IPARZINE-SKR study: randomized, double-blind clinical trial of a new topical product versus placebo to prevent pressure ulcers

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ABSTRACT
This study compared the efficacy of a new topical agent (IPARZINE-4A-SKR) on preventing category I pressure ulcers (PUs) over a 2-week period, compared with a placebo. A double-blind, randomised, multi-centre, placebo-controlled clinical trial in two parallel groups was conducted. The primary objective was to compare PU incidence between groups. Hospital and socio-sanitary centre patients (n = 194) at risk of developing a PU (Braden scale) were randomised into two groups. The intervention group included 99 patients, and the placebo group comprised 95 patients. Patients were comparable in terms of age, sex and PU risk. In both groups, patients had a high risk of developing PUs. The product was applied on the sacrum, trochanters and heels. Six PUs (incidence = 6.1%) were detected in the intervention group versus seven (incidence = 7.4%) in the placebo group. Differences were not statistically significant (z = 0.08; P = 0.94), relative risk = 0.82 (95% confidence interval = 0.29–2.36). The main limitation of the study was the sample size and, therefore, the main difficulty encountered was in determining whether the product is ineffective or simply has not been used with sufficient patients. In conclusion, it is not possible to confirm that there are any differences between the studied and the placebo treatments in the prevention of PUs. The results obtained were similar to those obtained in studies of PU prevention using products based on topical fatty acids.

Key words: Incidence • Pressure ulcers • Prevention • Randomised clinical trial • Skin care

INTRODUCTION
Pressure ulcers (PUs) are not a new process; such lesions have coexisted with humankind down the centuries since the origin of our species and occur when a person has to remain lying down and motionless due to illness or old age. The treatment of PUs has varied through time and this fact has been reflected, from prehistoric times to the present day, in the different procedures and materials used by humans to take care of and treat these wounds. Nevertheless, despite advances in the health sciences and the evolution of healthcare systems, they continue to be an important health problem affecting patients at all health levels.

Undoubtedly, the best treatment for PUs is their prevention. Thus, it has been suggested that these lesions can be prevented in at
least 95% of cases (1). Human, material and methodological resources are necessary to achieve this goal.

The first step in prevention would be to identify patients at risk of developing PUs. However, no unanimous criteria currently exist regarding the use of a universal scale for this purpose (2). Risk assessment scales are useful instruments that, when used systematically, allow risk to be stratified and prevention measures to be applied which are tailored to different needs. Thus, these scales should be the first element to include in clinical practice guidelines or prevention protocols, together with specific recommendations for effective pressure management by means of active repositioning programmes as well as the use of special pressure management surfaces according to the characteristics of the risk situation (3–6). All of the above should be complemented with adequate skin care and maintenance of optimum nutrition and hydration states based on current knowledge, periodic updated training programmes for nursing staff and caregivers and epidemiological monitoring of the problem.

Focusing on adequate skin care, when skin is in good condition it is much more resistant to aggressions such as pressure, friction and shearing. For this reason, in some of the published studies it has been suggested that patients with dry or cracked skin present up to 2.5 times more probability of developing PUs than patients in control groups (7), or of having frequent PUs on the gluteal area. Despite consisting of a considerable muscular mass, the gluteal area is vulnerable to skin aggressions produced by urinary and faecal incontinence, which causes the skin to deteriorate and produces erosions that reduce skin resistance to pressure and friction, therefore making it more vulnerable to PUs. In addition, other authors (8) have related the physiopathological process implied by the formation of a PU, above all in its initial stage, to two critical situations: on the one hand, a local inflammatory response mediated by prostaglandin release, and on the other, oxygen radical release caused by hyperaemic reactions, which grow in number as hyperaemia becomes more intense.

References to the use of essential fatty acids (EFA) for skin care date back to 3000 BC (9): more recently, studies have been published on EFA (10) and also on modifications of these, the hyperoxygenated fatty acids (HOFA). HOFAs are for topical use and are employed in the prevention of PUs and in the treatment of category I PUs (11–19). Nevertheless, the use of such compounds is not widespread internationally, being limited almost exclusively to Southern Europe and Brazil.

