical wounds with critical colonisation/infection. Efficacy was defined as resolution of inflammatory/infective symptoms.

Method: A randomised, controlled, single-blinded, parallel-arms phase III study was conducted comparing the experimental medication to silver-based dressings. All patients were evaluated at enrolment, on days 7, 14, 21 and 28. Improvement of inflammatory/infective symptoms was measured by detecting seven items of the Bates–Jensen Wound Assessment Tool (BWAT). Pain was assessed using the Numeric Rating Scale (NRS).

Results: The study enrolled 99 patients. Follow-up was completed in 49 patients in the experimental group and 48 patients in the control group. Overall BWAT evaluation demonstrated similar outcomes between the groups: t=0.23, p-value=0.81, 95% confidence interval (CI): −13.3–10.8. Furthermore, when evaluating the seven items of the BWAT relating to inflammatory signs, there was not a significant difference between the groups: t=0.38, p=0.35, 95% CI: −2.8–2.7. However, when an analysis using the NRS pain scale was performed, a statistically significant pain reduction was demonstrated in favour of the experimental group: t=7.8, p<0.0001, 95% CI: 2.918–4.8819.

Conclusion: This randomised controlled trial confirmed the efficacy of 1PWD, an investigational product, in the management of surgical dehiscence with critical colonisation or infection, with the added benefit of significant pain reduction when compared with a silver-based dressing.

Declaration of interest: The authors have no conflicts of interest to declare.

colonisation • dressing • hypericum oil • infection • inflammation • neem oil • pain • surgical dehiscence • wound • wound care • wound healing

The process of tissue healing involves four phases: haemostasis, inflammation, proliferation and remodelling. The skin is a complex endocrine organ that has a vital role in hormone production, receptor expression and cytokine production modulation.[1] Skin injury activates the coagulation cascade in the haemostasis phase of wound healing. In the inflammatory phase, cells and debris are removed from the site of tissue injury. The proliferation phase, characterised by neoangiogenesis, collagen deposition and the development of granulation tissue, allows re-epithelialisation and contraction of the wound, ultimately leading to wound closure.

The primary goal of wound care is to achieve a good functional and cosmetic outcome for the patient. Healing by secondary intention can be delayed due to infection and conditions like diabetes, pulmonary and vascular insufficiencies, cardiovascular disease and various immunological disorders. When this delay in the healing process occurs, it can result in surgical wound dehiscence, defined as separating the margins of a closed surgical incision.

The incidence of surgical site infection (SSI) is underestimated and therefore underreported as infection often develops outside the hospital.[2] Data from healthcare facilities have identified SSI as the main cause of nosocomial infection in low- and middle-income countries.[3] SSI represents a serious global problem that can lead to unnecessary additional surgeries and antibiotic use, which can have a negative impact on morbidity and mortality rates.

Maintaining a moist wound bed environment to enable healing by secondary intention is one of the pillars of good wound care.[4–6] The current standard of care for wounds includes hydrocolloids, hydrogels, alginates, polyurethane foams and hydrofibre dressings. In recent years, there has been ongoing innovative development of new types of secondary dressings and wound management options, such as plant oil formulations rich in essential fatty acids (EFAs), to further promote healing through secondary intention. Plant oils rich in EFAs are useful in maintaining epidermal integrity and create a hydrolipid film barrier. EFAs play a part in wound healing by mediating the production of resolvins and maresins that counteract inflammatory processes.[7–13]

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Primary Wound Dressing [ONE] (1PWD) (Kerecis AG, Switzerland), an investigational medical product, contains hypericum oil and neem oil, with the purpose of maintaining an optimal wound healing environment after application to a wound. The oil layer prevents secondary wound dressing adhesion.[7] Also, previously conducted observational studies have highlighted its antimicrobial effect, although this has not been confirmed in randomised controlled studies. Neem extracts have been used for centuries in Indian traditional medicine. The oil is obtained by cold extraction from berries. Not surprisingly it is included in the Ayurvedic pharmacopoeia.[14]

