

Utility of RECELL® for Traumatic Skin Defects: A Study Protocol

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Submitted to: JMIR Research Protocols
on: April 09, 2025

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Table of Contents

Original Manuscript..... 4

Supplementary Files..... 18

 Figures 19

 Figure 1..... 20

CONSORT (or other) checklists..... 21

 CONSORT (or other) checklist 0..... 22

Utility of RECELL® for Traumatic Skin Defects: A Study Protocol

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Abstract

Background

RECELL® (Avita Medical, Cambridge, UK), a non-cultured skin cell suspension technique, provides results comparable with skin grafting in terms of duration and healing quality. However, in Japan, the clinical use of RECELL® for burn trauma has become possible but not for skin defects associated with trauma. Reports using RECELL® with split-thickness skin grafting for burn trauma showed good results. The purpose of this study is to evaluate the utility of the RECELL® skin reconstruction technique in trauma cases with significant skin defects.

Methods

This is a single-center, open-label, uncontrolled, single-arm comparative prospective study. The inclusion criteria are age ≥ 16 years with skin defects ≥ 160 cm² due to trauma (excluding the hands and face and burn trauma) or skin defects due to skin flaps. The test site should exhibit sufficient dermal-like tissue formation. Under general anesthesia, skin grafts will be harvested from healthy skin donor sites (groin, thigh, or scalp). In addition to RECELL® skin grafts, the necessary amount of mesh skin grafts will be collected. A mesh graft will be applied to the defect where the graft is to be placed, and the non-cultured cell suspension previously prepared using the RECELL® technique will be sprayed onto the mesh grafted area. A non-adherent gauze will be applied to the skin graft, and the gauze will be placed over the gauze for bandage fixation. The primary endpoints are healing of the recipient and donor sites. The secondary endpoints are scar assessment using the Vancouver Scar Scale, pigmentation, vascularity, pliability, and contracture. The observation period will be 24 weeks after surgery.

Discussion

We intend to validate the utility of RECELL® for skin defects due to trauma by observing wound closure, scar formation including its adverse events, delayed healing, infection, and its durability.

(JMIR Preprints 09/04/2025:74159)

DOI: <https://doi.org/10.2196/preprints.74159>

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Original Manuscript

Title: Utility of RECELL® for Traumatic Skin Defects: A Study Protocol

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Abstract

RECELL® (Avita Medical, Cambridge, UK), a non-cultured skin cell suspension technique,

provides results comparable with skin grafting in terms of duration and healing quality. However, in Japan, the clinical use of RECELL® for burn trauma has become possible but not for skin defects associated with trauma. Reports using RECELL® with split-thickness skin grafting for burn trauma showed good results. The purpose of this study is to evaluate the utility of the RECELL® skin reconstruction technique in trauma cases with significant skin defects.

This is a single-center, open-label, uncontrolled, single-arm comparative prospective study. The inclusion criteria are age ≥ 16 years with skin defects $\geq 160 \text{ cm}^2$ due to trauma (excluding the hands and face and burn trauma) or skin defects due to skin flaps. The test site should exhibit sufficient dermal-like tissue formation. Under general anesthesia, skin grafts will be harvested from healthy skin donor sites (groin, thigh, or scalp). In addition to RECELL® skin grafts, the necessary amount of mesh skin grafts will be collected. A mesh graft will be applied to the defect where the graft is to be placed, and the non-cultured cell suspension previously prepared using the RECELL® technique will be sprayed onto the mesh grafted area. A non-adherent gauze will be applied to the skin graft, and the gauze will be placed over the gauze for bandage fixation. The primary endpoints are healing of the recipient and donor sites. The secondary endpoints are scar assessment using the Vancouver Scar Scale, pigmentation, vascularity, pliability, and contracture. The observation period will be 24 weeks after surgery.

We intend to validate the utility of RECELL® for skin defects due to trauma by observing wound closure, scar formation including its adverse events, delayed healing, infection, and its durability.

Ethics

Nara Medical University Certified Review Board 89 (CRB5200002), and the study period is planned from April 1, 2024 to March 31, 2026.

The organization of the study is shown in jRCTs052230203.

