Original Research

Platelet-Rich Plasma in Skin Ulcer Treatment

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Abstract: Introduction. Chronic vascular ulcers are associated with a high use of resources. Conventional treatment consists of wound cleansing, necrotic tissue debridement, prevention, diagnosis, and, if necessary, treatment of infection and dressing application; although conventional treatment has limited effectiveness with wound healing (around 15-30%).8-11 Platelet-rich plasma, used in various fields of medicine, improves chronic vascular ulcer results, but is more expensive. Methods. A cost-effectiveness analysis was performed using a 48-week period comparing platelet-rich plasma with standard care. A meta-analysis of papers identified by a literature search was done. Results. A combined measure of effectiveness at 12 weeks for each treatment option was calculated and served as the basis for estimating the probability of healing at 48 weeks with a Markov model. Conclusions. The probability of healing and associated costs were 56% and €5224 using platelet-rich plasma and 31% and €5133 with usual care. The incremental cost that must be assumed to achieve additional healing with platelet-rich plasma is €364.

Key words: varicose ulcers, skin ulcers, platelet-rich plasma, cost-benefit analysis

Chronic vascular ulcers require multidisciplinary management that is associated with a high use of resources, especially in primary care. It is estimated that in Western countries 1% of adults will have a chronic vascular ulcer at some stage in their lives, the prevalence being 1.3 to 3 individuals out of 1000.1 In Spain, according to the first national study on leg ulcers carried out between 2002 and 2003, the prevalence of vascular ulcers was found to be 1.65 per 1000.2

Vascular ulcers can be arterial, venous, or both, with the most common etiology being venous and representing 80%-90% of all vascular ulcers.3,4 Venous ulcers tend to be persistent—among patients with venous ulcers, 30% have a > 5-year history of this condition and an estimated 72% rate of recurrence.5,6 The conventional treatment of vascular ulcers consists mainly of wound cleansing; debridement of necrotic tissue; prevention; diagnosis; and, if necessary, treatment of infection and application of dressings.7 The effectiveness of the conventional treatment is still relatively low, around 15%-30%.8,11,22 Moreover, the mean duration of skin ulcers is approximately 1 year, indicating the seriousness of the problem for many patients, given the associated pain and disability.

The use of platelet-rich plasma (PRP) and plasma rich in growth factors...
(PRGF) is a relatively new approach considered clinically useful in various fields of medicine (ie, dentistry, traumatology, cosmetic surgery, ophthalmology, and dermatology). Platelets contain proteins, known as growth factors, that trigger biological effects including directed cell migration (ie, chemotaxis), angiogenesis, and cell proliferation and differentiation, which are key in the processes of tissue repair and regeneration. Various studies have been published on the role of platelet concentrates in the treatment of skin ulcers with positive results in favor of this technology.8-13

However, since this biotechnological approach has higher associated costs than conventional practice, it is necessary to assess whether it is economically justifiable through cost-effectiveness analysis comparing it with the usual treatment provided in clinical practice.

The current use of health care resources for the treatment of vascular ulcers is very high, both because complete closure of the wound is very difficult to achieve and because the ulcers tend to recur.14 In a study carried out by Ragnarson Tennvall et al,15 it was estimated that the

### Table 1. Clinical trials included in the meta-analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Groups</th>
<th>Focus of the treatment</th>
<th>Period of treatment (weeks)</th>
<th>Number of patients and ulcers treated</th>
<th>Healed n (%; 95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver et al,23 2006</td>
<td>Control: Usual care Intervention: autologous PRP</td>
<td>Diabetic ulcers</td>
<td>12</td>
<td>Control: 19 PRP: 16 (adjusted for the initial size of the ulcer)</td>
<td>8 (42.1; 19.9-64.3) 13 (81.3;54.5-96.0)</td>
<td>P = 0.036</td>
</tr>
<tr>
<td>Friese et al,8 2007</td>
<td>Control: Usual care Intervention: autologous PRP</td>
<td>Diabetic ulcers</td>
<td>12</td>
<td>Control: 21 PRP: 20</td>
<td>5 (24.5;7-42.0) 11 (55;33.2-76.8)</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>&gt;&gt;&gt;Knighton et al,9 1990</td>
<td>Control: Usual care Intervention: autologous PRP</td>
<td>Chronic ulcers</td>
<td>8</td>
<td>Control: 11 patients (13 ulcers) PRP: 13 patients (21 ulcers)</td>
<td>2/13 (15.4;1.9-45.5) 17/21 (81;64.2-97.7)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Aguirre (personal communication)</td>
<td>Control: Usual care Intervention: PRGF</td>
<td>Chronic ulcers</td>
<td>8</td>
<td>Control: 11 PRGF: 12</td>
<td>3 (23; 1.0-53.6) 6 (50; 21.7-78.3)</td>
<td>P = 0.4</td>
</tr>
</tbody>
</table>

