Systematic review of the efficacy of fat grafting and platelet-rich plasma for wound healing

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Keywords

Fat grafting; Platelet rich plasma; Fat transfer; PRP; wound healing

Suggested Reviewers

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Abstract

Background

Adipose derived stem cells found in fat grafts may have significant healing properties. When fat is combined with autologous platelet-rich-plasma (PRP) there may be enhanced healing effects due to the pro-angiogenic and anti-inflammatory effects of PRP. This study aimed to evaluate the current evidence on fat grafting in combination with PRP for wound healing to establish the efficacy of this technique.

Methods

A comprehensive search in the MEDLINE, EMBASE, CENTRAL, Science Citation Index, and Google Scholar databases (to March 2017) was conducted to identify studies on fat grafting and PRP for wound healing. Case series of less than 3 cases and studies only describing harvest technique were excluded.

Results

The database identified 571 articles, of which three articles which used a combination of fat and PRP for wound healing (one RCT and two case series) were included in this review. A total of 69 wounds in 64 patients were treated with an average wound size of 36.32cm^2. Of these, 67% of wounds achieved complete healing. When reported, the mean time to healing was 7.5 weeks for those who underwent a single treatment. There were no significant complications in any patients.

Conclusion

The combination of fat grafting and PRP may achieve adequate wound healing with relatively quick wound healing time compared to standard wound management options. However evidence is extremely limited and further studies are required to evaluate its efficacy for wound healing.

Introduction

Wound management places a significant burden on healthcare, costing the National Health Service (NHS) approximately 5.5% of its annual expenditure (1), equating to billions of pounds per annum (2). The incidence of chronic wounds and ulcers is greater than 100000 cases per year, with this number expected to rise due to the ageing population and increasing prevalence of diabetes (3). Traditional wound management options include regular dressings and skin grafting.

Dressings management can often be a slow, time consuming process with variable results and one in ten cases in loss of limb (4). There is no strong evidence base to support the majority of traditional dressings options (5).

Autologous skin grafts are an important wound management option. Standard treatment options primarily consist of full thickness skin grafts (FTSG) and split thickness skin grafts (SSG). FTSG consist of the entire epidermis and dermis and consequently the donor site must be closed directly after harvest. Therefore only donor sites with sufficient skin laxity, such as the post-auricular or supra-clavicular areas, are suitable for skin harvest limiting this technique to areas of small wound areas only (6). FTSG also rely more significantly on the vascularity and nutrients of its recipient bed compared to SSG and therefore are at higher risk of graft failure. SSG include the epidermis and part of the dermis, and can be meshed to cover a larger wound area and are more versatile with regards to donor sites compared to FTSG. However the donor site is left to heal by secondary intention which can cause donor site pain, infection and scarring (7). Epidermal grafting is becoming an alternative wound coverage option with wound healing rates comparable to SSG with reduced donor site morbidity (8) and higher patient satisfaction (9). However evidence on this technique remains very limited.

Fat grafting has become increasing popular in contouring procedures over the last few decades (10), however more recently there is becoming an emphasis on it's regenerative potential. Adipose-

derived stem cells or MSCs found in fat are believed to facilitate healing through differentiation into cells which effect wound healing e.g. fibroblasts, keratinocytes (11). They also release pro-healing growth factors and anti-inflammatory cytokines (12) as well as healing-related peptides such as leptin and adiponectin which together may enhance wound healing (13). Several small studies have shown that autologous fat grafting may show significant healing qualities in chronically scarred tissue after radiotherapy (14), chronic wounds (15,16), arterial ulcers (17), pressure ulcers (18), and diabetic foot ulcers (19). However the evidence remains limited with no randomised controlled trials reported.

Platelet-rich plasma (PRP) is an autologous blood-derived product enriched in platelets, growth factors, chemokines and cytokines. It is a reservoir of essential growth factors, including platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor-beta 1, and insulin-like growth factor which facilitate repair and healing. Platelet-derived biologic mediators have two primary effects on wound healing: recruiting and activating cells that effect wound healing, and regulation of angiogenesis (20,21). Platelets may also have antimicrobial and immune modulation properties which help to reduce wound infection and facilitate healing (22). Some studies have found enhanced healing and reduced healing time of split thickness skin grafts when used in combination with PRP (22-25) and improved healing when used as the primary treatment for chronic wounds (26-28). However several higher level evidence studies have shown no clear benefit for wound healing over conventional treatments (29-31).