Key words: skin grafting; autograft; wound healing; extremity trauma; non-cultured skin cell suspension technique

Introduction

Skin grafting is currently the gold standard method for managing skin defects. The most common technique in skin grafting is segmental skin grafting, which is problematic owing to the limited amount of skin harvested and the use of healthy skin as a donor, resulting in a new wound at the donor site. In cases of extensive skin defects due to trauma such as open fracture or degloving injuries, the amount of fractionated skin harvested is limited; thus, coverage is usually extended with mesh grafting. The mesh area epithelializes and forms the epidermis—this may require a long time to heal and may be less cosmetically pleasing. Free flap transfer is another technique frequently used for skin defects due to severe trauma, but this technique also results in skin defects at the donor site, thus requiring skin grafting.^[1]

RECELL® (Avita Medical, Cambridge, UK) is a regenerative technique that uses a patient's own skin cells to create a non-cultured skin cell suspension for wound healing. The suspension is sprayed on the wound, enabling wound closure without extensive skin grafting. The process is minimally invasive and can be performed at the point of care. In the context of skin reconstruction after burn trauma, RECELL® provides results comparable with skin grafting in terms of duration and healing quality.^[2] This technique also can minimize donor site skin defects. However, RECELL® has been widely used for skin defects due to burn trauma but not for severe trauma in Japan. To our knowledge, only a few small studies have investigated the use of RECELL® in trauma patients. In this study, we therefore aimed to evaluate the use of the RECELL® skin reconstruction technique in post-traumatic patients with significant skin defects.

METHODS

Design

This is a single-center, open-label, uncontrolled, single-arm comparative prospective study. We aim to investigate the practical feasibility of skin grafting with a non-cultured cell suspension for traumatic skin defects.

Ethics

This study will be conducted in compliance with the Declaration of Helsinki and Clinical Trial Act by the Ministry of Health, Labor, and Welfare in Japan. The study investigators will provide sufficient explanation of the study to each study subject and obtain written informed consent. This study protocol was approved by the Nara Medical University Certified Review Board (CRB5200002), and the study period is planned from April 1, 2024 to March 31, 2026. The organization of the study is shown in jRCTs052230203.

Inclusion and exclusion criteria

Inclusion criteria

- 1) Patients with skin defects due to trauma (excluding burns caused by flames, excessive heat, or skin exposure to steam or hot water) and skin defects due to skin flaps
- 2) Patients with skin defects $\geq 160 \text{ cm}^2$, excluding the hands and face
- 3) Patients with sufficient dermal-like tissue formation at the test site
- 4) Patients aged > 16 years on the date consent is obtained
- 5) Patients who have obtained or provided written consent. If the patient is aged < 18 years, written consent must also be obtained from a guardian.

Exclusion criteria

- 1) Patients aged < 16 years
- 2) Patients with hypersensitivity to sodium lactate (washing solution)
- 3) Patients hypersensitive to anesthetics, adrenaline, povidone–iodine, chlorhexidine
- 4) Patients with allergies to ingredients derived from pigs
- 5) Patients judged by the principal investigator (or sub-investigator) to be unsuitable as study subjects

Study protocol

The overview of the study protocol is shown in Table 1.

Surgical treatment protocol

Enrolled patients will undergo the study protocol surgery. Under general anesthesia, skin grafts will be harvested from healthy skin donor sites (groin, thigh, or scalp). In addition to RECELL® skin grafts, the necessary amount of mesh skin grafts will be collected. A mesh graft will be applied to the defect where the graft is to be placed, and the non-cultured cell suspension previously prepared using RECELL® will be sprayed onto the mesh grafted area. A non-adherent gauze will be applied to the skin graft, and the gauze will be placed over the gauze for bandage fixation.

Postsurgical treatment

The bandaged treatment site will be opened 6–8 days postoperatively. The wound will be examined until 24 weeks after the protocol surgery. Administration of antibiotics, anticoagulants, steroid ointment, and any type of dressing materials are acceptable. However, the following combined treatment is prohibited: full-layer skin graft, negative pressure wound closure therapy only for skin graft fixation, and cytotoxic drug use (e.g., sulfadiazine silver–containing preparations)

Treatment after completion of protocol treatment may include washing, ointment therapy, or negative

pressure closure therapy. Treatment will be at the discretion of the principal investigator and research associate.

Observation, examination, and treatment information

- 1) Study subject background information: age, sex, height, weight, blood pressure, pulse rate, body temperature, current and previous medical history, underlying medical conditions at study inclusion
- 2) Blood tests: white blood cell count, red blood cell count, hemoglobin level, hematocrit level, platelet count, prothrombin time–international normalized ratio, activated partial thromboplastin time, fibrinogen level, fibrin degradation product level, aspartate aminotransferase/alanine aminotransferase, lactate dehydrogenase, creatine phosphokinase, blood urea nitrogen/creatinine, c-reactive protein
- 3) Trauma data: cause and mechanism
- 4) Evaluation of recipient and donor sites at protocol surgery: measurements of the recipient site (long and short diameter, thickness, previous treatment to the test site, and excision method of the test site), magnification of the mesh skin graft, and area of the skin donor site (long and short diameter)

