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Efficacy and Safety of the Skin Adhesive Epinexus™ in Surgical Patients

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Abstract

This single-center, randomized, and controlled intervention study compared an acrylate skin adhesive, Epinexus™ (Mitsui Chemicals, Inc., Tokyo) with Dermabond Advanced® (Ethicon, Inc., Somerville, New Jersey). The primary endpoint was cosmetic outcome at 52 weeks after treatment (Manchester Scar Scale), and the secondary endpoints were cosmetic outcome at 4 and 26 weeks after treatment (Manchester Scar Scale), wound closure, and usability. We evaluated 59 patients (29 cases and 30 controls). Failures and adverse events were also evaluated, and 8 adverse events (5 cases and 3 controls) were reported (epidermolysis, n = 4; contact dermatitis, n = 1; eczema, n = 1; and surgical wound dehiscence, n = 2). No difference was observed between groups in cosmetic outcome at 52 and 24 weeks; however, at 4 weeks, cases showed better cosmetic outcome compared with controls. With regard to usability, the treatment duration and application time were significantly longer with Epinexus™, and ease of application was significantly better with Dermabond Advanced®.

Keywords

Acrylate Skin Adhesive, Single-Center, Comparative Randomized Control Study, Cosmetic Outcome

1. Introduction

Numerous methods have been developed to achieve minimal scarring after surgery. One effective method to make a scar finer and subdermal suturing, is widely used in plastic surgery to release tension on the wound edge. Tension on

the wound is said to make the scar worse, and it sometimes becomes a cause of hypertrophic scaring and keloids. Because it takes more than six months for a scar to be fixed, taping is usually used after surgery to prevent worse scarring.

For skin closure, skin adhesives are sometimes used instead of skin sutures for their ease of use and lack of a need for removal of sutures or staples. Among skin adhesives, Dermabond Advanced® (Ethicon, Inc., Somerville, New Jersey) [1] [2] is used worldwide. However, the low viscosity of Dermabond Advanced® may compromise its ability to keep the wound at rest to release tension on the wound. Also, because of its low viscosity, the Dermabond Advanced® material has the potential to flow into the wound, which may disrupt wound adhesion.

Epinexus™ (Mitsui Chemicals, Inc., Tokyo), the skin adhesive used for this study, was developed to prevent these risks. It is constructed primarily with polymethylmethacrylate, and it is biocompatible with appropriate viscosity according to its polymerization by mixing a methylmethacrylate monomer, polymethylmethacrylate powder, and polymerization initiator immediately prior to use [1]. Epinexus™ is hard enough to keep the wound at rest after it becomes stiff. Therefore there were no reports using Epinexus™ in clinical use so far; we have published the results of a pilot study of Epinexus™ that showed its safety for application to the suture [2]. The current single-center, open-label, and parallel-group study compared the efficacy, safety, and cosmetic outcome of Epinexus™ with Dermabond Advanced® in 59 subjects.

2. Materials and Methods

Epinexus™, an acrylate skin adhesive, consists of a prefilled syringe containing polymer powder, 2 prefilled vials containing monomer liquid and polymerization initiator, respectively, a transfer needle for mixing the above 3 ingredients, and an application nozzle (**Figure 1**). The operators' technique was standardized by preliminary training based on the description in the package insert and during the first study [3]. All of the operators had experiences more than 10 years in surgery field. The patients were randomly assigned two groups (the Epinexus™ group (EG) and the Dermabond Advanced® group (DG)). The primary endpoint was cosmetic outcome at 52 weeks after treatment (Manchester Scar Scale) [4] [5], and the secondary endpoints were cosmetic outcome at 4 and 26 weeks after treatment (Manchester Scar Scale), wound closure, and usability. We evaluated 59 patients (29 cases and 30 controls). In addition, failures and adverse events were appropriately evaluated in accordance with the Japanese version of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) (Japan Clinical Oncology Group/Japan Society of Clinical Oncology: JCOG/JSCO v.4.0). Eligibility criteria were as follows: 1) male or female adults aged 20 or older, 2) no diseases that affect wound closure based on medical history, and no recently used or concomitant medications, 3) expecting a surgical incision of 2 - 6 cm, 4) underwent tumor removal at the Department of Breast Surgery or Plastic Surgery, 5) voluntarily agreed to participate in the