When fat and PRP are used in combination there may be increased survival of the fat graft which may in turn increase the healing properties of the adipose-derived stem cells. This is believed to be due to the pro-angiogenic effects of PRP which allows early vascularisation of the fat therefore reversing the early ischaemic phase of the graft (32). Another pro-survival effect may be the release of anti-inflammatory chemokines which help reduce inflammation and swelling which encourage degeneration of the graft. Hypotheses also exist which suggest PRP may provide nutrient support to the fat cells through its plasma component and that the fibrin component allows formation of a scaffold for fat cells (33-35). Several studies have shown that PRP may increase the longevity of fat grafts in contouring procedures (36-38).

The use of combination fat and PRP for wound healing is beginning to be tested, however evidence on its efficacy is extremely limited. This systematic review synthesises the current evidence on fat grafting and PRP for wound healing to establish the efficacy of this technique in the clinical setting by measuring the proportion of wounds healed and the mean wound healing time. It is timely that the evidence is assessed to guide clinical decision making and to facilitate future research.

Materials and Methods

The protocol for this systematic review was registered with PROSPERO international prospective registration of systematic reviews (registration number: CRD42016049881) and has been subsequently published in a peer-reviewed journal (39). It was intended that this systematic review would be conducted and reported according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (40). However, given the wide heterogeneity between the three studies identified a narrative review was reported and meta-analysis was not performed.

Search Strategies

We conducted searches of the MEDLINE (Ovid SP), EMBASE (OvidSP), (CENTRAL), Science Citation Index and Google Scholar databases from 1946 to March 2017 to identify studies of relevance to this review. The search strategy included a combination of text words and Medical Subject Headings (MeSH) terms relating to the use of fat grafting and PRP for treating wounds. No language or publication restrictions were applied. A sample search strategy for MEDLINE (OvidSP) is shown and similar strategy was adapted for other databases.

1. ([fat graft] OR [fat transfer] OR [adipose graft] OR [adipose stem cell] OR [adipose derived stem cell] OR [adipose tissue transplantation]) AND [wound healing] AND ([platelet-rich-plasma] OR [PRP])

Inclusion criteria

All animal and human studies evaluating combination fat grafting and PRP for wound healing were included.

Exclusion criteria

The exclusion criteria were: case reports or case series of fewer than three patients; studies describing only the harvest technique without treatment outcome; studies evaluating the cellular or molecular outcomes of fat and PRP without assessing wound healing.

Outcome measures

The primary outcome measures were intended to be the efficacy of EG for wound healing measured by the proportion of wounds healed and the mean wound healing time (time for complete re-epithelialisation). However, given the small number of studies no specific outcome measures were analysed and the findings of each paper were discussed descriptively.

Study selection

The articles' titles and abstracts were scanned for potential eligibility by two authors (AK and MP), using the predetermined selection criteria, after excluding duplicate records. Full-text review was undertaken for studies that met the inclusion criteria. Abstracts and conference proceeding without full text were not included because of the difficulty in evaluating incomplete information. Ongoing trials without complete data were not included. A formal risk of bias assessment was not performed as the included studies were mostly small case series.

Results

Literature search results

We found 571 articles in the MEDLINE, EMBASE and CENTRAL database search. References from these searches were combined and after removing the duplicates, 380 articles were available for title and abstract reviewing. Of these, 363 articles did not meet the inclusion criteria and were excluded. Following full text review of the remaining 17 articles, 14 articles were excluded as the inclusion criteria was not met. A total of three articles (one randomised controlled trial, two case series) were included and data extracted from these formed the basis of this systematic review (41-43). A comprehensive study attrition flow diagram is provided in **Figure 1**. Cross-checking of the reference list revealed that no article was missed by the initial search. Details of the included studies are summarised in Table 1.

Wound healing outcomes

In the three studies, a total of 69 wounds were treated with a combination of autologous fat and platelet rich plasma in 64 patients. The average wound size was 36.35cm^2 (only reported in two studies) and the mean age of the patients was 66 years. The number of wounds that achieved complete wound healing was reported in both studies. The total number of wounds achieving full healing was 46 and the proportion of wounds achieving complete healing was 67%. One study (Cervelli et al 2010) reported average time to healing as 7.5 weeks (42). The same authors reported 100% of patients showed wound healing improvements from ‘mild to moderate’ which is reported as dermic and epidermic regeneration although exact wound size parameters are not reported. One study (Cervelli et al 2009) also reported mean time for complete healing as 7.5 weeks, although this was only in the 13 patients who underwent a single treatment (41). The same authors reported that in patients who underwent a second PRP and fat treatment their time to complete healing was a further 5 weeks but the time from first treatment was not recorded so average time to complete healing could not be ascertained. No study reported the rate of partial wound healing or the rate of treatment failure (no change in the size of wound).