Photographic records of the recipient site right before and after the protocol surgery

- 5) Healing of the recipient site
- 6) Scar assessment using the Vancouver Scar Scale (VSS)^[3]
- 7) Subject satisfaction after treatment
- 8) Delayed healing of the recipient site
- 9) Infection of the recipient site
- 10) Scars requiring surgical interventions
- 11) Pain assessment at the recipient and donor sites using the visual analog scale (VAS)

12) Disease/failure

13) Concomitant treatment survey: names of antibiotic and anticoagulant drugs, daily dose and duration (days), dressing material, and steroid ointment application

For items 5, 6, and 7, the same evaluator will evaluate the same subject's site whenever possible.

Outcome

Primary endpoint

Healing of the recipient and donor site: re-epithelialization status $\geq 95\%$ is considered successful.

Secondary endpoints

- 1) Scar assessment using VSS with the following variables: pigmentation (normal, hypopigmented, mixed, hyperpigmented), height (flat, <2 mm, 2–5 mm, and >5 mm), vascularity (normal, pink, red, purple), and pliability (normal, supple, yielding, firm, ropes, and contracture)
- 2) Subject satisfaction after treatment: satisfied, somewhat satisfied, normal, somewhat dissatisfied, dissatisfied
- 3) Delayed healing (test site): if the patient is not cured after 4 weeks, the healing process is considered delayed
- 4) Presence of wound infection: comprehensive evaluation of pus, exudate, blood test–determined inflammatory response, and fever. Results of culture tests are also included.
- 5) Scars requiring surgical intervention
- 6) Pain assessment at sites using VAS

Safety assessment indicators

Diseases and serious illness

The term “Disease” shall include any disease, disability, or death or infectious disease suspected to

have been caused by the implementation of the Specified Clinical Research as well as any abnormal laboratory values or various symptoms. Serious illnesses are defined as those that fall into any of the following categories:

- (1) Death
- (2) Diseases that may result in death
- (3) Diseases requiring hospitalization or extended hospitalization* for treatment

*Extension of hospitalization is defined as a case in which the discharge date is fixed and then postponed for some reason. In addition, hospitalization/extended duration of hospitalization for the subject's convenience or hospitalization/extended duration of hospitalization that is not medically necessary shall not be considered under serious illness.

- (4) Disability
- (5) Diseases that may lead to disability
- (6) (3) through (5) and illnesses as serious as death or illnesses that may result in death
- (7) Congenital diseases or anomalies in subsequent generations

Malfunction of the study equipment

This means that the medical devices used in this research are not in good condition in terms of quality, safety, and performance including breakage or malfunction. It does not matter whether it is caused by design, delivery, storage, or use.

In the event of illness or malfunction, physicians at the medical institution concerned will first treat the subject, ensure his/her safety, and report the incident to the principal investigator. If the principal investigator is not available, a sub-investigator will assume the responsibilities of the principal investigator. The principal investigator will continue to observe the subject until the subject recovers from the disease or is no longer in need of observation. In the event of a malfunction, a spare kit will be used, and appropriate measures will be taken.

All illnesses and defects will be recorded. The case report form will be completed according to the instructions. Other reports and record forms specified in the research protocol will be filled, if available. The investigator(s) will evaluate the following items for the event:

Seriousness

Serious/non-serious: evaluation based “8.2 Definition of Disease, Serious Disease.”

Severity

- (1) Mild: no treatment required and the study can be continued
- (2) Moderate: research can be continued with some measures
- (3) Advanced: study should be suspended or terminated

Predictability

If the disease is not described in the following documents and cannot be predicted, it is treated as an “unpredictable” disease. Even if the disease is predictable, if its nature and severity are not consistent with the following documents, it is also treated as an “unpredictable” disease.

- (1) Research protocol or consent document
- (2) Attachment
- (3) Notification documents for alerting by regulatory authorities

Outcome

The principal investigator (or sub-investigator) shall confirm the outcome of the disease or other conditions.

Statistical analysis

Descriptive analyses including central tendency (mean and median) and variability will be performed after data collection has been completed. No interim analysis will be performed.

