Allogenic platelet gel in the treatment of pressure sores: a pilot study

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ABSTRACT

Although platelet gel is considered one of the most popular tools in the treatment of chronic ulcers, current consensus on its use is not unanimous. A prospective randomised trial was carried out at the Plastic Surgery Unit of the ‘Salvatore Maugeri’ Foundation Hospital of Pavia (Italy). The study involved 13 patients affected by spinal cord injury with 16 pressure sores over a period of 20 months. The ulcer was considered the experimental unit of the study irrespective of the number of ulcers per patient. Each consecutive ulcer was randomised to be treated either with allogenic platelet gel or with current best practice approach to chronic wounds dressing protocol. At the end of the treatment 15 ulcers out of 16 improved clinically. No statistically significant difference was demonstrated in volume reduction between the two groups, although a statistically significant difference could be demonstrated in the onset time of granulation tissue proliferation as in the wounds treated with platelet gel the healing process was triggered earlier. Our study suggests that platelet gel is mostly effective within the first 2 weeks of treatment while a prolonged treatment does not provide any significant advantage versus the current best practice approach to chronic wounds protocols.

Key words: Chronic wound • Difficult-to-heal wound • Growth factors • Platelet gel • Pressure sores • Ulcer

INTRODUCTION

Platelet gel is one of the most easily available sources of growth factors that are recognised to play a key role in the wound healing process (1–7), although, to date, there is still lack of evidence for platelet gel derived growth factors to improve healing in chronic wounds. Actually platelet gel is generally considered one of the most popular tools in the treatment of chronic ulcers, but current consensus on its use is not unanimous (8–21). Such a figure is mainly as a result of extreme heterogeneity in the assessment methodology of the different clinical studies on platelet gel.

The aim of our study is an objective assessment of the effects of platelet gel on chronic ulcers through a prospective randomised controlled open clinical pilot trial in a very homogeneous sample.
MATERIALS AND METHODS

Study design
A prospective randomised controlled open clinical pilot trial was carried out at the Plastic and Reconstructive Surgery Unit of the ‘Salvatore Maugeri’ Foundation Hospital of Pavia (Italy). The study involved the joint partnership of the Neuro-rehabilitation Unit and Spinal Unit of the ‘Salvatore Maugeri’ Foundation Hospital, and the Immuno-haemathology Department of the ‘San Matteo’ Hospital of Pavia (Italy).

Thirteen patients (three females and ten males), affected by stable spinal cord injury with single or multiple pressure sores, were enrolled in the trial over a period of 20 months, from December 2005 to July 2007. All patients were in a compensated stable nutritional status. Exclusion criteria were metabolic, endocrine and collagen pathologies, ischaemic cardiopathy, corticosteroid or immuno-suppressive therapy, obesity, malignancies, and organ failure.

The patients were admitted both on inpatient and outpatient basis.

The ulcer was considered the experimental unit of the study irrespective of the number of ulcers per patient. Only III and IV grade ulcers, according to the National Pressure Ulcer Advisory Panel classification (22), with no signs of necrosis or infection and stable after at least 2 months, were considered eligible for the study. Concerning wound infection, a positive swab for the resident bacterial flora did not exclude the ulcer from the trial, while a local and/or general septic status did so (23).

Sixteen ulcers, ten sacral and six ischiatic, were enrolled in the trial.

Pressure ulcer stage and patient general status were carefully evaluated in a pre-screening consultation. Each consecutive ulcer, which fulfilled the entry criteria, was randomised to be treated either with allogenic platelet gel (group A – GEL protocol) or with a dressing protocol inspired to the current best practice approach for chronic wounds (group B – NO GEL protocol). Ulcers were randomised according to a completely randomised design.

Informed written consent was obtained from the patients.

The trial was approved by the local Ethical Committee.

Materials

**Allogenic platelet gel**

Allogenic platelet gel was supplied by the Immuno-haemathology Department of the ‘San Matteo’ Hospital of Pavia (Italy) according to the approved national guidelines for human use of allogenic blood derivates.