The combination of fat grafting and PRP were used to treat a wide variety of wound aetiologies although these were only reported in two studies: ‘vascular’ wounds (n=27), post traumatic wound (n=13) and diabetic ulcers (n=11). All wounds treated in the studies were chronic. There was no subgroup analysis in either group regarding efficacy of the treatment for specific wound aetiologies. Only one study (Cervelli et al 2010) reported post-operative complication rates with two cases of wound infection documented. None of the included articles measured the health related quality of life or patient satisfaction of the treatments. The cost-effectiveness of the treatment was also not reported in any study.

Study Characteristics and Methodology

One study (43) was a poorly reported randomised controlled trial with two arms: control group (n=31 wounds) who received standard dressings care and experiment group (n=21 wounds) who received a combination of fat and PRP. Details of patient screening, the randomisation process and enrolment of patients were not included. PRP was obtained through peripheral venopuncture and centrifuging of whole blood. Fat was harvested through a standard Coleman technique (10). The PRP was combined with fat in a 1:1 ratio and injected into wound edges and base. No rationale for volume of fat injected and size of the wound was provided. 5ml of activated PRP gel was applied onto the wound. It is reported that patients were followed up weekly for wound management (including further debridement and dressing) but the duration of weekly followup is not stated and details of postoperative wound care are not reported. Wound pictures were taken at 1,3,6,12 and 18 months after treatment and the end point of the study for complete healing was 18 months. Patients who underwent fat+PRP treatment had significantly better wound healing (in relation to average size of the wound) compared to the control group, although average time to healing was not measured.

One study (42) was a case series of 30 patients with 30 wounds who were treated with PRP and fat grafting plus a hyaluronic acid medicated biologic dressing. The methodology clearly states the

inclusion and exclusion criteria and the pre-operative assessment and wound care protocol. PRP was obtained through peripheral venopuncture and centrifuge of whole blood. Fat was harvested using a standard Coleman technique and then mixed with PRP in a 1:1 ratio. The volume of fat/PRP mix infiltrated in relation to the wound size was not reported. Wounds were dressed with a 3-dimensional polymerised hyaluronic acid medicated biologic dressing. The rationale, as stated by the authors, for using this dressing was that hyaluronic acid has a synergistic effect with the PRP and allows for better recovery and availability of growth factors although evidence provided to support this is limited. Wounds were followed up weekly until healing was achieved. At week 2 dressings were removed and another application of hyaluronic acid was applied and a further application was done at week 3 if required, however the rationale for further applications was not reported. Complete wound healing was observed in 57% of cases with mean time to healing reported as 7.5 weeks. Wound biopsies were also taken intraoperatively, at one, two and three weeks and one month post treatment. Immunohistochemical analysis of the biopsies taken intraoperatively and at two weeks showed an increase in cell proliferation indexes for wound repair however quantitative data is not provided.

One study (41) was a case series of 30 patients with 30 wounds. Eighteen of these patients were treated with a combination of fat and PRP, 2 patients were treated with PRP alone and a control group of 10 patients were treated with hyaluronic acid and collagen dressings only. The methodology is unstructured and does not provide clear rationale for evaluating and comparing these different treatments. Inclusion and exclusion criteria of the patients was not reported. Although demographic details of the overall study population were reported, details (including age, gender, wound size, wound duration, aetiology) of the PRP+fat subgroup were not specifically reported. PRP was also obtained through peripheral blood collection and centrifuging in a similar fashion to the other studies. Fat was also harvested through a standard Coleman technique. PRP was combined with fat in variable ratios with no clear rationale. Rationale with regards to volume of fat/PRP grafted into each wound in relation to size was not reported. Wounds were ‘dressed’ with PRP gel. Postoperative followup was at 2 and 5 weeks and then 3,6, and 12 months and then

annually. Details of postoperative wound care were not reported. Thirteen patients underwent a single treatment and five patients underwent a second treatment of PRP and fat. A total of 14 patients achieved complete re-epithelialisation (77.8%).

Discussion

The aim of this systematic review was to evaluate the efficacy of combination fat and platelet rich plasma for wound healing. We found three articles, one of which was a poorly reported randomised controlled trial and two small case series. Therefore the current evidence of the efficacy of this treatment is extremely limited.

We found that complete healing was achieved in 67% of cases, and although mean time to healing was not accurately reported in any study in those undergoing a single treatment this was reported as 7.5 weeks. This outcome is comparable with the healing rate of 73% in split skin grafts (44) and 71.5% in epidermal grafts (45). There were no reported significant complications or donor site morbidity with only two reported cases of simple wound infection. Although all wounds treated were chronic there was a lack of complete reporting on the exact aetiology of the wounds treated with no subgroup analysis and therefore it is impossible to suggest which wounds the treatment would be most appropriate for.

