Allogeneic platelet gel therapy for refractory abdominal wound healing: A preliminary study

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Abstract

Background. Refractory abdominal wounds are commonly complicated by surgical site infections, which prolong hospital stays and increase medical costs. There is little clinical data on the use of allogeneic platelet gel (PG) therapy for refractory infected wounds.

Objectives. This study aimed to evaluate the efficacy and safety of allogeneic PGs in the treatment of refractory abdominal wounds.

Materials and methods. A prospective single-center study was performed in a national abdominal trauma referral center between June 2019 and June 2021. A total of 11 patients with refractory abdominal wounds were treated with allogeneic PGs after the failure of standard medical treatments. The PGs were derived from platelets collected from healthy donors using apheresis, and each PG was tested for platelet count, transfusion-related diseases, aerobic and anaerobic bacteria, and growth factor concentration. Clinical efficacy was evaluated by assessing the wound surface and observing the condition of the wound, including wound area and percentage of granulation.

Results. The median age of the patients was 37 years (1st quartile, 3rd quartile (Q1, Q3): 31–55 years), median (Q1, Q3) hemoglobin level was 95 g/L (78–120 g/L) and median (Q1, Q3) serum albumin level was 39.9 g/L (34.9–42.7 g/L). The PG platelet count was 976.5 ±174.9×10^9/L. Results of transfusion-associated contagion tests for aerobic and anaerobic bacteria were negative. Growth factor contents (pg/mL) were: for transforming growth factor beta 1 (TGF-β1); 2542.39 ±430.60, for platelet-derived growth factor BB (PDGF-BB); 23230.03 ±4236.14 and FOR vascular endothelial growth factor (VEGF); 91.41 ±23.31. The rate of wound healing was 100%, and the median (Q1, Q3) healing time was 30 days (18–40 days). The follow-up period was 5–27 months, during which no recurrence of the wounds was found.

Conclusions. The present study demonstrated that allogeneic PGs are a safe and effective treatment for refractory abdominal wounds.

Key words: wound healing, growth factor, surgical site infection, allogeneic platelet gel, refractory abdominal wound

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Background

Surgical site infection (SSI) is a wound infection that occurs within 30 days of an operative procedure, or within 1 year if an implant is left in place and the infection is thought to be related to the operative procedure.[1] Surgical site infections increase the burden on the healthcare system and prolong the hospital stay by 7–10 days.[2] The SSIs occur after 1–3% of all surgical procedures[3] and are categorized as superficial, deep or organ/space, based on the depth of infection involvement.[4] Abdominal surgeries are related to a high incidence of SSIs and are an independent risk factor for SSIs.[5] Indeed, the incidence of organ/intra-abdominal SSIs ranges from 2.9% to 22.1%,[5–9] which is much higher than for other types of surgery. Furthermore, data indicate that 77% of deaths in patients with an SSI are directly related to the SSI.[10] Currently, the management strategies for refractory wounds include the treatment of primary disease, wound treatment, negative-pressure wound therapy, and wound dressing.[11,12] However, such therapies usually take a long time and the effects seem to be unsatisfactory, with many patients still suffering from wounds after SSI therapy. Thus, there is a growing need to develop new therapeutic options that can achieve better clinical outcomes.

Platelet-rich plasma (PRP) is a platelet derivative that contains a higher concentration of platelets than baseline and is capable of promoting wound healing.[13] A platelet gel (PG) takes on a colloidal shape and is produced after PRP is activated by adding bovine thrombin or calcium.[14,15] The PG contents are released from α-granules[16] and other granules, and they include various classes of bioactive mediators such as growth and clotting factors, chemokines, adhesion molecules, and integral membrane proteins, as well as immune mediators that are primed to respond to tissue injury.[17] Once tissue injury occurs, all of the above contents are ready to respond. At present, PGs have been used in a variety of clinical conditions including dental applications,[18] sports injuries[19] and wound healing.[15]

Platelet-rich plasma is either autologous or allogeneic, the former of which makes up the majority. However, autologous PRP use may be limited for some patients (e.g., patients in this study), for whom harvesting or administering derivatives is difficult or even dangerous. This includes patients from whom large quantities of platelets cannot be collected (such as those with thrombocytopenia, severe anemia or hypoproteinemia), the elderly, neonates, and severe trauma patients. Fortunately, PRP from allogeneic sources may help overcome the above problems.

