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BRIEF REPORT

Evaluation of the efficacy of polydeoxyribonucleotides in the healing process of autologous skin graft donor sites: a pilot study

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Key words: Polydeoxyribonucleotides – Re-epithelialisation – Skin graft – Wound healing

SUMMARY

Objective: The article presents the results of a pilot study performed to evaluate the efficacy of polydeoxyribonucleotides (PDRNs) in shortening the healing times of autologous skin graft donor sites.

Research design, methods: Two groups of patients were studied, the PDRN group (n = 20) and a control group (n = 20). In the control group dressings were performed with non-adherent gauzes and bulky gauzes with chloramine solution, whereas in the PDRN group a PDRN ointment was spread under the same medication as the controls.

Results: In the PDRN group, dressing procedures were not painful (whereas in the controls they often were), re-epithelialisation occurred earlier (12.5 vs 24.45 days) and there were no infections (9 in the controls).

Conclusions: Results are encouraging for the use of PDRNs in shortening the healing times of autologous skin graft donor sites, although further studies are necessary to obtain clinically relevant results.

Introduction

In this paper we report on the investigation of the effect of polydeoxyribonucleotides (PDRNs) in the healing process of autologous skin graft donor sites.

PDRN is a natural product, formed by polymers of deoxyribonucleotides with chain lengths ranging between 50 and 2000 base pairs; 100 g of ointment (Placentex® fiale) contains 80 mg of PDRN and the following excipients: decyl oleate 8.97 g, cetyl-stearlic alcohol 17.95 g, anhydrous lanolin 4.49 g, alkyl p-hydroxy benzoates 0.4 g, imidazolepydinurea 0.3 g, aromatic base 0.014 g, purified water q.s. for 100 g. The active component of the drug, which is species-specific, follows the normal metabolism of PDRN of both endogenous and exogenous derivation.

In the literature it has been demonstrated that PDRN is capable of stimulating the proliferation, both in vitro and in vivo, of a wide range of cell types involved in the healing process of surgical wounds. From a clinical point of view, PDRNs have been used for lower limb post-phlebitic ulcers, burns and other conditions in which an enhancement of the wound healing process

* Placentex is a registered trade name of Mastelli Srl, Sanremo, Italy
was necessary\textsuperscript{2-4}. This drug is approved in Italy for both parenteral and topical use.

The aim of our study was to compare the efficacy of two different treatments in the wound healing process of autologous skin graft donor sites in two experimental groups of 20 patients each.

Patients and methods

Polydeoxyribonucleotides (Placentex stale, Mastelli, Sanremo, Italy) were used in this pilot study: the drug is approved in Italy for parenteral and topical use. The study was conducted in accordance with the ICH Good Clinical Practice guidelines and the Declaration of Helsinki.

From January to July 2002, all patients in whom we harvested autologous split-thickness skin grafts for reparative purposes were included in our study. We also enrolled in our pilot study, patients affected by diseases that could negatively influence the wound healing process: diabetes mellitus, peripheral vasculopathy, hepatic cirrhosis, auto-immune diseases under cortisone therapy and haemathologic disorders (Table 1). None of our 40 patients were undergoing treatment with drugs that could improve the mechanisms of wound healing; none had previously shown hypersensitivity to PDRN and the ointment excipients. Forty patients of both sexes were randomly divided into two groups: control and PDRN. All patients provided written informed consent; however, the ointment is available as an over-the-counter preparation in retail pharmacies.

In both groups grafts were taken with a dermatotomy apparatus (Aesculap GB 230, Germany), calibrated in order to obtain slices of 6 cm width, 10 cm length and 0.3 mm thickness from the anterolateral side of thighs. If the operation required two or more slices of skin grafts for reparative purposes, only one slice of 60 cm\textsuperscript{2} area was considered for this study. Skin graft harvesting was performed under general anaesthesia in 30 patients (75%), spinal anaesthesia in 9 patients (22.5%), and local anaesthesia with Mepivacaine 1% in 1 patient (2.5%) (Table 2). In both groups, as soon as skin grafts were cut, haemostasis was obtained by compression with gauzes soaked with H\textsubscript{2}O\textsubscript{2} for 20 min; in the meantime the reparative procedure was performed. Subsequently in the control group a single layer of non-adherent gauzes was applied on the donor sites of skin grafts, followed by bulky gauzes soaked with claramine solution.