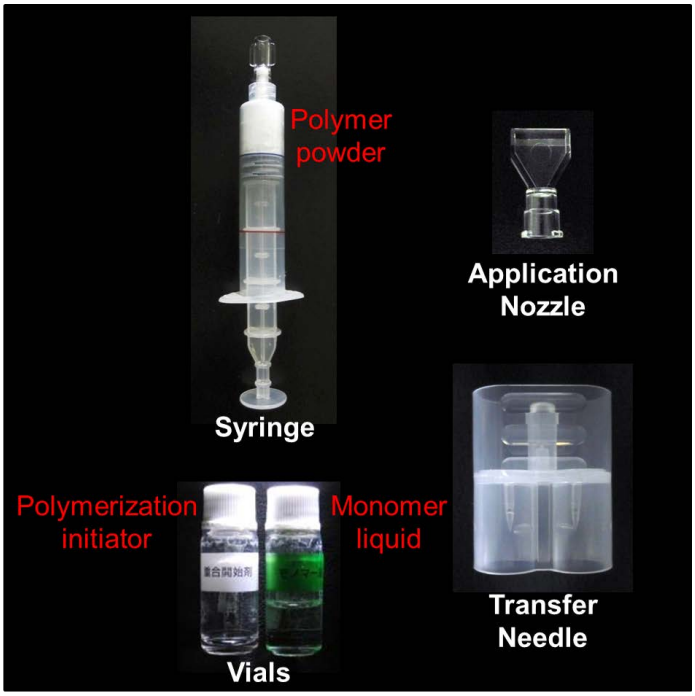

Figure 1. Epinexus™ Components.

study and submitted signed, written informed consent, and 6) agreed to visit the medical institution for the follow-up evaluation. This study was conducted in Keio University School of Medicine from 2015-2017.

2.1. Ethical Considerations

This study was conducted in compliance with the ethical principles based on the Declaration of Helsinki, the Ethical Principles for Medical Research Involving Human Subjects (6th revision, Seoul, 2008), and the Ethical Guidelines for Clinical Studies (Japan Ministry of Health, Labour and Welfare, Notification No. 415, July 31, 2008). This study was reviewed and approved by the Ethical Review Board of Keio University in advance (approval code No. 20140391). The subjects were given sufficient explanation on the informed consent form and voluntarily submitted a signed, written informed consent form at least 2 days prior to surgery. Careful consideration was paid to the protection of the privacy and personal information of the subjects.

2.2. Statistical Analysis

The Full Analysis Set (FAS) was defined as all enrolled subjects except those who did not use Epinexus™ or whose data were not available for the endpoints. The Per Protocol Set (PPS) contained subjects included in the Full Analysis Set except those in whom efficacy was difficult to evaluate or who were found to meet the exclusion criteria or deviated from the protocol after enrollment.

The FAS was used for the safety analysis. Data for the safety endpoints were accumulated from the start date to the end or discontinued date of the use of

Epinexus™. The PPS was used for the efficacy analysis. The number of subjects with or without wound dehiscence and their percentages were calculated, respectively. Cosmetic outcomes at 4 weeks ± 7 days, 24 weeks ± 14 days, and 52 weeks ± 28 days were evaluated with the Manchester Scar Scale by 2 sub-investigators. For the comprehensive evaluation of the wound, the length to the mark on the 10-cm Visual Analog Scale (VAS) was measured, and 1 cm was calculated as 1 point. The VAS score was added to the total score of the individual endpoints for the final Manchester Scar Scale result. The mean value of the scores of the 2 sub-investigators was calculated for each subject, observation time point, and endpoint, and then the mean, maximum, and minimum values were determined for each endpoint for the PPS.

To ensure the objectivity of this study, a safety and efficacy evaluation committee was established separately, in advance, to evaluate wound closure, cosmetic outcome, usability, and safety for all subjects.

3. Results

Of the 63 enrolled subjects, 1 was excluded because the application site was found not to meet the inclusion criteria after enrollment. As a result, the number of subjects in both the FAS and the PPS was 62 (Figure 2).

The demographic and baseline clinical characteristics of the Epinexus™ group (EG) and the Dermabond Advanced® group (DG) did not show any statistically significant differences (Table 1). These characteristics included gender, original

Table 1. Patient background.

		EG (n = 31)	DG (n = 31)	Total (n = 62)
Age	Average	55.3 ± 13.8	51.6 ± 12.3	53.4 ± 13.1
Height (cm)	Average	157.81 ± 7.59	159.26 ± 7.66	158.54 ± 7.6
Weight (kg)	Average	52.28 + 11.14	57.60 + 13.68	54.94 + 12.66
Gender	Female	29	28	57
	Male	2	3	5
Primary disease	Breast cancer	22	23	45
	Breast scar	4	3	7
	Blepharoptosis	2	1	3
	Subcutaneous tumor (breast)	0	1	1
	Lipoma (shoulder)	0	1	1
	Lipoma (hip)	0	1	1
	Soft tissue tumor (abdomen)	1	0	1
	Scar contracture (abdomen)	1	0	1
	Phyllodes tumor (breast)	1	0	1
	Soft tissue tumor (hip)	0	1	1
Medical history	No	26	24	50