Objectives

There is currently little experience with PG therapy for refractory abdominal wounds in SSI. Also, the patient's condition often does not meet the requirements for extracting autologous PG of sufficient quality and quantity. Therefore, this study aimed to investigate the efficacy and safety of allogeneic PGs in the treatment of refractory abdominal wounds.

Materials and methods

Study design and setting

A single-arm pilot study was performed on patients with refractory abdominal wounds from June 2019 to June 2021 at Jinling Hospital, a national abdominal trauma referral center in Nanjing, China. This study was approved by the local Institutional Review Board (Ethics Committee of Jinling Hospital, approval No. 2019(KY)-008). The study adhered to the Declaration of Helsinki.

Participants

Patient inclusion,[20,21] exclusion and withdrawal criteria are reported in Table 1. After obtaining written informed consent, 11 patients were included. The number of participants included reflected the preliminary nature of the study.

Table 1. Inclusion, exclusion and withdrawal criteria

Criteria	Details
Inclusion criteria	refractory infectious wounds caused by SSIS, resistant to traditional treatment
	duration > 6weeks
	reached 1 or more of the following: spontaneous wound dehiscence necrotizing fasciitis necrotic tissue with/without formation of purulent secretion
Exclusion criteria	patient's age <18 years
	cachectic or terminal patient
	metastatic tumor, lesions with evidence or high risk of neoplastic degeneration
	pregnant patient
	patient with mental illness and unable to cooperate with treatment
Withdrawal criteria	patient's condition turning for the worse
	serious treatment-related adverse events

SSIS – surgical site infections.

Data sources and measurement

Preparation of allogeneic platelet-rich plasma

To prepare allogeneic PRP, platelets were obtained from healthy donors using apheresis (Jiangsu Province Blood Center, Nanjing, China). Each 250–300 mL donor unit had at least 2.5×10^{11} platelets suspended in donor plasma

containing approx. 30 mL of anticoagulant citrate dextrose solution (formula A (ACD-A)) and was qualified by testing for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), human immunodeficiency virus (HIV), treponema pallidum (TP), and alanine transaminase (ALT). Each unit was subdivided into 10–20-milliliter portions using a 4-bag system (Fresenius Kabi, Guangzhou, China). Next, all aliquots of PRP were frozen at –80°C[22,23] until further use.

Platelet-rich plasma characterization

After PRP preparation, 0.5 mL of them was collected within 30 min and a platelet count was taken for each unit of PRP before cryopreservation, using the XE2100™ automatic hematology analyzer (Sysmex Corporation, Hyogo, Japan). Each unit of PRP was tested for the presence of aerobic and anaerobic bacteria using Plus Aerobic/F and Lytic/10 Anaerobic/F (9184994 and 0301023; BD Biosciences, Franklin Lakes, USA), respectively. Calcium gluconate (10%) was added to each PRP sample at a ratio of 1:4 in a 37°C water bath. The PG formed within a few minutes. To isolate platelet growth factors (GFs), PG was ultracentrifuged at 10,000 × g for 15 min to eliminate fibrous protein and platelet debris,[24] and the GF concentration in the supernatant was measured. The following 3 GFs were evaluated: transforming growth factor beta 1 (TGF-β1), platelet-derived growth factor BB (PDGF-BB) and vascular endothelial growth factor (VEGF).[15] To change the latent form into an immune-reactive form, the content of TGF-β1 was tested after acidic activation and neutralization of the sample. The GF concentrations were measured using Human VEGF enzyme-linked immunosorbent assay (ELISA) Kit (A18310135; Multi Sciences, Hangzhou, China), Human/Mouse/Rat TGF-β1 ELISA Kit (A98110121; Multi Sciences), and Human/Rat PDGF-BB ELISA Kit (A913700823; Multi Sciences), and were tested using Hamilton Microlab FAME (M8; Hamilton Corporation, Bonaduz, Switzerland). All of the above tests were performed before PG treatment.

