The effectiveness of a hyperoxygenated fatty acid compound in preventing pressure ulcers

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Efectividad de un compuesto de ácidos grasos hiperoxigenados en la prevención de úlceras por presión

**Objetivo**
Comprar los efectos de Mepentol®, un compuesto de ácidos grasos hiperoxigenados con extractos de plantas, frente a un placebo en la prevención de las úlceras por presión. Para verificar la eficacia de Mepentol®, se valoraron las diferencias existentes en la incidencia de úlceras por presión.

**Material y Métodos**
El estudio de investigación consistió en un ensayo clínico aleatorizado, multicéntrico y doble ciego. Se calculó: la incidencia de úlceras por presión, Riesgo relativo (RR), Fracción Prevenible (FP) y Número necesario a tratar (NNT). Además, se aplicaron curvas de supervivencia de Kaplan-Meier con pruebas de log-rank y modelos de riesgos proporcionales de regresión de Cox para comparar ambos grupos.

Los pacientes recibieron los mismos cuidados, aplicándose 2 veces al día el producto (Mepentol® o placebo) en un mínimo de 3 localizaciones.

**Resultados**
Completaron el estudio un total de 331 pacientes: 167 en el grupo control y 164 en el grupo a estudio. La incidencia de las úlceras por presión durante el estudio fue de 7,32% en el grupo de intervención frente a 17,37% en el grupo placebo (p=0,006).

Estos resultados muestran que por cada 10 pacientes tratados con Mepentol® se previene la aparición de una úlcera por presión (NNT=9,95). Las curvas de supervivencia y los modelos de regresión muestran una diferencia estadísticamente significativa para ambos grupos (p≤0,001).

**Conclusión**
Mepentol® es una medida mucho más efectiva para prevenir las úlceras por presión que la utilización de cremas grasas, presentando además una excelente dimensión coste/beneficio.
The effectiveness of a hyperoxygenated fatty acid compound in preventing pressure ulcers

- **Objective:** To compare the effects of Mepentol, a hyperoxygenated fatty acid preparation, with a placebo treatment in preventing the development of pressure ulcers.

- **Method:** The research study consisted of a multicentre double-blind randomised clinical trial. The incidence of pressure ulcers, relative risk (RR), preventable fraction and number necessary to treat (NNT) were calculated. In addition, Kaplan-Meier survival curves, with log-rank test, and Cox’s proportional hazards regression model were used to compare both groups.

- **Results:** A total of 331 patients completed the study: 167 in the control group and 164 in the study group. Pressure-ulcer incidence during the study was 7.32% in the intervention group versus 17.37% in the placebo group (p<0.006). These results show that for each 10 patients treated with Mepentol one pressure ulcer was prevented (NNT = 9.95). Survival curves and the regression model showed a significant statistical difference for both groups (p<0.001). The average cost of Mepentol during the study was €7.74.

- **Conclusion:** Mepentol is an effective measure for pressure ulcer prevention. It was more effective than a greasy placebo product, and was found to be cost-effective.

- **Declaration of interest:** This study was sponsored by Laboratorios Bama-Geve SA, Barcelona, Spain.

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The use of compounds containing essential oils has been found to have beneficial effects in wound care. In particular, it has been shown that application of hyper-oxygenated fatty acids — essential fatty acids that have undergone hyperoxygenation — helps to prevent the development of grade I pressure ulcers. Essential oils have the following beneficial properties:

- They protect against pressure and friction
- They provide optimal skin hydration
- They reverse non-blanching erythema caused by anoxia.

Essential fatty acids increase the cohesiveness of cells in the stratum corneum and prevent transcutaneous water loss and skin decamation (hyperproliferative skin growth).

They are also precursors to prostaglandins, or arachidonic acids, which are absorbed through the skin. Prostaglandins help regulate cell division and epidermis differentiation.

Excess oxygen free radicals damage endothelium tissue. Incomplete elimination of these molecules at the start of reperfusion will result in a concentration of hydrogen peroxide in tissue that has been subjected to pressure.

Hyperoxygenation of essential fatty acids facilitates anti-radical activity in the oxidative stress process of cells in reactive hyperaemia.

Mepentol (Laboratorios Bama-Geve SA, Barcelona, Spain) is a hyperoxygenated fatty acids compound consisting of:

- Oleic acid
- Palmitic acid
- Stearic acid
- Palmitoleic acid
- Linoleic acid
- Gamma linoleic acid
- Arachidonic acid
- Eicosenoic acid, which contains extracts of *Equisetum arvense* and *Hypericum perforatum.*

Mepentol influences the renewal of keratinocytes and microcirculation. It can also prevent the development of pressure ulcers and facilitate the healing of grade I pressure ulcers.