Continued

History of allergy	Yes	5	7	12
	No	21	14	35
Concomitant medications	Yes	10	17	27
	No	11	16	27
	Yes	20	15	35

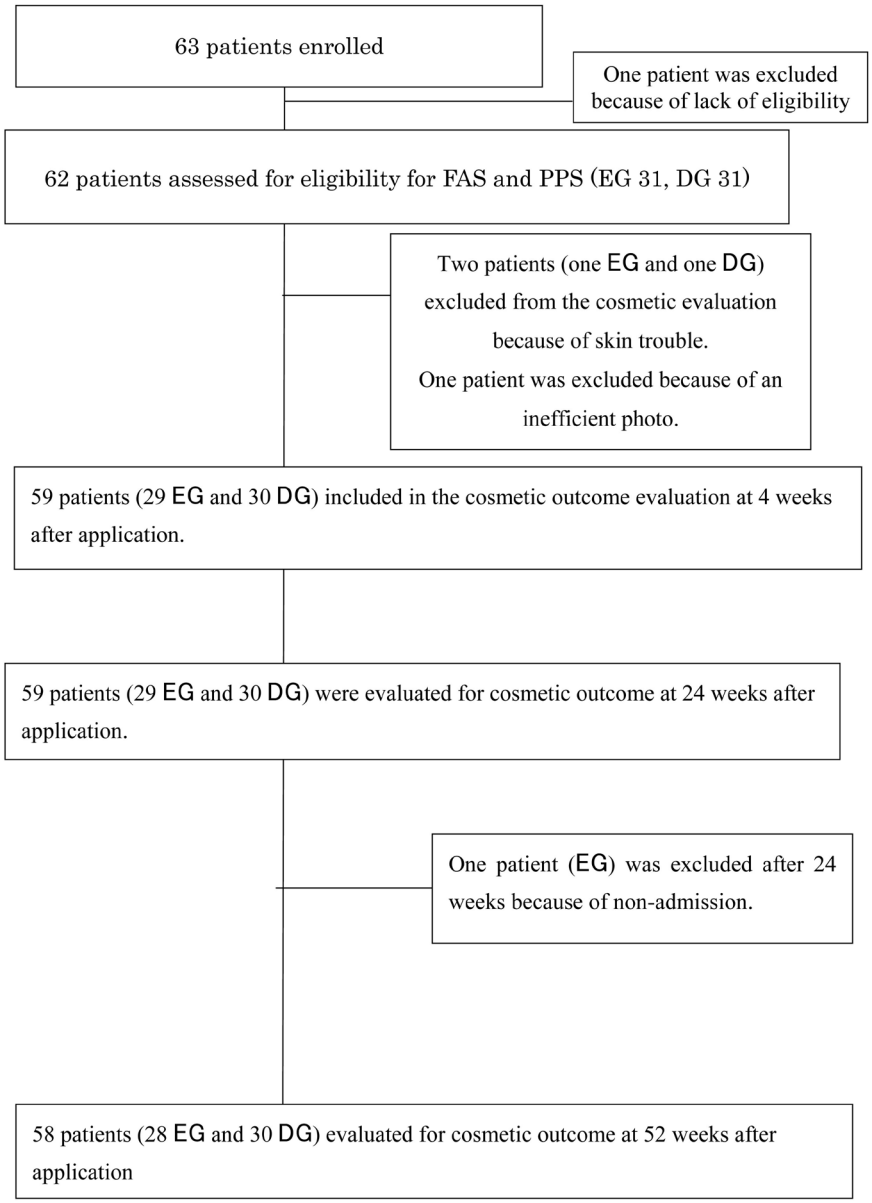

Figure 2. Patient Disposition.

disease, height, body weight, past history, allergies, and concomitant medications. The two groups did not show any differences in physical examinations.

We observed 47 adverse events in 28 subjects (17 EG and 11 DG). None of the

adverse events was severe. Among them, 8 cases (5 EG and 3 DG) were considered related to treatment (Table 2). In 4 cases (3 EG and 1 DG), erosion was observed. Two cases of non-adhesion were observed in the DG group. All cases of erosion were resolved by applying ointment to the affected sites.

With regard to the evaluation of usability, usage times for both treatment and application were significantly longer in the EG (Table 3). The ease of application was significantly better in the DG (Table 4).

With regard to cosmetic results, there were no significant differences between groups at 24 and 52 weeks (Table 5 and Table 6). However, at 4 weeks after application, the cosmetic results were significantly better in the EG (Table 7). Five cases discontinued the observations (Table 8).

Table 2. Treatment-related adverse events.