In the interests of developing new products to improve skin care and contribute to PU prevention, EUREKA funds were obtained by ASEPTA (Monaco) and INIBSA laboratories (Spain) to conduct a project to this end. The EUREKA project, known as MONOICOS (2005–2009), enabled the development of a new effective galenic formula (IPARZINE-4A and SKR) adapted to PU prevention. Tolerance studies were carried out, as well as ‘in vitro’ studies of human cells and tissues and studies on animals and healthy individuals (data on file). Consequently, the following phase was to compare the efficacy, in terms of PU incidence, of IPARZINE-4A and SKR against a placebo in the prevention of category I PUs, with the hypothesis that the group of patients treated with the product under study would present a lower PU incidence than patients treated with the placebo.

PATIENTS AND METHODS
This was a two-arm parallel-group, multi-centre, double-blind, randomised, placebo-controlled clinical trial conducted with 194 patients from eight centres (Fundació Sant Josep de Igualada, Centre el Carme de Badalona, Centro la Molineta de Petrer, Hospital General y Universitario de Elche, Complejo Hospitalario de Jaén, Residencia de Mayores de Elche, Fundación Matía de San Sebastián and Hospital Germans Trias i Pujol de Badalona) located in different regions of Spain.

Ethics
The study protocol was submitted to the local ethics and clinical research committees for approval and the clinical trial was conducted in compliance with Good Clinical Practices and with the principles of the Declaration of Helsinki. All patients gave written consent to participate after having received full written information regarding the study objectives and content. In addition, the authors wrote this article in accordance with the recommendations set out in the CONSORT guide (20).
Patient population
Included in this study were male and female subjects over 18 years of age presenting medium, high or very high risk of PU development according to the Braden scale (scoring 15 points or lower) (2,21), without PU at the moment of inclusion and receiving treatment at hospitals or socio-sanitary centres.

The following patients were excluded from this study: terminally ill patients, subjects who had active PUs or peripheral vasculopathy, had a history of allergies to some of the components of the products under study, were receiving ongoing treatment with vasopressor or chemotherapy agents, were participating in a clinical study or who had participated in one within the previous month.

Sample size determination
The reference value used to determine sample size was the PU incidence obtained in the RCT carried out by Torra et al. (17), and programme used for calculations was the open source software programme G*Power 3.0.8 (22). Therefore, taking an alpha risk of 0.05 and a beta risk of 0.10, in a bilateral contrast, 434 subjects would be required (217 each group) in order to detect a difference equal to or greater than 0.10 between both groups. A follow-up loss rate of 0.1 was estimated, and hence 478 subjects were required (239 per group).

Design and procedures
Subjects who met the selection criteria and who gave their written consent to participate in this study were randomly allocated on a 1:1 ratio to be treated either with topical application of IPARZINE-4A-SKR or with placebo. The quantitative and qualitative composition of both the tested product and the placebo are presented – exactly as stated by the laboratory – in Table 1, whilst the prevention protocol is given in Table 2.

Bearing in mind the ‘occurrence within 2 weeks’ hypothesis, according to which the greatest probability of PU appearance occurs in the first 2 weeks (7,10), each patient was included and treated for a maximum period of 2 weeks or until he/she abandoned the study for any of the following reasons: patient was discharged from the service where he/she was included in the study, was transferred to another service, developed a category I PU (in this case, the patient received the necessary care to solve the problem) or patient died during the study.

The product was applied according to the following procedure: on at least 3 PU risk areas, namely, sacrum, trochanters and heels. Application frequency was every 12 hours, and the skin was also checked with the same frequency in order to determine if category I PU or higher had appeared. The necessary amount of product was administered on each of the application areas (taking into account that these areas, the sacrum, trochanter and heels, do not have the same surface area), and it was administered with a gentle massage until it was completely absorbed. In general terms, the quantity needed was that obtained after three pushes of the dispenser employed. As the product is completely absorbed, it was not necessary to remove excess. In addition to application of the product under study, the PU prevention protocol presented in Table 2 was applied with all patients.