In the PDRN group, after haemostasis, a layer of PDRN ointment was spread, covering completely the donor sites; non-adherent gauzes and bulky gauzes soaked with claramine solution, as in the control group, completed the medication. After surgery, those in the control group soaked their thigh bandages daily with claramine solution and the dressings were superficially renewed on alternate days until wound healing. In the PDRN group, patients soaked their thigh bandages daily with claramine solution; on alternate days, bandages were completely removed (Figure 1A), donor sites were cleansed with saline solution, a layer of PDRN ointment spread to completely cover the donor sites and the thigh redressed as in the operating theatre, until completely re-epithelialisation occurred.

If infection occurred, complete removal of dressing with daily medication was performed.

Evaluation of donor sites was performed at days 7 and 15 in both groups (Figure 1B, C): we checked the percentage re-epithelialisation of lesions by the following formula:

\[
\text{Area of re-epithelialisation (cm}^2\text{)} \times 100 \\
\text{Total area (60 cm}^2\text{)}
\]
Figure 1. A: Donor site healing at 2 days after a complete removal of bandages in a PDRN patient. B: Donor site healing at 7 days in a PDRN patient. C: Donor site healing at 15 days in a PDRN patient.

Table 3. Pathologies affecting the PDRN and control groups

<table>
<thead>
<tr>
<th>Diseases</th>
<th>PDRN Group (n = 20)</th>
<th>Control Group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant skin tumours</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Burns</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Scars</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rhinophyma</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Vascular ulcers</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Post-traumatic ulcers</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

In order to evaluate the epithelialised areas we took photographs of donor sites during the healing process at days 7 and 15 and we analysed the images with a PC incorporating a control grid with a single area of 0.5 cm².

The occluded areas were considered de-epithelialised areas.

Subjective symptoms (pain, itching) were evaluated on the following scale: 0 = absent; 1 = moderate, 2 = marked, 3 = serious.

Figure 2. Evolution of the re-epithelialisation process in a PDRN group and in a control group.
Figure 3. Graphical distribution of the percentage of re-epithelialisation at the 7th and 15th days in the two groups

Statistical Methods

The results were reported as means and/or percentages, with minimum and maximum values. The distribution of diseases causing skin graft was analysed by variance analysis and Tukey Kramer multiple comparison test. Statistical significance was fixed at $p < 0.05$.

Results

The control group was made up of 7 females and 13 males; the average age was 56.25 (range 26–89 years). The PDRN group was made up of 6 females and 14 males; the average age was 62.1 (range 41–84 years) (Table 2).

The diseases affecting patients in both groups are shown in Table 3: the most frequent pathology in the control group was burn, while in the PDRN group malignant skin tumour was the most frequent pathology (chi square: 5.415; $p$ n.s.). Figure 2 shows the evolution of re-epithelialisation in the two groups; in the PDRN group re-epithelialisation occurred earlier than in the control group with a statistically significant difference ($p < 0.01$) at T7 and at T15.

In the control group, complete re-epithelialisation occurred on average in 24.45 days (range 17–41) (Figure 3). At day 7 the average percentage of re-epithelialisation was 19.25% (range 0–55%), corresponding to 11.5 cm$^2$ (range 0–33 cm$^2$); at day 15 the average percentage of re-epithelialisation was 53.5% (range 0–95%), corresponding

Figure 4. Graphical representation of the subjective symptoms evaluated of following scale: 0 = absent, 1 = moderate, 2 = marked, 3 = serious

406 PDRNs in the healing of skin graft donor sites
to 32.1 cm² (range 0–57 cm²) (Figure 2). Infections occurred in 9 cases.