Treatment procedure

To minimize the residual infection risk, a single unit of platelets was used to treat just 1 patient. A frozen PRP aliquot was thawed at 37°C for 15 min before use. The refractory wounds were first debrided to remove the necrotic and infected tissues. Then, the wound area was thoroughly cleaned with iodine solution and 3% perhydrol liquid. After that, the wound was rewashed with normal saline and dried with sterile gauze. Wound volume was calculated as lesion area × depth. Based on the wound size, the appropriate volume of PRP was added to 10% calcium gluconate (PRP:calcium gluconate ratio of 4:1) with sufficient mixing, and the mixture was sprayed onto the wound. A PG was formed on the wound within 1–3 min, exploiting the contact with body heat,[25] and a vaseline gauze was used to cover the wound followed by a dry sterile gauze. The dressing was changed every day and wound healing was observed.

During the PRP therapy, the patient's wounds were not treated with therapeutic agents containing basic fibroblast GFs or with negative pressure wound therapy.

At least 3 months after the last treatment, patient blood samples were tested for transfusion-related diseases. In addition, wounds were photographed before each treatment and during the follow-up visit using a digital camera, and examined for abnormalities such as bleeding, exudation, infection, and poor wound healing. These observational indexes were used to evaluate the safety of allogeneic PG therapy.

Several parameters were selected to evaluate the efficacy of PG therapy, including the presence of infection, granulation growth in wounds, wound healing rate, and healing time. If the patient had a skin graft after PRP therapy, graft survival and graft edema were assessed after the transplantation. The following formula was used to calculate the wound healing rate:

$$\text{wound healing rate (\%)} = ((\text{the original wound size} - \text{wound size})/(\text{the original wound size})) \times 100.$$

Statistical analyses

The IBM SPSS v. 25.0 software (IBM Corp., Armonk, USA) was used for statistical analysis. Data of patients are expressed as median (Q1–Q3), and PRP data ($p > 0.09$ in the Kolmogorov–Smirnov normality test of the variables) are expressed as mean ± standard deviation (M ±SD). The statistical analysis of differences was not conducted because of the small number of patients enrolled.

Results

Patients

Eleven patients, having 1 or more wounds caused by SSI that had not healed after extensive conventional wound management, were included and treated with topical administration of an allogeneic PG. Their mean age was 37 years (range: 31–55 years), with mean hemoglobin of 95 g/L (78–120 g/L) and serum albumin of 39.9 g/L (34.9–42.7 g/L). The characteristics of patients are presented in Table 2.

Platelet-rich plasma characterization

The M ±SD platelet count of the PRP was 976.5 ±174.9×10^9/L, and M ±SD ALT was 19.00 ±5.60 U, while the results of aerobic and anaerobic bacteria tests were negative. At the same time, testing for HBsAg, HCV, HIV, and TP also yielded negative results. The GF concentrations of PRP samples are shown in Table 3.

Table 2. Characteristics of the study population (n = 11)

Parameter	Number of patients (n)	Percentage
Age [years]		
18–30	2	18.18
31–40	4	36.36
41–50	2	18.18
51–60	2	18.18
61–70	1	9.09
Gender		
Male	8	72.73
Female	3	27.27
Nutritional condition		
Serum albumin >30 g/L	9	81.82
Serum albumin ≤30 g/L	2	18.18
Anemia		
No	3	27.27
Yes	8	72.73
Wound infection		
No	4	36.36
Yes	7	63.64

Clinical efficacy and healing rate analysis

During the study period, no patients were found to have treatment-related adverse reactions or immune responses. Before the first treatment and after the last (the exact time was 4 (3–8) months after the last treatment), patients' blood samples tested negative for HBsAg, HCV, HIV, and TP. Each patient's data and wound characteristics are reported in Table 4. The mean number of PG treatments was 8 (5–11), and the mean healing time was 30 (18–40) days (Fig. 1); the healing was observed as early as 10 days after PG application. One week after the PG treatment, small islands of granulation tissue appeared over the wound, and tissue granulation increased from 90% (33.84–95.00%) to 100% (98–100%). At the same time, the wound size was reduced by 67.82% (54.20–74.51%). Only 1 patient (patient number 2) underwent skin grafting after the last PG treatment. The follow-up period was 5–27 months, during which no recurrence of the wound was found.