Subject demographics, baseline characteristics and therapeutic measures applied were recorded on the first day, and photographs were taken of the areas where the product was

| Table 1 Chemical composition of the product under study and the placebo* |
|-----------------|-----------------|------------------|
| Ingredients     | Intervention (g/100 g) | Placebo (g/100 g) |
| Eau Purifiee    | 64.940           | 82.740           |
| Miglyol B12 N  | 7.000            | 7.000            |
| Ginkgo et Centella Asiatica Extraitglycerine | 8.000 |
| Huiles Vegetales a Forte Teneur en A.G.E. | 7.000 |
| Sepigel 305    | 3.240            | 3.240            |
| Lanette SX     | 3.000            | 3.000            |
| Emulpharma 30  | 2.000            | 2.000            |
| Glycerine pH Euro 99.5% PF | 2.000 |
| Cosmocil CQ    | 1.000            | 1.000            |
| Iparzine-4A    | 0.500            | 0.500            |
| Symdiol 68     | 0.500            | 0.500            |
| Huile Silicone Baysilone M350 | 0.300 |
| L-Serine       | 0.300            | 0.300            |
| Coviox T50C    | 0.200            | 0.200            |
| Perfume        | 0.020            | 0.020            |
| Total          | 100.000          | 100.000          |

*The names appearing in the table are identical to those given by the laboratory.
Table 2  Pressure ulcer prevention protocol used in addition to product application

<table>
<thead>
<tr>
<th>Pressure ulcer prevention</th>
<th>Braden risk scale score (13–15)</th>
<th>Braden risk scale score (&lt;12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance of pressure points</td>
<td>Every 12 hours</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Skin protection</td>
<td>Product under study</td>
<td>Product under study</td>
</tr>
<tr>
<td>Pressure relief surfaces</td>
<td>Alternating</td>
<td>Alternating</td>
</tr>
<tr>
<td></td>
<td>Large cell</td>
<td>High performance or large cell</td>
</tr>
<tr>
<td>Air mattress</td>
<td>Air mattress</td>
<td></td>
</tr>
<tr>
<td>Heel and elbow protection</td>
<td>Non adhesive</td>
<td>Non adhesive</td>
</tr>
<tr>
<td></td>
<td>Hydrocellular heel dressing</td>
<td>Hydrocellular heel dressing</td>
</tr>
<tr>
<td>Seating (if pathology permitting)</td>
<td>4 hours maximum</td>
<td>2 hours maximum</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Static/alternating cushion</td>
<td>Alternating cushion</td>
</tr>
<tr>
<td>Food control</td>
<td>With every intake</td>
<td>With every intake</td>
</tr>
<tr>
<td></td>
<td>Nutritional profile</td>
<td>Nutritional profile</td>
</tr>
<tr>
<td></td>
<td>Nutritional supplements</td>
<td>Nutritional supplements</td>
</tr>
<tr>
<td>Repositioning</td>
<td>Every 4 hours</td>
<td>Every 4 hours</td>
</tr>
<tr>
<td></td>
<td>Cyclical</td>
<td>Cyclical</td>
</tr>
</tbody>
</table>

to be administered. The purpose of taking photographs was to monitor skin condition and to compare it with that of patients who might present category I PUs, and also in order to check and compare the skin on the final day of assessment.

The following procedure was followed daily during assessment:

1. A PU risk evaluation was conducted and the results registered, and the prevention measures employed were recorded.
2. A skin inspection was carried out before applying the product (every 12 hours) over the bony prominences, with the aim of ruling out category I or higher pressure injuries. In those cases where the skin had reddened, the ‘transparent disk technique’ was used in order to differentiate blanching from non blanching erythema (category I PU), in which a transparent disk was applied on the skin for a period of 3 seconds to check whether the skin was blanchable or not.
3. If reddening appeared, photographs of the transparent disk on the lesion were taken to document whether it was a category I PU or not. If the diagnosis corresponded to a category I PU or higher, the patient was excluded from the study and was administered the corresponding treatment to solve the problem. The actions that were taken from that moment were included in the final assessment sheet.