Neem oil and hypericum oil showed healing,[15] bacteriostatic[16] and anti-inflammatory properties. Anti-inflammatory activity is thought to come from limonoid in the neem oil, effective on inflammatory markers of the family of inhibitor factors of macrophagic migration.[17]

The main objective of the study was to test the efficacy of a hypericum (*Hypericum perforatum*) and neem (*Azadirachta indica*) oil dressing, as 1PWD (aerosol-spray dressing) had been shown to be effective in critical colonisation/infection control in hard-to-heal skin lesions in observational studies and case series. In this context, the introduction of innovative compounds/dressing devices represents the possibility of introducing a novel approach for infection management in clinical practice, reducing pain, skin sensitisation, allergy and bacterial resistance. Therefore, this study aimed to verify the efficacy of 1PWD as an alternative treatment option for dehisced surgical wounds compared to dressing products with antimicrobial activity.

Specific scope

The study evaluated the clinical efficacy of an experimental dressing with the best clinical and healthcare practice for patients affected by dehisced surgical wounds with critical colonisation/infection. Wound bed improvement was defined as resolution of infection and inflammatory symptoms.

Method

Study design

A randomised, controlled, single-blinded (outcome assessor), parallel-arms phase III study was conducted. This study took place in outpatient facilities, mostly surgical ambulatory care facilities, in three centres from two Italian regions (Emilia Romagna and Sicily). All of the centres used antiseptic dressings in the management of dehiscent surgical wounds with critical colonisation/infection as standard of care.

In setting up the study, the authors made an assumption that a difference in efficacy of study dressings would be equal to 10%, which would indicate a moderate effect of the experimental intervention. Assuming an error of α=0.05, an error of β=0.10, a power of 80% and a drop-out rate of ≤15%, a sample size of 102 viable wounds (51 per arm) was required to detect a statistical significance.

Ethical approval

All procedures were performed in compliance with relevant laws and institutional guidelines, and this study has been approved by the institutional ethical committee.

Patient recruitment

Patients meeting the inclusion criteria were eligible to participate in the study. In addition, patients were required to present to the study centres for routine nursing care for the duration of the study.

The inclusion criteria were:

- Patient with at least one dehisced surgical wound, with inflammatory signs and/or biofilm in the wound bed
- Wound treated with advanced dressings containing silver, such as polyurethane and alginates
- Wound size <80cm^2 (included within 10×10cm dressing)
- Patient aged ≥18 years
- Provided informed consent and consent to personal data treatment at the enrolment.

The exclusion criteria were:

- End-stage disease
- Ongoing systemic steroid therapy/radiotherapy/immunosuppressive therapy
- Confirmed or suspected allergy to the medication device
- Patient had denied informed consent
- Wounds with dry necrotic tissue
- Wounds requiring local antiseptic treatment based on clinical evaluation.

Interventions

The experimental medical device 1PWD was compared to silver-based dressings. The study protocol only allowed for a silver-based polyurethane foam or alginate dressings in the control group.

In the experimental group the wounds were irrigated with isotonic solution (normal saline/Ringer's lactate) and dried through tamponade at each dressing change. The experimental dressing was applied to the entire wound surface and covered with a non-woven gauze held in place with tape.

In the control group, at each dressing change, wounds were irrigated with isotonic solution (normal saline/Ringer's lactate), dried and covered with a silver-based dressing (alginates or polyurethane foam).

In the case of irritation or maceration, the patients in the experimental group could be treated with barrier products, excluding cortisone or zinc oxide topical products.

The patients in the control group could be treated with zinc oxide paste and additional products as judged necessary by the treating physician, but excluding the use of topical cortisone products.