Overall, the wound size was reduced and the wound healing rate was 100% in all of the treated patients. To depict the reduction in wound size with time after PG administration, Fig. 2–4 show pre-treatment and follow-up pictures of 3 patients (patients 1, 2 and 8).

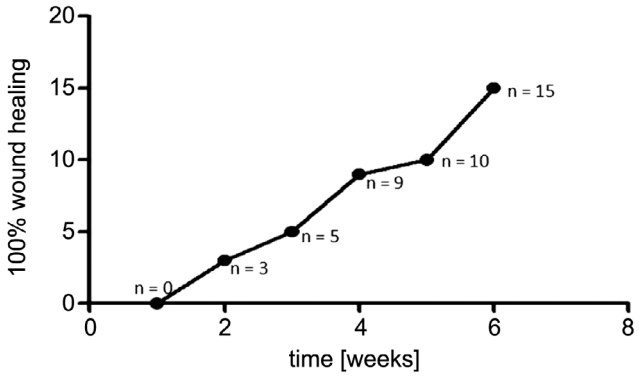

Fig. 1. Distribution of cumulative wound healing following platelet gel treatment

Discussion

The current study is the first to characterize the safety and efficacy of allogeneic PGs in the treatment of refractory abdominal wounds after SSI. All patients achieved a 100% healing rate in a short time, and no treatment-related adverse reactions or immune responses occurred during the treatment. This indicates that allogeneic PRP has low immunogenicity.

Refractory wounds are one of the outcomes of SSIs and are challenging to treat. Conventional treatment for refractory wounds includes control of infection, adequate debridement, avoidance of excessive pressure, revascularization of ischemic tissue, changing the wound environment, and medical management of comorbidities.[26,27] However, these treatments are ineffective. Wound healing involves the phasic production of GFs and cytokines to progress the wound to a scar.[27] In vitro and in vivo studies analyzing refractory wounds have demonstrated the deregulation of several GFs and indicated them as potential targets for therapy.[28] Exogenous GFs and cytokines are used in a clinical setting to promote refractory wound healing. They have become a promising approach for the treatment of intractable wounds.

Platelet gels are colloidal in shape, and form after PRP is activated by calcium. This delays the loss of platelets and makes platelets secret GFs on the wound surface over a long period at a high concentration. With the deepening of PG research, PGs have been used as a new application to promote favorable wound healing.

The benefit of allogeneic PRP is that it can be collected from voluntary blood donors, and be ready to use at any time without having to collect any samples from the patient.[17,29] Moreover, it has been demonstrated that the potential

Table 3. Platelet growth factor concentrations of PRP samples (M ±SD; n = 11)

Measure unit	TGF-β1	VEGF	PDGF-BB
pg/mL	2452.39 ±430.60	91.41 ±23.31	23230.03 ±4236.14
pg/10^9 platelets	2537.58 ±393.26	94.87 ±22.97	24495.91 ±6186.57

PRP – platelet-rich plasma; M ±SD – mean ± standard deviation; TGF-β1 – transforming growth factor-β1; VEGF – vascular endothelial growth factor; PDGF-BB – platelet-derived growth factor BB.

Table 4. Individual patient data, number of PG treatments, follow-up time, and wound conditions at enrollment and after 1 week of treatment