To maintain uniformity as regards protocol and clinical evaluation, all researchers were equivalently trained for all the assessments and the procedures employed. A training session was held where all aspects were explained and the researchers could raise any questions. In addition, all individuals conducting patient assessments were fully trained before the study commenced. Furthermore, the local researcher and the nurse responsible for the patient confirmed the skin assessments. Control was maintained by a clinical study manager who audited the study report. Audits were also conducted at each participating centre by the main researchers.

Outcomes/endpoints
The primary efficacy outcome was PU incidence in each group, measured as cumulated incidence and as incidence rate. The secondary outcome was tolerance (occurrence of local adverse events).

Randomisation and blinding method
The patients were randomly allocated on a 1:1 ratio to be treated either in the control group or in the experimental group, according to a randomisation code contained in a sealed envelope. Randomisation envelopes were provided to sites whereby the next lowest
randomisation was carried out using a randomisation code generated with random numbers by the SPSS 18.0 software package, thus producing block randomisation. Besides randomising the patients, these numbers ensured allocation concealment, as only the main researcher knew which group corresponded to which code. The envelope would be opened once the decision on the patient’s participation in the study had been taken. The inclusion of the patient and the randomisation code was communicated to the principal researcher to be recorded.

In both groups under study, the containers of the products to be assessed were identical, only differing in their randomisation code. Each product container was labelled with an identification code (random number) showing the phrase: ‘FOR CLINICAL STUDY USE ONLY’. To avoid researcher bias, the principal researcher distributed identical flasks, and only this researcher had access to the flask codes. Thus, the clinical practice professionals, the local researchers and the patients had no indication of which group each patient belonged to. When the analyses were performed, the person who conducted the analysis was blinded to the groups.

**Statistical analysis**

All randomised subjects were included in the analysis. In accordance with the study objectives and the characteristics of the variables, the following statistical analyses were carried out:

- **Descriptive analysis** establishing the basal levels of the groups (in order to determine their comparability) and the PU incidence in both groups. Incidence was calculated in terms of cumulated incidence and by means of incidence rates.

- **Inferential analysis** in which comparison of the groups at their initial stage required the corresponding parametric or non-parametric tests depending on the characteristics of the variables under study. Relative risk (RR) was also calculated, as well as the preventable fraction (PF) and the necessary number to treat (NNT). To determine if there were any differences in PU incidence between both groups, the z-test for difference between two independent proportions was employed. In order to study temporal evolution and treatment effect in time, as well as the effect of other variables, a survival analysis according to Kaplan–Meier (log-rank test) was carried out and the Cox proportional hazards risk model regression was used. The hypothesis of proportionality of risks was checked with a term in the time interaction model.

Two statistical software packages were used for the analyses: SPSS 18.0 and EPIDAT 3.1. SPSS was used for all descriptive analyses, comparisons of the variables and for multivariate analysis (Kaplan–Meier and Cox regression). EPIDAT 3.1 was used for the epidemiological analyses (RR, PF and NNT) and the z-test for the difference between two independent proportions.

**RESULTS**

**Patient recruitment process**

In spite of the timeline set out in the research protocol, patient recruitment for the study did not start until April and May 2009, principally due to bureaucratic problems and the delay in receiving ethics committee approval. The process of finding patients for the study proved to be laborious and more complex than expected. A large number of patients were assessed for inclusion, but on many occasions either the patient or their legal representative decided against participation after being properly informed. Eventually, it was only possible to recruit a sample of 194 patients [99 in the experimental group (EG) and 95 in the placebo group (CG)], representing only 39% of the required sample size previously calculated (478 subjects). There were no dropouts during the study period.

**Description of the participants**

In this section, the demographic and general clinical characteristics of the patients in the study are described. Regarding age, EG patients were 78.16 ± 13.85 years old (median = 81, extremes = 39–101) and CG patients were 78.51 ± 13.25 years old (median = 82, extremes = 29–98). With regard to sex, 61.2% were women in the EG, compared to 62.1% in the CG.