Study outcomes

Primary outcome

Significant improvement of inflammatory and infective

symptoms, as measured by detecting seven items of the Bates–Jensen Wound Assessment Tool (BWAT): type of peripheral tissue; oedema and induration; skin colour surrounding wound; type of exudate; amount of exudate; type of necrotic tissue; and amount of necrotic tissue (slough). All patients were evaluated at the enrolment (T0), on day 7 (T1), on day 14 (T2), on day 21 (T3) and on day 28 (T4). The seven items of the BWAT scale detect 13 different variables (wound size, wound depth, wound edges, undermining, necrotic tissue type, amount of necrotic tissue, exudate type, exudate amount, skin colour surrounding wound, peripheral tissue oedema, peripheral tissue induration, amount of granulation tissue and epithelialisation) that are also evaluated. The total score of the BWAT scale ranges from a minimum of 13, which is the best situation, to a maximum of 65, the worst situation. The minimum total score of the seven items considered by the study, added to the wound dimension, is 7 (the best situation), whereas the maximum score, 39, corresponds to the worst situation.

Secondary outcomes

- Pain was defined as the physical discomfort induced by dressing application. Pain was assessed using the Numeric Rating Scale (NRS), ranging from a minimum score of 0 to a maximum of 10 (a score equal to 0 represents the absence of pain, and 10 represents the worst pain imaginable)
- Prevention of complications such as allergies, sepsis and septic shock.

Randomisation

Allocation sequence generation

The randomisation sequence was generated by an external centre (using software available on http://www.randomizer.org).

Method of randomisation list concealment

Patients were allocated to the study groups, once verbal consent was provided to the study and written consent to the randomisation centre. The randomisation centre was then responsible for assigning the patient to the study groups.

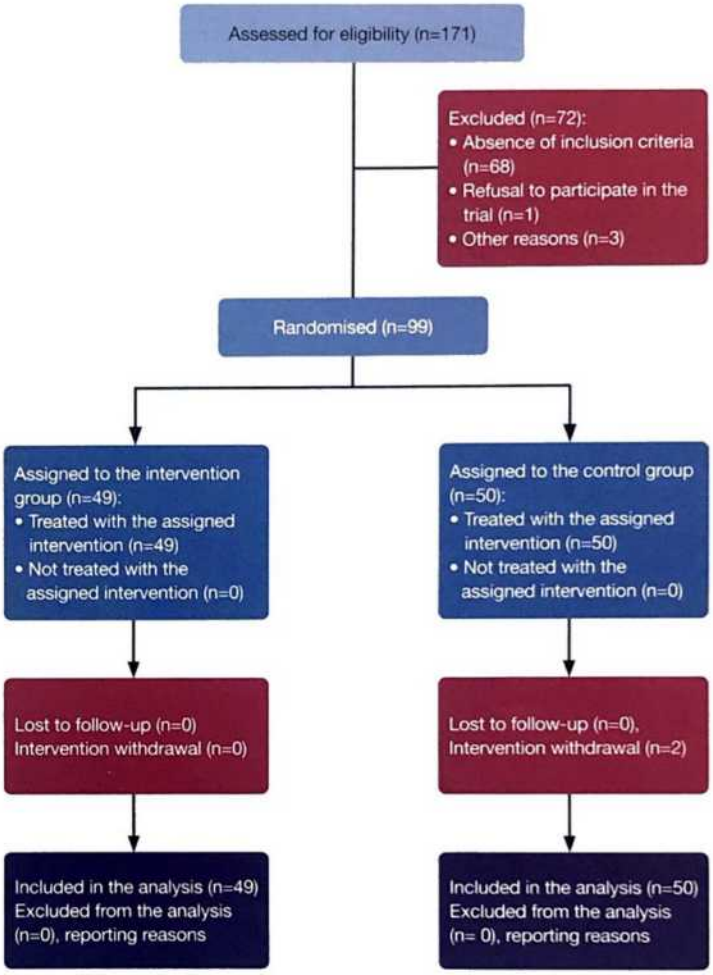
Blinding

The outcomes were assessed by study nurses blinded to the treatment received by the patient. At outpatient clinical checks (T1, T2, T3, T4) the evaluator nurses were trained to perform a standardised wound assessment.