Jude et al. suggested that hyperoxygenated fatty acids increase the concentration of inflammatory mediators such as nitric oxide and prostaglandins. Combined with the effect of mediators on the stratum corneum and increased keratinocyte renewal, this appears to counteract the impact of long-term pressure and friction forces. This can be observed in both the dermis and the subcutaneous tissue.

This multicentre double-blind randomised clinical study set out to compare the effects of Mepentol with a placebo treatment in preventing the development of pressure ulcers.

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Method

The following inclusion criteria were applied:

- Patients had to be at medium, high or very high risk of developing pressure ulcers
- Patients had to be able to participate for an evaluation period of 30 days
- Patients or their carers needed to provide written consent to take part.

Patients were excluded if they:

- Were terminally ill or receiving chemotherapy
- Had more than three pressure ulcers
- Were allergic to hyperoxygenated fatty acids or topical fatty products
- Had peripheral vascular disease.

The sample size was determined according to the incidence of pressure ulcers in the control group (35%) reported in a previous paper. Accepting an alpha risk of 0.05 and a beta risk of 0.20 in a bilateral contrast to detect a difference that was equal to or greater than 15% between the two groups, 188 patients would be needed in each group. A monitoring loss rate of 10% was estimated.

The placebo was a compound consisting of triisostearin (99.4%) and perfume (0.6%), and was specially manufactured for the study by Laboratorios Bama-Geve SA. Triisostearin is a greasy substance with no known therapeutic effect. The placebo, therefore, had the same appearance and fragrance as Mepentol.

Patients were randomised to the intervention (Mepentol) group or the control group using a randomised code in a closed envelope.

The two treatments came in the same packaging, which could only be distinguished by the sample codes. Only the study coordinator had access to the packaging codes, so neither the investigators nor the patients knew which group a patient had been allocated to.

All 13 participating centres used the same pressure ulcer prevention protocol. This was applied to both study groups.

The intervention product or placebo was applied twice daily to at least three areas of the body:

- Sacrum
- Trochanter
- Heels.

The following patient variables were considered:

- Demographic data
- Risk assessment
- Time a patient spent during the day in a recumbent/semi-recumbent position and seated in a chair
- Frequency of repositioning
- Pressure-relieving surfaces used
- Use of barrier products to protect skin from the effects of incontinence (relevant to the development of sacral ulcers only)
- Systolic and diastolic pressures (generally measured twice a day using a sphygmomanometer in accordance with guidelines of the participating centres)
- Vasosuppressor drug treatment
- Anti-inflammatory drugs
- Presence of diabetes.

The Ethical Committee for Clinical Investigations at the Consorci Sanitari de Terrassa approved the study, which took place between April 1 2003 and November 15 2003.

Analysis

The recorded variables were subjected to a series of statistical analyses:

- A descriptive analysis to establish baseline levels and the incidence of pressure ulcers
- An inference analysis to compare study groups at the initial stage — the Student’s t-test was used for quantitative variables (to analyse means) and the Chi-square test \( \chi^2 \) was used for quantitative variables (to analyse proportions)
- Relative risk (RR), predictable fraction (PF) and the number needed for treatment (NNT) estimates
- A Chi-square test to determine differences in the incidence of pressure ulcers between the groups
- Survival analyses, applied using the Kaplan-Meier (log-rank) test and the Cox proportional hazards

Box 1. Investigators and participating centres

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joan-Enric Torra i Bou</td>
<td>Montserrat Arboix i Perejamo, CAP Terrassa Nord, Barcelona</td>
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<tr>
<td>Justo Rueda López</td>
<td></td>
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<tr>
<td>Fernando Martínez Cuervo</td>
<td>Residencia mixta de la tercera edad Gijón, ERA, Asturias</td>
</tr>
<tr>
<td>Elvira Hernández</td>
<td>Residencia los Robles (Mortera) Cantabria</td>
</tr>
<tr>
<td>Luis Miguel Novillos Briceño</td>
<td>Residencia de personas mayores Manoteras, Madrid</td>
</tr>
<tr>
<td>Carme Rossell</td>
<td>Fundació Sanitaria Sant Josep (Igualada) Barcelona</td>
</tr>
<tr>
<td>Isabel Majoral</td>
<td>Fundació Sant Hospital (La Seu d’Urgell) Lleida</td>
</tr>
<tr>
<td>María Jesús Salvador Morán</td>
<td>Residencia Talía (Aravaca Ia) Madrid</td>
</tr>
<tr>
<td>Ana Orbegozo</td>
<td>Fundación Matía, San Sebastian</td>
</tr>
<tr>
<td>Marta Ferrer</td>
<td>Hospital de la Sta. Creu (Vic), Barcelona</td>
</tr>
<tr>
<td>Jesús Aneas</td>
<td>Residencia Mossen Homs (Tarrasa) Barcelona</td>
</tr>
<tr>
<td>Pablo López Casanova</td>
<td>Residencia de la Tercera Edad (Elche), Alicante</td>
</tr>
<tr>
<td>Eduardo Ramírez Gómez</td>
<td>Residencia de la Tercera Edad (Elche), Alicante</td>
</tr>
<tr>
<td>Merce Comellas</td>
<td>Carmen Santos, Clínica Barcelona, Barcelona</td>
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<tr>
<td>Carmen Santos</td>
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</tr>
<tr>
<td>Eulàlia Gónzález</td>
<td>Residencia Torres Falguera (Tarrasa), Barcelona</td>
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</tbody>
</table>
model, to study the effects of treatment over an extended period and the effect on other variables.