Patient (wound) No.	Age, gender	Number of PG treatments	Timepoint	Wound size [cm]	Tissue type	Percentage of granulation (%)	Healing rate (%)	Healing time [days]	Follow-up time [months]
1 (1)	47, M	6	before treatment	8.1×6.1×0.2	granulation + slough + necrotic tissue	33.84	–	30	27
			after 1 week of treatment	5.7×2.7	granulation tissue	90.65	72.13		
1 (2)		5	before treatment	3.8×3.7	granulation + necrotic tissue	16	–	21	27
			after 1 week of treatment	2.8×2.3	granulation tissue	100	54.20		
1 (3)		5	before treatment	4.7×3.6	granulation + necrotic tissue	20	–	18	27
			after 1 week of treatment	2.8×2	granulation tissue	100	66.90		
2	31, M	18	before treatment	18×8×1.8	granulation + slough + necrotic tissue	17.25	–	42	26
			after 1 week of treatment	11.7×5.6×1.27	granulation + slough + necrotic tissue	68.26	67.82		
			after 4 weeks of treatment	skin grafting	granulation tissue + skin graft	–	–		
3	56, M	4	before treatment	6×7×0.4	granulation + necrotic tissue	45	–	28	24
			after 1 week of treatment	3.6×3×0.2	granulation tissue	100	87.14		
4	37, M	10	before treatment	5.5×5	granulation + necrotic tissue	95	–	42	23
			after 1 week of treatment	5.5×3	granulation tissue	98	40		
5	43, M	8	before treatment	8.8×3.2×3.3	granulation + necrotic tissue	90	–	40	15
			after 1 week of treatment	5.9×2.4×2.4	granulation + necrotic tissue	98	63.43		
6 (1)	32, F	10	before treatment	2×1×0.3	granulation + necrotic tissue	75	–	10	13
			after 1 week of treatment	1.4×0.4×0.2	granulation tissue	100	81.33		
6 (2)		11	before treatment	1.8×0.5×0.3	granulation + necrotic tissue	90	–	14	13
			after 1 week of treatment	1.5×0.5×0.2	granulation tissue	100	44.44		
6 (3)		16	before treatment	1.7×0.8×0.3	granulation + necrotic tissue	90	–	28	13
			after 1 week of treatment	1.3×0.4×0.2	granulation tissue	100	74.51		
7	67, M	15	before treatment	4.5×2×1.4	granulation tissue + slough	95	–	40	11
			after 1 week of treatment	6.5×2×0.8	granulation tissue	100	17.46		
8	27, M	10	before treatment	10×7×4.6	granulation + necrotic tissue	78.26	–	30	10
			after 1 week of treatment	7×5×2.6	granulation + necrotic tissue	87	71.74		
9	19, F	7	before treatment	3×1.5×1.2	granulation + necrotic tissue	90	–	38	9
			after 1 week of treatment	2.3×1×0.8	granulation tissue	100	65.93		
10	55, F	5	before treatment	1.7×0.5×1.3	granulation tissue	100	–	35	8
			after 1 week of treatment	0.8×0.5×0.8	granulation tissue	100	71.45		
11	33, M	6	before treatment	13.5×1.8×1.2	granulation tissue	100	–	14	5
			after 1 week of treatment	10×1.3×0.3	granulation tissue	100	86.63		

PG – platelet gel.

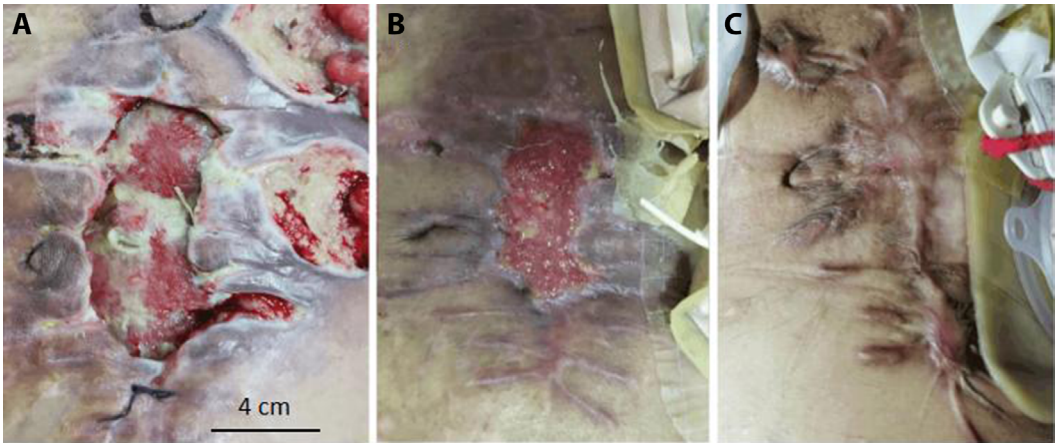

Fig. 2. Wound of patient No. 1. A. The wound size before treatment was 8.1×6.1×0.2 cm; B. After 1 week of treatment with platelet gel (PG), and also after the last treatment, the wound size was 5.7×2.7 cm; C. After 53 weeks of PG treatment, the wound exhibited no ulceration or exudation