Statistical analysis

The analysis of the primary endpoint complied with intention-to-treat (ITT) principles, including all randomised patients according to the initial group allocation. An interim analysis was not carried out. For the analysis of the results, a two-tailed Chi-framework test was used.

Fig 1. Consort flow diagram



Analysis of the results was conducted (experimental and control groups) through descriptive statistics. Significance was calculated on the mean difference between the two groups using SPSS version 16.0 (SPSS Inc., US) and using Chi-squared and Student t-testing. Normal distribution and statistical significance test was confirmed, and statistical significance was defined as $p<0.05$ (confidence interval (CI) 95%).

Results

From August 2018 to September 2019, the authors enrolled 99 patients, as reported in the Consort flow diagram (Fig 1). A further 72 patients were excluded from randomisation: 68 due to unsuitable wound dimensions, three due to logistical problems (inability to participate in follow-up visits) and one patient withheld consent. In the control group, two patients were hospitalised: one with heart failure, and one after a road accident.

Differences in patients enrolled in the two groups were not statistically significant in terms of individual pre-treatment variables: patient demographics, type of

Table 1. Patient demographics, type of intervention and site of wound at enrolment. Comparison of differences between groups was conducted with Student t-testing

Enrolled patients	Experimental group	Control group	p-value
Age, years, mean±standard deviation	59.5±11.2	58.2±10.2	≥0.05
Male, n	20	27	≥0.05
Diabetes, n	28	22	≥0.05
Cardiovascular disease, n	28	29	≥0.05
Lung disease, n	5	2	≥0.05
Oncological disease, n	25	22	≥0.05
Surgery for:			
Cancer, n	22	17	≥0.05
Traumatic wound, n	1	2	≥0.05
Implants, n	18	23	≥0.05
Incisional hernia, n	5	3	≥0.05
Fistula, n	3	5	≥0.05
Intervention site			
Abdomen, n	23	19	≥0.05
Knee, n	18	23	≥0.05
Thorax, n	2	0	–
Perianal, n	6	8	≥0.05

intervention and the site of the wound, as described in Tables 1 and 2.

At T0, all enrolled patients showed surgical dehiscence with a wound surface (length×width) falling into the BWAT category wound dimension equal to 36.1–<80cm^2. Dehiscence characteristics at enrolment are described in Table 2.

Follow-up was completed by 49 patients in the experimental group and 48 patients in the control group. Available results of all the enrolled patients have been reported and included according to the ITT analysis principles.

Primary outcome

Primary outcome (wound improvement), represented by a change in the seven-item total score of the BWAT scale, was evaluated by comparing data obtained at T0 with data reported at T1, T2, T3 and T4.

Results analysis showed no significant differences between T0 and T4 for the BWAT scores reported in Tables 2 and 3.

Data on total BWAT score relating to wound progression are reported in Table 3 and Fig 2. Overall BWAT evaluation showed the following results in patients in both the experimental and control groups: t=0.23, p=0.81, 95% CI: −13.3–10.8. Average BWAT score related to the seven items assessing inflammatory signs improvement per group and at different detection time is reported in Table 4 and Fig 3.

The evaluation of the seven items of the BWAT relating to inflammatory signs showed the following results in patients in both the experimental and control groups: t=0.38, p=0.35, 95% CI: −2.8–2.7.

Secondary outcomes

Pain

Pain assessment was carried out using the NRS scale. Pain was only assessed during the time between two dressing changes. The results demonstrated statistically significant differences in pain reduction, already detected at T2, in the experimental group compared with the control group. Results are shown in Table 5 and Fig 4.

NRS scale evaluation demonstrated a statistically significant difference in terms of pain reduction in patients treated in the experimental group compared with patients in the control group: t=7.8, p<0.0001, 95% CI: 2.9–4.9.

Complications

No patients in either the experimental group or the control group developed allergies to medication products, severe sepsis and/or septic shock.