- To check the proportional hazards hypothesis, we introduced an interaction term into the model. This measures the amount of time taken for a pressure ulcer to develop following application of the intervention treatment. The Cox proportional hazards model assumes that a risk is constant over time. The interaction term tested this assumption.

The Department of Community Nursing, Preventive Medicine, Public Health and History of Science of Alicante, Spain, designed the statistical analysis. SPSS 11.0 software was used to evaluate the results.

Results
In total, 380 patients were enrolled into the study, 331 of whom completed the study — 167 in the control group and 164 in the intervention group.

Forty-nine patients withdrew from the study:

- Two died
- Seven were transferred to other units or were discharged
- Two suffered a general deterioration in condition
- Thirty-eight patients did not complete the questionnaire, or staff caring for them did not follow the study protocol.

Tables 1 and 2 outline baseline descriptive and comparative data.

The incidence of new pressure ulcers that developed during the study period was 7.32% (12 out of 164) for the intervention group and 17.37% (29 out of 167) for the control group (p=0.006) (Fig 1).

This gave a relative risk of 0.42 (IC<sub>95%</sub> = 0.22-0.80) and a preventable fraction of 58%. In other words, the analysis showed that patients treated with

### Table 1. Baseline data (qualitative variables)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo group</th>
<th>Mepentol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (28.1)</td>
<td>41 (25.0)</td>
</tr>
<tr>
<td>Female</td>
<td>120 (71.9)</td>
<td>123 (75.0)</td>
</tr>
<tr>
<td>Pressure ulcers at inclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (21.6)</td>
<td>40 (24.4)</td>
</tr>
<tr>
<td>No</td>
<td>131 (78.4)</td>
<td>124 (75.6)</td>
</tr>
<tr>
<td>Uses special support surface to manage pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (52.7)</td>
<td>87 (53.0)</td>
</tr>
<tr>
<td>No</td>
<td>76 (45.5)</td>
<td>76 (46.3)</td>
</tr>
<tr>
<td>Uses local management pressure system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>89 (53.3)</td>
<td>97 (59.1)</td>
</tr>
<tr>
<td>No</td>
<td>76 (45.5)</td>
<td>65 (39.6)</td>
</tr>
<tr>
<td>Use of barrier products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>97 (58.1)</td>
<td>99 (60.4)</td>
</tr>
<tr>
<td>No</td>
<td>67 (41.9)</td>
<td>63 (39.6)</td>
</tr>
<tr>
<td>Administration of vaso-suppressor drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (10.2)</td>
<td>22 (13.4)</td>
</tr>
<tr>
<td>No</td>
<td>143 (85.6)</td>
<td>139 (84.8)</td>
</tr>
<tr>
<td>Administration of anti-inflammatory drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (9.0)</td>
<td>18 (11.0)</td>
</tr>
<tr>
<td>No</td>
<td>149 (89.2)</td>
<td>144 (87.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (21.0)</td>
<td>27 (16.5)</td>
</tr>
<tr>
<td>No</td>
<td>131 (78.4)</td>
<td>133 (81.1)</td>
</tr>
</tbody>
</table>

*Data are missing for some patients. All variables had a non-significant statistical difference.