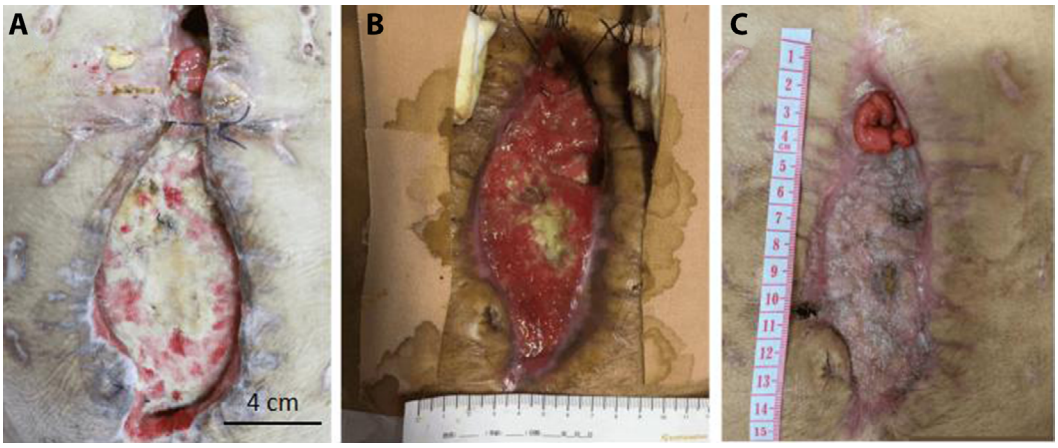

Fig. 3. Wound of patient No. 2. A. The wound size before treatment was 18×8×1.8 cm; B. After 4 weeks of treatment with platelet gel (PG), and also after the last treatment, the wound size was 10.5×4.3×0.5 cm, after which the patient underwent skin grafting; C. After 7 weeks of PG treatment, the wound exhibited no ulceration or exudation

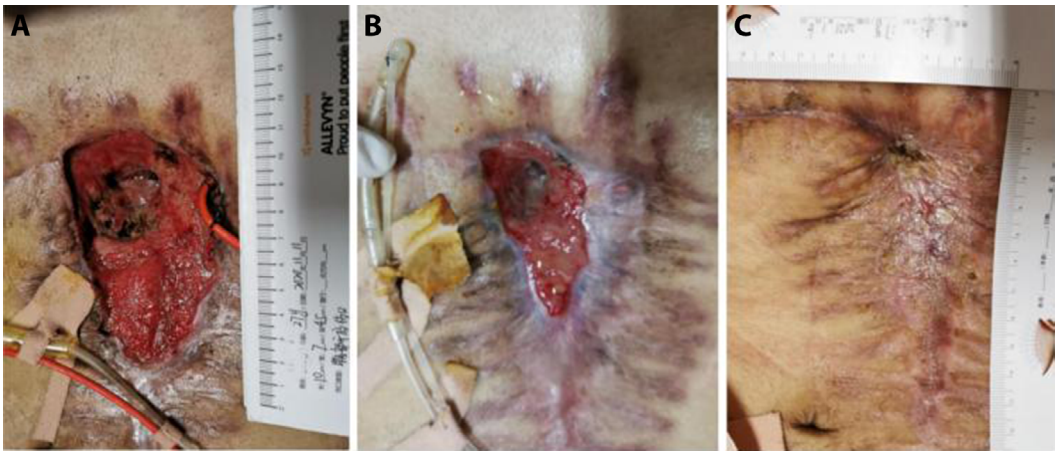

Fig. 4. Wound of patient No. 8. A. The wound size before treatment was 10×7×4.6 cm. B. After 2 weeks of platelet gel (PG) treatment, and also after the last treatment, the wound size was 7.0×3.5×2.2 cm. C. After 8 weeks of treatment with PG, the wound exhibited no ulceration or exudation