As for the risk of developing PUs according to the Braden scale, this risk in the EG was on
average 12.28 ± 1.80 (median = 12, extremes = 9–15), whilst in the CG it was 12.65 ± 1.82 (median = 12, extremes = 8–15). This indicates that in both groups, patients presented a high risk of developing PUs.

Clinical diagnosis of patients
With regard to the patients’ base pathologies, the vast majority was patients with advanced neurodegenerative diseases (Alzheimer, dementia, ICTUS, etc.) in both groups. This indicates the patients’ lack of mobility and the possible risk of their developing PUs, apart from the Braden scale score.

Prevention measures applied besides the application of the product or the placebo
Table 3 presents the main prevention measures carried out at the beginning of the study. Where repositioning was performed, this was carried out in the EG, on average, every 4:43 hours (median = 4 hours) and in the CG, every 4:66 hours (median = 4 hours). In most cases, patients were seated every 12–13 hours in both groups (i.e. twice a day). Those patients who required nutritional supplements took two supplement containers a day on average, regardless of the study group to which they belonged. As regards the preventive measures, these were maintained for the duration of the patients’ participation in the study.

Areas of application of the product
The product was applied to all the patients on the areas of sacrum, trochanters and heels.

Efficacy results
In the areas where the product had been applied, six PUs were detected in the EG compared to seven in the placebo group.

Table 3 Preventive measures applied to both groups*

<table>
<thead>
<tr>
<th>Preventive measure</th>
<th>EG (%)</th>
<th>CG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repositioning</td>
<td>92.9</td>
<td>89.5</td>
</tr>
<tr>
<td>Sitting in an armchair</td>
<td>88.8</td>
<td>90.5</td>
</tr>
<tr>
<td>Use of dressings on heels–elbows</td>
<td>32.3</td>
<td>29.5</td>
</tr>
<tr>
<td>Pressure relieving surfaces</td>
<td>62.6</td>
<td>61.1</td>
</tr>
<tr>
<td>Nutritional supplements</td>
<td>25.3</td>
<td>20.0</td>
</tr>
</tbody>
</table>

CG, placebo group; EG, experimental group.
*Percentage of patients to whom these measures were applied.

The distribution of ulcers per location was as follows:
- Sacrum: three in EG and four in CG
- Trochanters: two in EG and two in CG
- Heels: one in each group

This therefore implies a cumulated incidence of 6.1% (incidence rate = 4.7 PUs × 1000 patients/day) in EG and 7.4% (incidence rate = 5.4 PUs × 1000 patients/day) in the placebo group. When applying the z-test for difference of proportions to these cumulated incidence results, no statistically significant differences between the two groups were found (z = 0.08; P = 0.94).

Regarding association and impact measures, the following results were obtained:

Association measures
Relative risk
An RR = 0.82 [95% confidence interval (CI) = 0.29–2.36] was obtained. Both the CI and the chi-square test show that this RR was not statistically significant.

Rate ratio
The incidence rate ratio obtained was 0.86, but again, since the confidence interval includes 1 (95% CI = 0.29–2.56), the rate ratio was not statistically significant, and this was confirmed by the z-test for ratio comparison.

Impact measures
Absolute risk reduction = 0.01 (risk or incidence difference)

Prevented fraction in the exposed population study (PFe) = 17.75% (percentage of prevention that could be attributed to the product). In the case of incidence rates, the prevented fraction in the exposed was 13.81%, which was not statistically significant either.

NNT = 76.50 (77 patients should be treated to prevent an event).

Figure 1 presents the Kaplan–Meier survival curves, and the log-rank test was used to establish whether any statistically significant differences existed. As can be seen in the Figure 1, there were no statistically significant differences in the survival curves, as was also the case for PU occurrence, and this was confirmed by the log-rank test. The analysis according to the Cox regression model was not carried out since the previous analyses did not
identify differences between the two groups, and it was considered pointless to carry out this analysis to see if there was any variable which explained the result.