### Table 2. Baseline data (quantitative variables)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo group</th>
<th>Mepentol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>83.64 ± 7.37</td>
<td>84.18 ± 9.74</td>
</tr>
<tr>
<td>Hours spent lying down/semi-recumbent</td>
<td>15.27 ± 3.58</td>
<td>15.30 ± 3.85</td>
</tr>
<tr>
<td>“Hours sitting”</td>
<td>8.59 ± 3.54</td>
<td>8.60 ± 3.81</td>
</tr>
<tr>
<td>Frequency (in hours) of postural changes*</td>
<td>2.55 ± 0.94</td>
<td>2.44 ± 0.81</td>
</tr>
<tr>
<td>Frequency (in hours) of postural night changes*</td>
<td>3.34 ± 1.5</td>
<td>3.46 ± 1.46</td>
</tr>
<tr>
<td>Systolic arterial pressure*</td>
<td>123.57 ± 18.66</td>
<td>126.09 ± 16.01</td>
</tr>
<tr>
<td>Diastolic arterial pressure*</td>
<td>68.01 ± 10.23</td>
<td>69.37 ± 11.78</td>
</tr>
<tr>
<td>No. of active pressure ulcers</td>
<td>0.91 ± 1.01</td>
<td>0.76 ± 1.00</td>
</tr>
<tr>
<td>Total score on Braden scale*</td>
<td>12.35 ± 2.63</td>
<td>12.44 ± 2.60</td>
</tr>
</tbody>
</table>

* Non-significant statistical difference
Mepentol had a 58% lower risk of developing pressure ulcers than patients given the placebo, thus indicating that one ulcer per 10 patients was prevented in the Mepentol group (NNT=9.95).

Comparison of the Kaplan-Meier survival curves with the log-rank test was statistically significant (p=0.0054) (Fig 2). The curves were different, showing that patients given Mepentol were less likely to develop pressure ulcers for any time period, particularly after day 20.

Accumulated incidences of pressure ulcers at days 10, 20 and 30 are listed in Table 3. The Cox’s proportional hazards regression model found that the following variables were significant:

- Gender
- Frequency of night-time patient repositioning
- Use of barrier products.

The relative risk of treatment did not alter after adjusting for the above variables (Table 4).

Regarding the use of the interaction term, interpretation of the model parameters found that the risk of pressure ulceration was not constant over time — that is, use of Mepentol reduced the level of risk over time (Table 5). This result was statistically significant. The relative risk reported in Table 4 is the average relative risk over the length of the study period.

**Discussion and conclusion**

Study design is crucial in enabling researchers to collect evidence rooted in clinical practice and to provide quality scientific data that can be analysed and classified.18-20

This study used a clinical randomised double-blind design and involved two large patient groups, which generated high-quality evidence in an area where there is a dearth of it.21

The randomisation process resulted in the distribution of similar variables and characteristics in both groups at baseline. The double-blind design prevented observer bias.

The results show that Mepentol was 58% more effective in preventing pressure ulcers than the placebo. We might have observed an even greater difference if we had compared outcomes of patients treated with Mepentol with those of untreated patients. However, this is ethically unacceptable as it would expose patients to an avoidable risk of pressure ulceration.

Interpretation of the survival curves (Fig 2) shows that patients treated with Mepentol presented higher accumulated probabilities for not developing...
pressure ulcers than those given placebo for any time period. These differences are more marked after about day 20 (Table 3 and Fig 2).

As already stated, the relative risk (RR=0.42) must be taken as an average as it varies over the treatment period. Therefore, the relative risk was the same in both groups at the start of the study, and progressively diminished in the treatment group but not in the control group.

In terms of epidemiology, relative risk is the risk that one group has against another (here, mepentol is 58% more effective than placebo). The results can be interpreted thus:

- If the relative risk equals 1, then the treatment has not had an effect (both groups are similar)
- If the relative risk is greater than 1, then the treatment has caused damage (that is, the placebo is better than treatment)
- If the relative risk is less than 1, then the treatment has worked (the treatment is better than the placebo).

Our analysis of the survival curves and regression models shows that the relative risk varied over time. At the start of the study, it was 1, whereas the trend over time was less than 1. This indicates that, if applied systematically, Mepentol can have a protective effect on pressure zones as time passes.

In the multivariate model (Table 4), the statistically significant variables (sex, barrier products and/or frequency of nighttime patient repositioning) did not have a major effect on the relative risk — RR=0.42 in the simple model versus RR=0.45 in the multivariate model.

In spite of this, these data suggest that women are at greater risk than men of developing pressure ulcers (RR=2.47) and that failure to apply barrier products increases the risk of developing pressure ulcers (RR=3.68).

Frequent repositioning at night is shown to help prevent pressure ulcers (RR=0.68).

This is supported by Verdu et al., who studied trends for pressure-ulcer mortality in Spain for 13 years (1987–1999) and found that women had a higher probability of dying than the men.

The average cost of Mepentol during the study period was €7.74, which is €9.3 a month or 30 cents a day (€0.2 packages used per patient x €7.74 = €9.3, where €7.74 is the price of one package of Mepentol at the time of the study).

In the context of these results, we believe that Mepentol is a more effective treatment than other greasy products for the prevention of pressure ulcers. This, in turn, indicates that it offers clinicians value for money.

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