*Estimated at 12 weeks

Steed DL,10 1995 | Control: placebo gel Intervention: rhPDGF | Chronic diabetic ulcers | 20 | Control: 57 PDGF: 61 | 14 (24.6; 13.4-35.7) 29 (47.6; 35.1-60.1) | P = 0.01 |

**Steed DL Extrapolated to 12 weeks** | | | | Control: 57 PDGF: 61 | 6 (10.5; 3.0-18.5) 18 (29.5;18.1-41.0) | P = 0.0198 |

*Estimated at 12 weeks

**Study was not included in the final cost-effectiveness analysis; *Estimation of the results at 12 weeks from the data at 8 weeks; **Extrapolation from the graph.
average cost of standard treatment for venous ulcers was €71 per patient per week, excluding inpatient care, and €103 in total. In the United Kingdom, the direct cost of vascular leg ulcers to the National Health Service has been estimated to be €400 million sterling. Given all this, it is necessary to analyze different treatment options, in terms of their associated costs and effectiveness.

**Methods**

A cost-effectiveness analysis comparing 2 treatment options—usual clinical practice and PRP—for the treatment of skin ulcers after 48 weeks was done. A Markov-based modeling that allows simulations of complex systems, such as health care processes, was used. The model was constructed following a previously established protocol, using estimations obtained from published or other available data on efficacy, toxicity, and costs of the various options being compared.

The clinical course of the ulcers was modeled using a hypothetical cohort of 200 patients with characteristics similar to those included in the clinical trials comparing the 2 options reviewed in this study (conventional treatment and PRP): patients with diabetes between the ages of 55 and 75 years, who have at least 1 ulcer on the lower extremities that had been detected at least 4 weeks earlier, and with a current area of 3 cm$^2$ - 10 cm$^2$. These 200 patients were randomly allocated to receive either 1) usual care: cleansing of the wound; debridement of necrotic tissue; prevention; diagnosis; and, as required, treatment of infection and the application of suitable dressings; or 2) PRP treatment: cleansing of the wound; debridement of necrotic tissue; prevention; diagnosis; and as required, treatment of infection and application of PRP as well as suitable dressings.

The treatment applied to these hypothetical cohorts consisted of 12-week cycles with 2 appointments per week. At each appointment, the wound was cleaned appropriately and covered with a suitable dressing. Additionally, the intervention group received PRP on 1 of the 2 days, always on the same day of the week. Once the first 12-week cycle of treatment had been completed, patients in whom complete healing had been achieved were considered to have finished their treatment and were monitored for the remaining 36 weeks to detect potential recurrences. Patients whose wound had not completely healed after 12 weeks, in either of the groups, continued with the conventional treatment until the ulcer was fully healed. Similarly, patients in whom the ulcer recurred after healing received the conventional treatment until the new ulcer was fully healed.

**Estimation of effectiveness.** To obtain data on effectiveness, a literature search was conducted in secondary databases PubMed, EMBASE, and Cochrane, using the following strategy: (“wound healing” OR “leg ulcers” OR “skin ulcers” OR “venous ulcers”) AND (“plasma rich in growth factors” OR “platelet rich plasma”) AND (“clinical trial” OR “controlled randomized trial”). Only published original papers and unpublished preliminary results provided by researchers describing studies involving a control group that received conventional treatment (ie, wound cleansing, debridement, infection management, and application of suitable dressings) and lasting for 8 to 12 weeks were selected. No restrictions were applied in terms of language or date. Research that considered a measure of effectiveness other than the number of healed ulcers at the end of the study were excluded.

A meta-analysis was performed on the data in the selected papers to obtain combined effectiveness results after 12 weeks for each of the treatment options. This was used as a starting point to estimate the probability of healing at 48 weeks.

For this estimate, the authors used a Markov model with 4 possible levels of health status: nonhealed ulcer, healed ulcer, recurrence (of the ulcer), and amputation (Tables 1 and 2), and 4 cycles of 12 weeks each. The probability of healing was different in each cycle, while the period for which each patient had a given health status depended on their treatment group allocation and the time elapsed since the start of the treatment.

Each patient in each treatment group began the study with the status of “nonhealed ulcer.” During each cycle in which the patients had this status, their ulcer might heal or not. In the latter case, amputation might then be required. If patients had the status of “healed ulcer,” they either continued to have no ulcers or their ulcer recurred. Table 2 summarizes the probability of changing between health status categories.