The lack of evidence for this treatment illustrates the fact that it is extremely new with very few studies evaluating the efficacy in wound healing. There are several studies which have evaluated the regenerative potential of fat grafting (46-48). Adipocyte-derived stem cells found within fat grafts are able to differentiate into various cell lineages (49) as well as secreting soluble mediators with angiogenic, immunosuppressive and anti-inflammatory properties (50). Several preliminary studies have demonstrated that autologous free fat transfer may significantly enhance healing of pressure sores (18,51), critical limb ischaemia (52) and post-radiation therapy scars (14). Platelet rich plasma in isolation has also been shown to have significant regenerative properties (53-58).

These properties are likely to be due to the release of platelet derived mediators such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor β (TGF- β) and insulin-like growth factor (IGF) (59,60) which promote the recruitment and activation of cells responsible for tissue repair, and they encourage new blood vessel formation. The addition of PRP to fat grafting has been shown to enhance graft survival through several mechanisms. Firstly, the secretion of pro-angiogenic factors by PRP may improve early graft vascularisation and minimise ischaemic injury (61,62); secondly, the release of anti-inflammatory cytokines is thought to have a role in preventing graft degeneration (63,64); and thirdly, PRP-secreted factors have been shown to enhance the differentiation of preadipocytes into their mature form (65-67). The majority of human (38,68-74) and animal (62-64,75,76) studies suggest that PRP and fat co-transplantation appears to increase graft survival rates.

However the benefit with regards to wound healing when PRP and fat are co-grafted is unproven and this study has not been able to illustrate a clear benefit over traditional methods. Furthermore, a small but well reported case series evaluating the efficacy of fat grafting alone in chronic wound healing (19) found a 88% complete wound healing rate which is significantly better than the pooled rate in this review.

The methodology of grafting in both papers was heterogeneous and undertaken without any clear rationale for key decisions e.g. ratio of fat to PRP, volume of graft in relation to wound size, postoperative wound care. A lack of standardised procedure protocol (77-79) also limits the usefulness of the evidence presented. However, in the literature there is no standardised protocol for either PRP (57) or fat grafting in isolation (80) and there is no evidence to suggest specific technical factors have a clear outcome of success of the treatment.

The evidence in this study is limited by the lack of high-quality level 1 evidence. The existing studies were small case series or poorly reported trials that are often at a risk of bias. There were no comparative data to evaluate the healing outcomes of PRP and fat against the current standard of care, such as advanced dressings or SSG. Formal bias assessment was not performed because of the study design of the included studies. In terms of the search strategy, as there is no MeSH term available for fat grafting or platelet rich plasma, potentially valuable and informative studies published with other keywords may therefore been missed.

In conclusion, combination PRP and fat grafting has the potential to be a simple and effective wound treatment option with no significant donor site or graft morbidity. However our conclusions are greatly limited by the lack of good quality evidence. A randomised controlled trial to compare combination PRP and fat grafting against standard of care is necessary to fully evaluate the efficacy of this treatment.

Financial Support

None

Conflict of interest

None

Acknowledgements

None

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Tables

Citation	**Cervelli et al 2009 (41)**	**Cervelli et al 2010 (42)**	**Raposio et al 2016 (42)**
Year	2009	2010	2016
Country	Italy	Italy	Italy
Study type	Case series	Case Series	Randomised trial
Number of patients	18	30	16
Male	Not reported	18	11
Female	Not reported	12	5
Mean age (years)	Not reported	61	71
Number of wounds	18	30	21

Wound aetiology			
Vascular	Not reported	9	18
Diabetic	Not reported	8	3
Post traumatic	Not reported	13	0
Mean wound duration (months)	Not reported	Not reported	26.6
Average wound size (cm^2)	Not reported	47.5	25.2
Fat graft harvest technique	Coleman technique	Coleman technique	Coleman technique
Volume harvested per patient	Not reported	Not reported	80ml
PRP:fat ratio	Variable	1:1	1:1
Anaesthesia	General	General	General
Wound dressing	PRP gel dressing	Hyaluronic acid medicated dressing	PRP gel dressing
Wounds with complete healing	14 (77.8%)	17 (56.6%)	15 (71.4)
Mean duration for complete healing	Not reported	Not reported	Not reported

Table 1: Overview of the included studies

Figure Legends

Figure 1: Flow diagram of the literature search