Discussion

Maintenance of a moist wound bed environment is crucial in achieving the desired wound healing outcomes for patients, paired with correct wound bed preparation.[18,19]

Health professionals are provided with a multitude of treatment options that sometimes do not follow the principle of moist wound care. This is a consequence of the development, by research in the field of wound care, of devices able to act/interact with different tissue components of the wound bed. Different dressing classes have emerged: passive medications that create a moist microenvironment, contributing to the wound healing through control of the local environment without modifications of their physical state (i.e. hydrogel or polyurethane foam, etc.); interactive medications that change their physical state once in contact with the exudate of the lesion (i.e. hydrofibre, hydrocolloid, etc.); and bioactive dressings that, as opposed to previously described dressings, are composed of biological materials such as collagen-based medications, hyaluronic acid, growth factors, epithelial substitute, regenerated plasma, etc.

The innovation represented by 1PWD is a part of this complex scenario. The product development is based on ancient and established principles, but in a new formulation, and integrates treatment options of hard-to-heal skin injuries represented by surgical dehiscence with critical colonisation and infection. With time, antibiotic treatment shows an exponential increase of bacterial resistance with a consequent reduction of treatment options.[20,21]

Standard of care options represented by antiseptic

Table 2. Initial characteristics of surgical dehiscence measured by the Bates–Jensen Wound Assessment Tool (BWAT) scale at enrolment. Comparison of differences between groups was conducted through Student t-testing

Initial assessment	Experimental group (n=49)		Control group (n=50)		p-value
	n	%	n	%	
Size					
Length×width <4cm²	3	6.1	5	10.0	≥0.05
Length×width 4–16cm²	8	16.3	10	20.0	≥0.05
Length×width 16.1–36cm²	28	57.1	25	50.0	≥0.05
Length×width 36.1–80cm²	10	20.4	10	20.0	≥0.05
Depth					≥0.05
Partial-thickness skin loss involving epidermis and/or dermis	7	14.2	12	24.0	≥0.05
Full-thickness skin loss involving damage or necrosis of subcutaneous tissue	42	85.8	38	76.0	≥0.05
Edges					
Distinct, outline clearly visible, attached, even with wound base	2	4.0	0	–	–
Well-defined, not attached to wound base	47	96.0	50	100	–
Exudate: type					
Serosanguineous: thin, watery, pale red/pink	1	2.0	4	8.0	≥0.05
Serous: thin, watery, clear	36	73.4	38	76	≥0.05
Purulent: thin or thick, opaque, tan/yellow, with or without odour	12	24.4	8	16	≥0.05
Exudate: amount					
Moderate	37	75.5	42	84.0	≥0.05
Large	12	24.5	8	16.0	≥0.05
Skin colour surrounding wound					
Bright red and/or blanches to touch	7	14.2	11	22.0	≥0.05
White or grey pallor or hypopigmented	10	20.4	9	18.0	≥0.05
Dark red or purple and/or not blanchable	32	65.4	30	60.0	≥0.05
Peripheral tissue oedema and induration					
Non-pitting oedema extends ≥4cm around wound	28	57.1	31	62.0	≥0.05
Induration <2cm around wound	21	42.9	19	38.0	≥0.05
Granulation tissue					
Bright, beefy red, >25–<75% of wound filled	18	36.7	23	46.0	≥0.05
Pink and/or dull, dusky red and/or fills ≤ 25% of wound	31	63.3	27	54.0	≥0.05
Average BWAT score	**27.7**	–	**27.1**	–	**≥0.05**

NB: The table sets out only BWAT items relating to the primary outcome assessment, and specifying only detected values. Other values have been omitted from this table

dressings mainly consist of silver dressings, povidone-iodine and polyhexamethylene biguanide (PHMB) dressings, the efficacy of which for infected wounds has been largely demonstrated. However, through continuous use, the risk of resistance increases as Hosny et al.,[22] highlighted by showing the growth of silver-resistant bacteria such as *Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli, Enterobacter cloacae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Hajská et al.[23] studied the topical efficacy of