In the PDRN group, complete re-epithelialisation occurred on average in 12.5 days (range 9–20) (Figure 3). At day 7 the average percentage of re-epithelialisation was 46.75% (range 0–90%), corresponding to 28.05 cm² (range 0–54 cm²); at day 15 the average percentage of re-epithelialisation was 98.5% (range 80–100%), corresponding to 59.1 cm² (range 48–60 cm²) (Figure 2). No infections occurred in this group.

Symptomatology is recorded in Figure 4; PDRN patients were nearly completely asymptomatic (four cases of moderate symptoms), while in the control group four cases had serious symptoms and nine marked symptoms, also in relation to infections.

No adverse reactions to the PDRN ointment or its excipients were reported during this study.

**Discussion**

The transplantation of autogenic split-thickness skin grafts is still the gold standard in many plastic surgery procedures (burns, chronic ulcers, closure of tumours ablation, etc.) and, above all in burn patients, it is often necessary to use skin graft donor sites several times. Thus, healing time is very important in order to harvest from a donor area multiple or serial split-thickness skin grafts. Usually, when a split-thickness graft is cut, a dressing of a single layer of non-adherent gauze is applied, covered by bulky gauzes, and left in place for the expected time of healing. Using this method of wound dressing in our control group, 45% of the patients became infected, causing a delay in re-epithelialisation (24.45 days as the mean healing time in the control group, 12.5 days in the PDRN group) and a worsening in the symptomatology (Figure 4): the forceful removal of the infected gauzes provoked bleeding, exacerbating the inflammatory response, increasing pain and healing time and worsening the final cosmetic appearance (hyperpigmentation and hypertrophy). We decided to change this way of dressing, trying to obtain better clinical results and to understand if our percentage of infections was related to the general surgical ward in which we admitted our patients or to the type of medication.

Logistic situations are changing as the expense of providing sterile environments in hospitals grows, such that many Plastic Surgery Divisions in Italy and Europe are placed in general surgery wards and share the same operating theatres. This situation puts our patients in contact with enteric and anaerobic microorganisms.

In the PDRN group, healing of the skin grafts donor sites was more rapid compared with the control group and no infections occurred, reducing symptomatology to only four cases of moderate symptoms: dressing procedures were not painful and the final cosmetic appearance was satisfactory.

In order to obtain these results it was mandatory to obtain a perfect haemostasis during surgery, otherwise a thick clot developed (four cases in the PDRN group) (Figure 5): this acted as a barrier, preventing adequate cleaning of the wounds and hindering the penetration of PDRN into the donor sites, so lengthening the healing time.

PDRN dressing offered the advantage of a moist environment for wound healing, in addition to the advantage of removing the gauzes on alternate days, contributing to keeping the wound checked and cleaned more frequently than in traditional medications. This is probably the reason for the 0% of frank infections in the PDRN group in spite of the fact our patients were admitted to the same general surgery ward as the control group.

The difference between the two groups was statistically highly significant but this is a pilot study, not double-blind randomised, so these should be considered preliminary conclusions, obtained performing two different types of wound dressing using an ointment in one group (PDRN) and not in the other. Nonetheless, the results indicate that PDRN treatment is deserving of wider clinical investigation.

*Figure 5. The figure shows that a thick clot developed after 2 days in a PDRN patient*
Furthermore, we enrolled in our study, even if homogeneously distributed (Table 1), patients affected by diseases that could negatively influence the wound healing process, reducing the clinical relevance of the study.

However, it could be postulated that PDRN ointment applied directly onto graft donor sites promotes a more rapid healing process; we are now performing clinical double-blind randomised placebo-controlled studies to test PDRN efficacy in the healing process for graft donor sites in order to demonstrate the clinical impact of this new kind of dressing.

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References


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