**Estimation of costs.** The economic analysis was performed from a health system perspective. The authors only took into account direct costs based on nursing staff wages from Lazaro-Martinez et al for the Spanish publish health
care system in 2007, and converted into euros; the mean cost of a PRP kit per treatment calculated from the price of 4 different formulations, in some cases from quotes provided by the corresponding supplier, and in others, as advertised on the company website; costs of the materials necessary for changing dressings, taken from Ragnarson and Hjelmgren, using the average between costs in Sweden and the United Kingdom; and costs of amputations due to ulcers not healing. Table 3 shows a breakdown of all costs included in study.

**Table 2. Probabilities of changing between health status categories.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At 12 weeks</th>
<th>At 24 weeks</th>
<th>At 36 weeks</th>
<th>At 48 weeks</th>
<th>Recurrence*</th>
<th>Amputation**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healed</td>
<td>Non-healed</td>
<td>Healed</td>
<td>Non-healed</td>
<td>Healed</td>
<td>Non-healed</td>
</tr>
<tr>
<td>Usual treatment</td>
<td>0.222</td>
<td>0.778</td>
<td>0.08</td>
<td>0.92</td>
<td>0.072</td>
<td>0.928</td>
</tr>
<tr>
<td>Usual treatment + PRP</td>
<td>0.468</td>
<td>0.532</td>
<td>0.123</td>
<td>0.877</td>
<td>0.042</td>
<td>0.958</td>
</tr>
</tbody>
</table>

*Percentage relative to cases in which the ulcer healed. **Percentage relative to cases in which the ulcer did not heal.

**Table 3. Direct costs included in the cost-effectiveness analysis per ulcer.**

<table>
<thead>
<tr>
<th></th>
<th>Usual care</th>
<th>Usual care + PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of visits</strong></td>
<td>24 (wound cleansing, debridement, application of dressings)</td>
<td>12 (wound cleansing, debridement, application of dressings)</td>
</tr>
<tr>
<td><strong>Duration of the appointment</strong></td>
<td>15 min</td>
<td>15 min</td>
</tr>
<tr>
<td><strong>Cost of the appointment</strong></td>
<td>€3.42 *</td>
<td>€3.42 *</td>
</tr>
<tr>
<td><strong>Change of Dressing</strong></td>
<td>€7.20**</td>
<td>€7.20**</td>
</tr>
<tr>
<td><strong>Kit preparation PRP</strong></td>
<td>–</td>
<td>€132.90***</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>€254.88</td>
<td>€1972.92</td>
</tr>
</tbody>
</table>

**Mean cost of amputations**

€41163****

*Salary of the nursing staff of the public health system in 2007 after conversion from US dollars to euros. **Average costs of the material necessary for changing dressings based on data from Sweden and United Kingdom. ***Average price of a PRP kit per session. ****Cost of amputations. The conversion was made using the official value of the US dollar and the euro of European Central Bank on October 26, 2012.

The authors calculated the number needed to treat (NNT) at the 95% level of confidence (the number of ulcers to be treated using PRP to achieve a higher rate of healing than that with usual care), and the incremental cost (the increase in costs associated with adding PRP to the usual care to heal 1 more ulcer). The measure of effectiveness used was the number of ulcers healed after 48 weeks, expressed in absolute numbers, with the percentage distribution and 95% confidence intervals (CIs), and the costs were calculated in euros. It was not considered necessary to adjust costs or benefits to present values given that the study period was less than 1 year.

A sensitivity analysis was performed recalculating the NNT and incremental cost with the CI percentages corre-
Results

Assessment of the effectiveness. In the literature search, the authors identified 5 randomized clinical trials (as communicated by JJ Aguirre, Biotechnology Institute, Vitoria, Spain, in an email dated September 2011) in which the treatment period was between 8 weeks and 12 weeks. The DerSimonian and Laird method yielded a $P$ value of 0.0963, indicating a lack of statistical homogeneity. After excluding the study by Knighton et al., which contributed the most to the observed heterogeneity, the combined results gave rates of healing of 46.8% (37.4%-56.2%) among those treated with PRP and of 22.2% (14.4%-30.1%) among those receiving standard care. The estimated probabilities of healing after 48 weeks, as assessed using the Markov model, were 56% (46.3%-65.7%) and 31% (21.9%-40.1%) for the PRP and standard care groups, respectively.

Assessment of costs. Total ulcer-related costs after 48 weeks of treatment averaged €5224 and €5133 in the PRP and standard care groups, respectively. In the group that received standard care, a high percentage of the figure is due to amputation-related costs, these being higher than in the other group due to the lower rate of healing.

The NNT was 4 (95% CI: 3 to 9), which is statistically significant, and the incremental cost to achieve the healing of 1 additional ulcer, when compared with the results of usual care, would be €364.

Discussion

Using a Markov model, the authors simulated the clinical course of skin ulcers with a hypothetical cohort of 200 patients randomly assigned to either receive standard care or to receive platelet-rich plasma (PRP) plus standard care. After 48 weeks of treatment, the overall estimates of effectiveness were 56% for the PRP group and 31% for the standard care group, while the estimated costs were €5224 and €5133, respectively.