Platelet gel is prepared in a Petri dish blending 4–8 ml of concentrated platelet preparation, including at least $2 \times 10^{10}$ platelets, with 2–4 ml of plasma activated with Calcium Chloride. Platelet gel develops in about 5 minutes and is then frozen at $-80^\circ$C to be stored. The whole preparation process is run in absolute sterile modality.

An intra-departmental agreement allowed withdrawal of platelet gel near the clinical application in order to minimise any inappropriate storage time. The Petri dish was transported within a hermetic sterilised custom made container at 4°C. Platelet gel was straw-yellow in colour and of a semi-liquid consistency.

**NO GEL treatment protocol**

The dressing protocol is summarised in Table 1.

**GEL treatment protocol**

The overall study structure is depicted in Figure 1.

Platelet gel was applied directly to the clean wound bed using a sterile syringe; the ulcer was then covered with a polyurethane sponge/semi-permeable film dressing system (Biatain Coloplast®).

The ulcers were treated twice weekly for 8 weeks with a total of 16 applications. The time points of the study were designed as follows:

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**Table 1** NO GEL dressing protocol for III and IV NPUAP stadium pressure ulcers

| Detersion: Saline at room temperature |
| Dressing: Packing with 10% iodoform impregnated gauzes or Sodium/Alginate foams or Cadexomer Iodine powder and/or Vacuum Assisted Closure therapy |
| Perilesional areas: Zinc Oxide paste or Silver Sulfadiazine in high contamination risk area (i.e. perineum) |

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Efficacy parameters

**Ulcer dimension**

Ulcer volume was calculated in millilitre by filling the cavity up to the skin surface plane with a liquid transparent gel (Aquasonic 100-gel-ultrasonic gel, Parker Laboratories, Fairfield, NJ, USA) using a graduated syringe. The measurements were made by the same operator with a same brand and same capacity syringe. This peculiar volume measurement method was considered the most appropriate and easy to perform in such a clinical context as the non toxic ultrasonic gel could both permeate the whole cavity and stay without draining away. In our study we were then interested in measuring differences between volumes in each ulcer rather than absolute volumes.

**Semi-quantitative data**

Granulation tissue colour and bleeding were assessed at the instant of scraping. The parameters of tissue vitality were subjectively assessed by the operators using a three-point ordinal scale: low (+), medium (++), and high (+++).

**General status parameters**

**Systemic parameters**

Body Mass Index, triceps fold, haemoglobin, White Blood Cells count, albumin, and pre-albumin were monitored at T0 and T5 times.

**Safety parameters**

As the potential risk of infection transmission via allogenic blood derivates was the most harmful event in this trial, B Hepatitis Virus
(HBV), C Hepatitis Virus (HCV) and Human Immunodeficiency Virus (HIV) serum pattern was determined at the beginning and at the end of the study (T0 and T6 times).

Data analysis
Efficacy of platelet GEL protocol versus NO GEL protocol was assessed by comparing the volume changes in the two groups. The absolute and percentage differences between volumes at each time between T0 and T5 were both considered. The trend of volume changes was tested with descriptive statistics, the t Student test, the Mann–Whitney test and the variance analysis.

RESULTS
The ulcer volumes measured at different times in the two groups are depicted in Table 2.

Only 11 ulcers completed the study at T6 time, owing to spontaneous drop out of five ulcers (four Gel and one NO GEL protocol). Sixteen ulcers (eight GEL protocol and eight NO GEL protocol) reached T5 time.

At T5 time 15 ulcers out of the 16 demonstrated a clinical improvement, with a statistically significant volume reduction regardless of the treatment \( (P < 0.001) \).

No statistically significant difference could be demonstrated in volume reduction between the two groups \( (P = 0.76) \). A better trend for the wounds treated with platelet gel could be demonstrated only between T0 and T1 times \( (P = 0.025) \). Mean volume changes at different times are depicted in Figure 2.

Semi-quantitative data (colour and bleeding of granulation tissue) did not show significant differences between the two groups either.

Safety of allogenic platelet gel treatment could be proved as no serum conversion for HBV, HCV, and HIV occurred at 1-month follow up (3 months since the first gel application).

Microbiological swabs collected both at T5 and T6 times did not show any increase or change of the resident bacterial flora.