**DISCUSSION**

According to the data above, the randomised assignment process enabled us to start from two comparable groups at the beginning of the study in terms of age, sex, risk of PU development and basal diseases. The preventive care applied, the product under study and the placebo were administered equally in both groups. Consequently, it can be confirmed that the two groups were comparable.

In this situation, whilst it may appear that there was a difference in favour of the experimental group at a descriptive level, statistical inference tests showed that there were no statistically significant differences between the two groups. This is mainly explained by the small size of the sample (underpowered), and it is impossible to say what the results would have been if a sufficient number of patients had been recruited, namely, the number considered necessary to achieve the required sample size calculated prior to commencement of the study. Thus, sample size constitutes an important limitation of the study and a possible source of bias, mainly due to random error, that is, the difficulty in extrapolating the data from our sample to the general population. We are not saying that there were no differences between the groups, but we cannot say that these stemmed from the study conditions. In fact, the situation of this study was quite different from those reviewed above (10,11,17,18) and was used to calculate sample size (17). In these studies on other topical prevention products (HOFA or others):

- Declair (10) used a combination of fatty acids obtained from sunflower seed oil (rich in linoleic acid) and vitamins A and E against a placebo (mineral oil and vitamins A and E), and obtained an incidence of 4.65% in the experimental group \((n = 43)\) and 27.90% in the placebo group \((n = 43)\).
- Gallart *et al.* (11) carried out a comparative study, which consisted of using Corpitol (HOFA product) and not. They obtained an incidence of 18.75% \((n = 96)\) against 35.42% \((n = 96)\).
- Torra *et al.* (17) conducted a double-blind clinical trial of Mepentol (HOFA product) against a placebo (mineral oil), and obtained an incidence of 7.3% \((n = 164)\) against 17.4% \((n = 167)\).
- Gouveia *et al.* (18) carried out an open trial of Mepentol versus no Mepentol, and also obtained an incidence of 2% \((n = 50)\) against 17.4% \((n = 46)\).
In our case, both the cream under study and the placebo, together with the prevention protocol applied, acted effectively since the number of PUs detected was very low (6 and 7 PUs, or 13 ulcers out of a total of 194 patients, representing a total incidence of 6.7%). Indeed, even if the situation was stable over time and it had been possible to achieve the sample size estimated previously (478 subjects), the analysis would have remained underpowered. With such a slight difference (1.3%) between product and placebo, more than 4000 subjects would be required to achieve good statistical power. At this point a further question emerges; independently of statistics, when should a difference be considered clinically relevant? On the basis of data provided by prior studies, a 10% difference was considered to be clinically relevant when designing this study.

The placebo acted almost as well as the product tested. In fact, the placebo is the same product as the one used in the intervention, but without the active principles under study. Thus, the placebo is a very good moisturising cream that maintains good skin condition regardless of possible aggressions. In each of the studies reviewed, different products were employed, different comparisons made, follow-up times varied, and even the measures or analyses carried out differed. However, all of the studies used topical fatty acids of a different composition, and PU incidences ranged from 2% to 18.75% in the experimental groups, and from 17.4% to 35.4% in the control groups. In this study, a PU incidence of 6.1% and 7.4% was obtained in the treatment and placebo groups, respectively, so both groups would fall in the interval of the experimental groups. Therefore, the finding that both the experimental product and the placebo have acted as effectively as the topical products used to date is confirmed. It is possible that the standardisation of care and procedures through a prevention protocol may play a role in the PU incidence recorded for both groups, and further research comparing this protocol with others is needed.

Health care professionals and patients have welcomed the product employed, due to ease of application and skin absorption.

Despite the methodological limitations mentioned above, the results of this study could be taken as a starting point for further research into the promising prospects of this product as adjuvant in the prevention of skin lesions. Moreover, it would be logical to carry out a study of its efficacy in the healing process.

CONCLUSIONS
On the basis of the study results it cannot be confirmed that there are any differences between the product under study and the placebo employed in the prevention of PUs. Regardless of the follow-up times, which were shorter in this study, the results obtained here were similar to those obtained in other studies on the prevention of PUs using products based on topical fatty acids.

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