	Group	Event	Severity	Treatment	Original disease
1	EG	Epidermolysis	mild	Bacitracin Fradiomycin sulfate ointment	Breast cancer
2	EG	Contact dermatitis	mild	none	Blepharoptosis
3	EG	Epidermolysis	mild	dressing	Phyllodes tumor
4	EG	Epidermolysis	moderate	none	Breast cancer
5	EG	Eczema	mild	0.05% Betamethasone Butyrate Propionate lotion	Breast cancer
6	DG	Epidermolysis	mild	0.1% Gentamicin Sulfate ointment	Breast cancer
7	DG	Surgical wound dehiscence	mild	none	Breast cancer
8	DG	Surgical wound dehiscence	mild	none	Breast cancer

Table 3. Time needed for treatment (sec).

	EG	DG	total
Mean	168.5	26.5	97.5
SD	46.2	17.6	79.5
SE	8.2	3.2	10.1

$p < 0.0001$.

Table 4. Ease of treatment.

	EG	DG	total
Very easy	2	21	23
Easy	14	8	22
Acceptable	8	1	9
Difficult	7	1	8
Total	31	31	62

Table 5. Cosmetic evaluation at 24 weeks.

	EG	DG	total
Mean	11.9	11.1	11.5
SD	3.0	2.3	2.7
SE	0.6	0.4	0.3
N	29	30	59

Table 6. Cosmetic evaluation at 52 weeks.

	EG	DG	total
Mean	9.4	8.8	9.1
SD	3.0	3.4	3.2
SE	0.6	0.6	0.4
N	28	30	58

Table 7. Cosmetic evaluation at 4 weeks.

	EG	DG	Total
Mean	11.8	12.8	12.3
SD	1.6	1.8	1.7
SE	0.3	0.3	0.2
N	29	30	59

$p < 0.05$.

Table 8. Discontinuations

	Original disease	Reason for discontinuation	Time of discontinuation
EG	Breast cancer	Worseness of the treated area	Before removal
DG	Breast cancer	Ineligible patient	Before treatment
DG	Breast cancer	Worseness of the treated area	Before evaluation at 4 weeks
EG	Blepharoptosis	Non-visit	Before evaluation at 24 weeks
EG	Breast cancer	Transferred to another hospital	Before evaluation at 52 weeks

4. Discussion

The purpose of this study was to compare the efficacy and safety of Epinexus™ with Dermabond Advanced®. We observed that the EG had a higher incidence of epidermolysis. As Epinexus™ is designed to have high viscosity and to be more adherent to the skin, these features may have contributed to the increased frequency of epidermolysis. Also, because Epinexus™ is designed to fix the wound firmly, it is harder than Dermabond Advanced®. Thus, in some cases, erosion at the margin of the application site was observed. As for non-adhesion, two cases were observed in the DG. Non-adhesion may have resulted from the flow of the solution into the wound.

The usability was significantly better in the DG. Epinexus™ requires several steps before application and requires more time to set. Ease of use is an important factor in surgery; thus, Epinexus™ should be made easier to use in the future.

Interestingly, the cosmetic results at 4 weeks were significantly better in the EG than in the DG. We used the Manchester scale for the evaluation of scars; this scale is usually used for mature scars, and it contains no elements for the evaluation of acute inflammation. Thus, it is impossible to determine why the evaluators found differences between the two methods. Large differences in redness sometimes occur at 4 weeks after surgery and reflect the amount of acute inflammation. During the course of scar rearrangement, differences may be counteracted that could not be evaluated with the Manchester scar scale. Although using Epinexus™ needs attention to epidermolysis, in our study, Epinexus™ showed the same efficiency and safety as existing product (Dermabond Advanced®).

Conflicts of Interest

The authors of this article have no conflicts of interest with, nor received any funding from the following organization or company with respect to this study: Mitsui Chemicals, Inc. (Provider of investigational device).

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Footnotes

NCI: National Cancer Institute.

CTCAE: Common Terminology Criteria for Adverse Events.

JCOG/JSCO: Japan Clinical Oncology Group/Japan Society of Clinical Oncology.

FAS: Full Analysis Set.

PPS: Per Protocol Set.

VAS: Visual Analog Scale.

Epinexus™: The product name of the investigational device, a skin adhesive manufactured by Mitsui Chemicals, Inc.

Manchester Scar Scale: Each of these parameters was given a score from 1 to 4, with increasing values indicating increasing scar severity. Whether a scar was matte or shiny was also recorded, the former scoring 1 and the latter 2. An overall assessment was also made and indicated on a visual analogue scale as a vertical mark on a 10-cm line, with 0 indicating an excellent scar and 10 indicating a poor scar. This score, expressed in centimeters to one decimal place, was then added to the sum of the individual parameter scores to give an overall score for each scar. The overall score ranged from 5 to 28, with low scores representing clinically well healed scars of good cosmetic appearance and high scores representing clinically poor scars.