At the end of the trial all the patients were in stable general conditions.

General parameters did not show any statistically significant difference between T0 and T5 in both groups apart from pre-albumin \( (P = 0.08) \) and albumin \( (P = 0.041) \) values which appeared slightly improved in both groups at the end of the study.

DISCUSSION
The use of growth factors and platelet gel for the topical treatment of chronic, difficult-to-heal wounds has been extensively reported in the literature (8–21). To date, few rigorous trials have been carried out with consistent outcomes.

Knighton et al. (8) in 1986 first demonstrated that autologous platelet-derived growth factors (PDGFs) promote healing of different chronic cutaneous ulcers. These results were subsequently confirmed by a prospective randomised study in 1990 (9). Several studies on the clinical use of platelet gel (10–13) and recombinant growth factors (14–21) then followed with conflicting outcomes. Chronic ulcers are an extremely heterogeneous group of pathologies where many different local and systemic factors play an aetio-pathogenetic role. An objective comparison of the different proposed treatments for the so-called chronic, difficult-to-heal wounds is therefore difficult if not impossible.

Recently, Nedeau et al. (24) demonstrated in vitro efficacy of PDGFs in recruiting adult bone marrow-derived mesenchymal stem cells (BM-MSCs) through activation of local resting resident fibroblasts. BM-MSCs are then able to differentiate into myo-fibroblasts and contribute to wound healing. Such a phenomenon is likely to happen in vivo during the acute wound healing process. Regrettably, chronic ulcers are not properly comparable with acute wounds as different biochemical and cellular interactions are most likely to occur.

In this prospective randomised study we established very restricted inclusion criteria in order to reproduce the most possible homogeneous clinical and experimental conditions. Such a rigorous methodology had a consequent reduction in patient suitability which rendered a low number of eligible ulcers despite the huge availability of patients in the clinical departments that were involved. The high compliance requirements for a long and intensive study protocol further reduced the pool of potential candidates. Indeed, it took us 20 months to accurately assess the 13 selected patients with the 16 ulcers.

Our clinical experience demonstrated better results with the use of platelet gel versus the current best practice approach to chronic wounds treatment only within the first 2 weeks.
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### Key Points
- Chronic ulcers are not properly comparable with acute wounds as different bio-chemical and cellular interactions are most likely to occur.
- In this prospective randomised study we established very restricted inclusion criteria in order to reproduce the most possible homogeneous clinical and experimental conditions.
- Indeed, it took us 20 months to accurately assess the 13 selected patients with the 16 ulcers.
- Our clinical experience demonstrated better results with the use of platelet gel versus the current best practice approach to chronic wounds treatment only within the first 2 weeks of treatment and such an advantage vanished as the treatment continued.
- A plausible explanation for such a short-lived efficacy of the platelet gel might be the depletion of other unknown local and/or systemic co-factors that would be essential for full expression of PDGFs action.
- Although PDGFs are demonstrated to be some of the most potent activators of BM-MSCs recruitment in the acute wound bed, their mobilisation and homing to injured tissues depends on the systemic and local inflammatory state.
- In conclusion our study suggests that allogenic platelet gel can be successfully used as a starter for any halted healing process within the first 2 weeks of treatment while a prolonged treatment does not provide any significant advantage in comparison with the current best practice approach to chronic wounds protocols.
- This trial eventually contributes to a better definition of a proper use of allogenic blood derivatives in the local treatment of chronic wounds.

### Table 2 Ulcer volumes in ml at different time points (T0–T6)

<table>
<thead>
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<th>Patients</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
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A, GEL protocol; B, NO GEL protocol.

### Figure 2.
Trend of the mean ulcer volumes along the trial: comparison between treatments.
statement about safety could be made considering the limited numbers of our sample.

In conclusion our study suggests that allogenic platelet gel can be successfully used as a starter for any halted healing process within the first 2 weeks of treatment while a prolonged treatment does not provide any significant advantage in comparison with the current best practice approach to chronic wounds protocols.

This trial eventually contributes to a better definition of a proper use of allogenic blood derivates in the local treatment of chronic wounds.

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