immunogenicity of allogeneic PRP is not a significant risk.[30] There is a non-systematic review that discusses allogeneic PRP for wound treatment,[17] including 3 case series and 5 randomized controlled trials. The refractory wound types included pressure sores,[31] venous ulcers,[32] diabetic lower limb ulcers,[33,34] lower extremity ulcers,[35] and ulcers of various etiologies.[36–38] All of these studies, with or without a control group, showed improvement in hard-to-heal wounds when treated with allogeneic PRP. There is scant literature on PRP as a treatment for refractory abdominal wounds after SSI, although in 1 case report, cord blood PG (CBPG) was used to enhance the healing of deep surgical site dehiscence.[39] The CBPG was applied twice a week for 4 weeks and then once a week for 4 weeks, which resulted in the cavities being completely filled.

In this study, 8 out the of 11 patients were anemic, 2 had hypoproteinemia, 7 had a wound infection, and 5 had suffered from surgical wound dehiscence resulting from wound infection. Repeated blood sampling (approx. 50 mL of whole blood is required for each 5 mL of PRP preparation) may have caused harm to these patients. The primary goal of any treatment is to achieve wound

closure expeditiously. Herein, blood bank platelet concentrate was used as a source of allogeneic PRP. The advantages are as follows: 1) the characteristics of platelet concentrates from the blood bank are well specified, and residual white and red blood cell content is highly standardized[38]; 2) the entire process of platelet collection is performed using a closed system and aseptic; 3) they are obtained without the need for a platelet separation system, and the concentrations of GFs are within the range of clinical efficacy[40]; and 4) they are suitable for the repeated treatment of large-sized wounds.

To avoid blood-borne diseases and after tests for transfusion-related diseases, the platelet concentrate from 1 donor was divided into several portions and used for 1 patient. Tests for transfusion-related diseases showed negative results for all patients after the last treatment of PRP.

To explore the mechanisms of wound healing promoted by PGs, 3 representative GFs were selected for detection, and the results were comparable to those reported in the literature.[41–45] However, the contents of GFs differed between various voluntary blood donors and blood biomaterials. As such, the relative amount of each factor may vary depending on donor characteristics, platelet count enrichment, production methods, and thrombin preparation.[46]

In recent years, PRP has emerged as a potential option for the prevention and treatment of acute and chronic postoperative wound infections.[47] In 7 patients with local infection, the results of bacterial culture were *Staphylococcus epidermidis* and/or *Staphylococcus aureus*. In the patients for whom conventional treatment was ineffective, necrotizing fasciitis may have been aggravated by the nonhealing wound. Therefore, to enhance wound healing, PG therapy was offered and the frequency varied from twice a week[39] to once a day. This provided adequate PRP and allowed for wounds to be cleaned every day, as well as gave the opportunity for the close inspection of the wounds.

Although our results showed that allogeneic PG exhibited positive effects in refractory abdominal wounds, the following aspects of this product still need to be considered: 1) to avoid the spread of blood-borne diseases, the allogeneic PGs from donor blood must undergo the same tests as platelets used for intravenous infusion; 2) the process of PG extraction must follow the standard operating procedures of the institution; 3) the PG process must adhere to the principles of sterility; 4) if the wound is accompanied by a suppurative infection, anti-infection therapy should be applied initially; and 5) PGs may be combined with vacuum suction and wound skin grafting.

Limitations

In this study, it was difficult to recruit a large enough number of patients with comparable lesions that would have allowed for a classic case-control study. Therefore, this single-arm study was designed.

Conclusions

In this study, the treatment of refractory abdominal wounds with allogeneic PGs achieved significant results in a short time. Allogeneic PGs are a feasible, effective and safe therapy for refractory abdominal wounds. More randomized controlled clinical trials should be conducted to bring more evidence of the value of allogeneic PGs in treating refractory abdominal wounds.

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