DISCUSSION

The potential of autologous skin cell suspension has been reported in the treatment of burn patients. Its impact on trauma patients, however, remains to be explored. There are very few reports on RECELL® applied in trauma cases. A preliminary study of 10 post-traumatic cases treated with RECELL® was reported in 2020.^[4] This report showed that RECELL® can be equivalent to a skin graft with complete healing at 30 days for smaller skin defects (<70 cm²). For larger skin defects (>70 cm²), however, the rate of wound healing dropped below 13%. The authors concluded that RECELL® cannot be the choice for skin construction of larger traumatic defects and the best reconstructive option remains traditional split-thickness mesh skin grafts. However, among burn patients, Holmes et al. compared the healing outcomes of RECELL® alone (mean area 168.2 cm²) and 2:1 meshed skin grafting (mean area 165.0 cm²) within-subject allocation of treatments and concluded that both treatment modalities were comparable among 87 patients 4 weeks postoperatively.^[5]

Although the target patients differ (trauma and burns) between these studies, because the results show conflicting efficacy of RECELL®, it seems premature to investigate the efficacy of RECELL® alone in trauma patients. We, therefore, refer to the prospective, multicenter, randomized trial by Gardien et al.^[6] They compared mesh grafting alone with grafting with cultured autologous proliferating epidermal cells in burn patients and found that mesh grafting with cultured epidermal cells was more effective than grafting with mesh alone on postoperative days 5–7 in terms of better wound closure and scar quality. To investigate the impact of RECELL® on early wound closure and scar quality, we designed the treatment protocol for 3:1 split-thickness mesh grafting in combination with RECELL®.

Another key feature of this study is that the subjects will not be enrolled unless a “good wound bed” is prepared. In trauma patients, controlling the wound infection is a critical key factor that needs to be addressed. Manning et al. conducted a randomized open-label trial of RECELL® for

contaminated diabetic foot gangrene and reported epithelialization in 66.7% of the subjects. The key factor^[7] of a relatively high wound closure rate in diabetic foot gangrene was that the study included patients with skin defects with “adequately vascularized” wounds. As the condition of the wound bed plays a major role in the success or failure of skin grafting, we believe that good epithelialization and wound closure can be expected by including this condition in trauma patients as well.

We will also investigate scar formation after the surgery. The observation period of this study is, however, relatively short (24 weeks). Holmes et al. recorded VSS scores for burn injuries with RECELL® at 16, 24, and 52 weeks.^[5] They reported that there was no significant difference between RECELL® and mesh skin grafting throughout the study period. We believe the study period of 24 weeks is sufficient to observe scar formation.

With this study protocol, we aim to validate the usefulness of RECELL® for skin defects due to trauma by observing wound closure, scar formation including its adverse events, delayed healing, infection, and its durability.

List of abbreviations

VAS, visual analog scale

VSS, Vancouver Scar Scale

Declarations

- Ethics approval and consent to participate nara0053 by Nara Medical University Certified Review Board (CRB5200002)
- Consent for publication Not applicable
- Availability of data and materials Not applicable
- Competing interests COSMOTEC Co.Ltd.
- Funding Nara medical University
- Authors' contributions

NM and HF contributed to the conceptualization. The study protocol was designed by NM and HF. The main manuscript text was written by NM, HA and HF. The manuscript was reviewed by HK, KM, AO, KM and YK. All authors read and approved the final manuscript.

- Acknowledgements

We thank the staff of the Institute for Clinical and Translational Science of Nara Medical University Hospital. We thank Editage (<https://www.editage.jp>) for editing a draft of this manuscript.

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Figure legend

Table1. protocol of observation

Supplementary Files

Figures

Untitled.

Regulation week of visit	Before treatment	Date of treatment After treatment	Length of treatment	Observation period					
	-7 days up to treatment	Day 0	After 1 week	After 2 weeks	After 4 weeks	After 6 weeks	After 8 weeks	After 12 weeks	After 24 weeks
Tolerance level	-	-	±1 day	±3 days	±5 days	±6 days	±7 days	±10 days	±14 days
Date from date of treatment	-7 days Up to the treatment	-	0-5 days	11-17 days	23-33 days	36-45 days	49-63 days	74-94 days	104-152 days
Obtaining consent	Period								
Eligibility verification	0/1								
Subject background	0/1								
Trauma-related characteristic	0/1								
Photography: test site		0/2	Period	Period	Period	Period	Period	Period	Period
Healing of the test site			Period	Period	Period	Period	Period	Period	Period
Scar assessment using the Vancouver Scar Scale								Period	Period
Subject satisfaction after treatment								Period	Period
Delayed healing (test site) P3					Period	Period	Period	Period	Period
Presence of wound infection			Period	Period	Period	Period	Period	Period	Period
Scars requiring surgical intervention			Period	Period	Period	Period	Period	Period	Period
Assessment of pain at the test site			Period	Period	Period	Period	Period		
Disease/suture									
Concomitant Treatment Survey ¹⁴		Period	Period	Period	Period	Period	Period	Period	Period

CONSORT (or other) checklists

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