Sensitivity analysis. For the sensitivity analysis, the authors selected the most unfavorable data, that is, the CI percentages corresponding to the measure of effectiveness for each treatment option that minimized the difference in outcomes with the 2 treatments. Hence, for the standard care group the authors used a probability of healing of 40.1% (40.1 ulcers) and for the PRP group a value of 46.3% (46.3 ulcers). With these new figures, the NNT and incremental cost was recalculated. In this case, the NNT was 16 (95% CI: 13 to 5), that is, to achieve healing of 1 additional ulcer, compared to the outcome with usual care, 16 more patients should be treated, and taking the worst case scenario, this would increase expenditure by €1456. In this new scenario, the difference between the 2 treatments is not statistically significant. Further, 1 of the 95% confidence limits is negative, indicating that PRP could have a detrimental effect, (PRP achieves less benefit than conventional treatment, which is referred to as the number needed to harm).24

Intangible costs (in particular, deterioration in quality of life caused by patient disability and pain due to the wounds) are particularly difficult to quantify in financial terms, and hence, have not been taken into account in this study. It would, however, be important to assess their impact in future studies, since pain is a symptom which is perceived by patients as a constant reminder of their ulceration and is also hard to control.25 Intangible costs can also be expected to be higher in the group receiving standard care given the
A lower rate of ulcer healing. In addition, the values of costs and effectiveness have been estimated for a time period of just under 1 year. An ulcer that has not healed after 52 weeks of treatment is considered unlikely to heal; however, the costs continue to increase since the probability of amputation at 5 years is 19%,\(^1\) so the overall costs associated with treating an ulcer after 5 years would be higher, especially in the group receiving the standard care, since there would be a higher rate of amputation.

Another important factor to take into account is the limited number of clinical trials identified with the required outcome variable as the main assessment criterion. Further, of the 4 studies reviewed, only 1 other made reference to vascular ulcers, with the other 3 focusing on the use of PRP in diabetic ulcers. In theory, this is unlikely to pose a problem given that diabetic ulcers have a poorer prognosis than vascular ones in general, and it can be assumed that if PRP is effective in diabetic ulcers, it would be at least as effective, or more effective, in vascular ulcers. In addition, in 2 of the 4 selected studies, the authors have estimated the number of ulcers healed at 12 weeks from the available data for 8 weeks and 20 weeks. This estimate has been performed considering the process of wound healing follows linear kinetics, but in actuality, wound healing depends on several factors such as age, infection presence, degree of nutrition, and length of time since development of the ulcer.

Despite the aforementioned limitations, the authors think this study has strengths. In particular, a thorough search of the scientific literature selecting the most homogenous studies was conducted, which allowed the authors to calculate a robust combined estimate of effectiveness, the starting point for the estimate of the probability of healing after 48 weeks of treatment. Further, the authors selected as the measure of the effect an outcome variable, namely the number of ulcers healed at the end of the study, that made the criteria for this study’s literature search more exacting, as in many studies the variable measured is the percentage reduction in ulcer size.

It would be interesting to perform a cost-effectiveness analysis within a clinical trial in order to address the aforementioned limitations. Further, it would be desirable to assess these treatments from a social perspective, considering factors important for patients such as quality of life, especially pain, and also to carry out a 5-year follow-up as completed several years ago by Dougherty,\(^1\) who obtained a positive cost-effectiveness ratio using PRP in diabetic ulcers.

**Conclusion**

The authors conclude that the use of PRP for the treatment of skin ulcers is cost effective; the extra cost for achieving the healing of 1 more ulcer than with usual care would be €364, much lower than the overall long-term costs of treating an ulcer with the usual approach of standard care without PRP (€5133).

**References**


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**Table 4. Ulcers healed at 12 weeks: results of the studies included in the meta-analysis.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healed</td>
<td>Nonhealed</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Driver et al,(^{23}) 2006</td>
<td>13 (81.3)</td>
<td>54.5-96.0</td>
</tr>
<tr>
<td>Friese et al,(^{8}) 2007</td>
<td>11 (55.0)</td>
<td>33.2-76.8</td>
</tr>
<tr>
<td>Aguirre (personal communication)*</td>
<td>9 (75.0)</td>
<td>50.5-99.5</td>
</tr>
<tr>
<td>Steed DL,(^{10}) 1995**</td>
<td>18 (29.5)</td>
<td>18.1-41.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51 (46.8)</td>
<td>37.4-56.2</td>
</tr>
</tbody>
</table>

*Estimation of the results at 12 weeks from the data at 8 weeks. **Extrapolation from the graph.