Table 3. Overall average values of the Bates–Jensen Wound Assessment Tool score per group at each visit. Comparison of differences between groups was conducted with Student's t-test

	T0 (enrolment)	T1 (day 7)	T2 (day 14)	T3 (day 21)	T4 (day 28)	Standard deviation
Experimental group	42.0	40.1	32.3	27	22.2	17.5
Control group	43.3	40.2	34.2	29	23.1	16.8

Table 4. Average Bates–Jensen Wound Assessment Tool score per group at each visit. Comparison of differences between groups was conducted with Student's t-test

	T0 (enrolment)	T1 (day 7)	T2 (day 14)	T3 (day 21)	T4 (day 28)	Standard deviation
Experimental group	27.7	26.1	23.1	15.2	13.7	6.4
Control group	27.1	24.3	19.8	16.1	12.4	6.0
p-value	0.72	0.32	0.10	0.37	0.35	–
95% confidence interval	from –4.9 to 5.0	from –3.9 to 4.8	from –2.1 to 2.7	from –3.7 to 4.8	from –2.8 to 2.7	–

Table 5. Average Numeric Rating Scale score for pain per group at each visit. Comparison of differences between groups was conducted with Student's t-test

	T0 (enrolment)	T1 (day 7)	T2 (day 14)	T3 (day 21)	T4 (day 28)	Standard deviation
Experimental group	7.9	7.2	4.0	2.2	0.2	3.2
Control group	7.5	7.3	7.1	5.6	4.1	1.4

Fig 2. Improvement of the Bates–Jensen Wound Assessment Tool (BWAT) score per group and visit. Comparison of differences between groups was conducted with Student's t-test. T0—enrolment; T1—7 days; T2—14 days; T3—21 days; T4—28 days

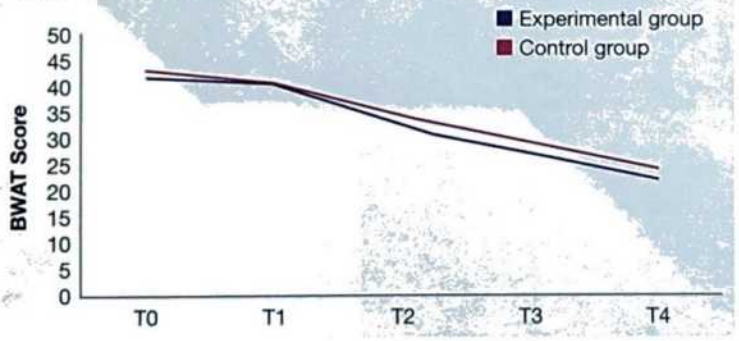
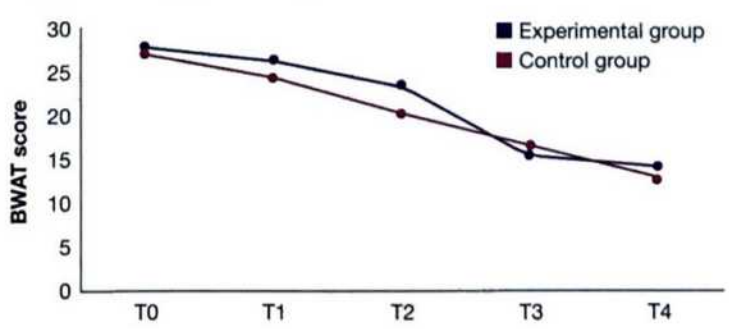


Fig 3. Improvement of Bates–Jensen Wound Assessment Tool (BWAT) score per group at each visit. Comparison of differences between groups was conducted with Student's t-test. T0—enrolment; T1—7 days; T2—14 days; T3—21 days; T4—28 days



antibacterial dressings, showing that silver and povidone-iodine decrease their antimicrobial activity. All available antiseptic treatments showed inactivation towards *Pseudomonas aeruginosa* at 24 hours. Availability of alternative treatment options could contribute to the reduction of bacterial resistance rates.

Healing by secondary intention of surgical wounds is considered a risk because comorbidities or side-effects of treatments can delay the healing process, particularly in the case of oncological disease.[24] When dehiscence occurs, patient discomfort and pain increase due to stimulation of pain associated with the inflammatory processes.

Even if we cannot attribute with certainty the observed improvements in the experimental group to one of the two components of the investigational product, based on literature searching we can speculate that both components might play a role in improving pain control and changing the inflammatory state of the wound.

In particular, *Hypericum perforatum* has well-known antidepressant properties, and it can be used in the treatment of mild inflammatory dermatological diseases. Due to the presence of hyperforin, its most important active substance, it promotes wound healing by acting on fibroblasts and keratinocyte proliferation and differentiation.[8,12,13] Some studies have highlighted the antimicrobial activity of hyperforin, particularly against Gram-positive bacteria.[25] In addition, preclinical animal studies have demonstrated the ability of low doses of *Hypericum perforatum* extracts to induce antinociception and to relieve acute and chronic

hyperalgesic states. In vivo and in vitro studies have shown that the main components responsible for pain control properties are hyperforin and hypericin.[26]

Azadirachta indica contains epoxyazadiradione, a limonoid that exhibits in vitro but also in vivo anti-inflammatory activity that can be explained by its ability to inhibit tautomerase, macrophage migration inhibitory factor, and to prevent the release of proinflammatory cytokines.[17]

We conclude that the two active components of 1PWD may act in a synergistic manner to achieve inhibition of inflammation and pain control. Future studies need to be conducted to better understand the mechanism of action of the two active components in the product.

This study showed that the use of 1PWD was non-inferior in the treatment of critical colonisation/infection and contributed to significant pain reduction as compared with silver-based dressings. This confirmed data from observational studies on the anti-inflammatory activity of this formulation, comprising neem and hypericum oils.[7,27]

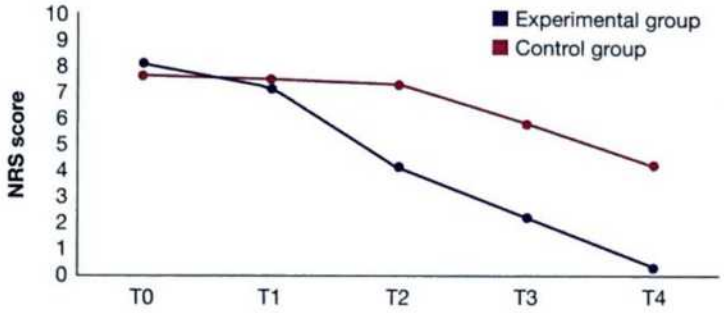
Limitations

Patients enrolled were affected by surgical wound dehiscence with inflammatory signs and suspected presence of biofilm, but no samples for culture examination were collected as this is not a routine practice in participating centres.

A potential route for further research could be the investigation of the underlying physiological mechanisms in pain control to refine current therapies in wound management.

A more in-depth cost-effectiveness study regarding the product should be performed to build on already existing cost-effectiveness studies for post-surgical wounds.[28]

Fig 4. Numeric Rating Scale (NRS) score for pain improvement per group at each visit. Comparison of differences between groups was conducted with Student t-testing. T0—enrolment; T1—7 days; T2—14 days; T3—21 days; T4—28 days



Conclusion

This randomised controlled trial confirms the efficacy of 1PWD in the management of surgical dehiscence with critical colonisation or infection, reducing pain significantly compared with polyurethane foam dressings containing silver and alginate dressings containing silver. **JWC**

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Reflective questions

- What are the benefits of using a product containing hypericum and neem oil?
- How do these oils seem to be effective in the wound healing process?
- What is the main advantage of using 1PWD over using polyurethane foam dressings and alginate dressings containing silver?