Scientific Research Publishing

Modern Plastic Surgery, 2017, 7, 31-38
http://www.scirp.org/journal/mps
ISSN Online: 2164-5280
ISSN Print: 2164-5213

A Single-Center Open-Label Single-Arm Study Evaluating Efficacy and Safety of Skin Adhesive Epinexus™ in Surgical Patients

Kazuo Kishi[1], Noriko Aramaki-Hattori[1], Yoshiaki Sakamoto[1], Keisuke Okabe[1], Tetsu Hayashida[2], Maiko Takahashi[2], Yuko Kitagawa[2], Masataka Saito[3], Takeya Adachi[3], Aki Honda[3], Hiromitsu Jinno[4]

[1]Department of Plastic and Reconstructive Surgery, Keio University School of Medicine, Tokyo, Japan
[2]Department of Surgery, Keio University School of Medicine, Tokyo, Japan
[3]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan
[4]Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan
Email: kkishi@a7.keio.jp

How to cite this paper: Kishi, K., Aramaki-Hattori, N., Sakamoto, Y., Okabe, K., Hayashida, T., Takahashi, M., Kitagawa, Y., Saito, M., Adachi, T., Honda, A. and Jinno, H. (2017) A Single-Center Open-Label Single-Arm Study Evaluating Efficacy and Safety of Skin Adhesive Epinexus™ in Surgical Patients. *Modern Plastic Surgery*, **7**, 31-38.
https://doi.org/10.4236/mps.2017.74004

Received: July 8, 2017
Accepted: August 15, 2017
Published: August 18, 2017

Abstract

Existing skin adhesives may, however, cause inflammatory response to toxicity of formaldehyde generated as hydrolysate of polycyanoacrylate (the main ingredient), delay in wound closure due to the adhesive's flowing into the wound from the edges, or a wide scar. Epinexus™ (Mitsui Chemicals, Inc.), the skin adhesive used for this study, was developed to prevent these risks. For the method of this study, This was a single-center, open-label, single-arm, intervention study of an acrylate skin adhesive, Epinexus™. The primary endpoint was safety. The secondary endpoints were wound closure, cosmetic outcome (Manchester Scar Scale), and usability. Failures and adverse events were also appropriately evaluated. As a result, there were no particular adverse events such as inflammatory findings, which demonstrated that there is no problem in safety. Some common adverse events were observed, but no adverse events for which a causal relationship cannot be ruled out or failures. As a conclusion, there was no problem in wound closure, cosmetic outcome, or usability. This was a pilot study of Epinexus™ of an ongoing, single-center, open-label, parallel-group, comparative study in 60 subjects comparing Epinexus™ with an existing skin adhesive, Dermabond® Advanced.

Keywords

Cosmetic Techniques, Clinical Study, Wounds and Injury

1. Introduction

While sutures have conventionally been used for surgical wound closure, more recently, skin adhesives are also used as a medical device for its easiness, quickness, shorter operative times, lighter physical and mental burden of patients, and higher safety, free from post-closure procedures including removal of sutures and staples. Existing skin adhesives may, however, cause inflammatory response to toxicity of formaldehyde generated as hydrolysate of polycyanoacrylate (the main ingredient), delay in wound closure due to the adhesive's flowing into the wound from the edges, or a wide scar. Epinexus™, the skin adhesive used for this study, was developed to prevent these risks.

Its main ingredient, polymethylmethacrylate, has a good biocompatibility and can be applied to the wound and hardened with appropriate viscosity and polymerization degree by mixing methylmethacrylate monomer, polymethylmethacrylate powder, and polymerization initiator immediately prior to use [1]. This study evaluated the efficacy, safety, and cosmetic outcome of Epinexus™ as a pilot study of an ongoing, single-center, open-label, parallel-group, comparative study in 60 subjects [2].

2. Methods

The investigational substance of this study was Epinexus™ (Mitsui Chemicals, Inc.), an acrylate skin adhesive, which consists of a syringe prefilled with polymer powder, 2 vials prefilled with monomer liquid and polymerization initiator, respectively, a transfer needle to be used 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. This was a single-center, open-label, single-arm, intervention study. The primary endpoint was safety evaluated by gross appearance. The secondary endpoints were wound closure evaluated by gross appearance, cosmetic outcome evaluated by photographs (Manchester Scar Scale), and usability of Epinexus™ (**Table 1**) [3] [4]. In addition, failures and adverse events were appropriately evaluated in accordance with the Japanese version of the CTCAE of the NCI (JCOG/JSCO v.4.0). The subjects were patients who: (1) are male or female adults aged 20 or older, (2) have no diseases that affect wound closure in view of the medical history, and recently-used or concomitant medications, (3) are expecting a surgical incision of 2 - 6 cm, (4) had a tumor removed from their body at the department of breast surgery or plastic surgery, (5) voluntarily agreed to participate in the study and submitted a written consent, and (6) agreed to visit the medical institution for the follow-up evaluation. The number of enrolled subjects was 7 (met eligible criteria was 5, exclude was 2), and total subjects was 5.

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

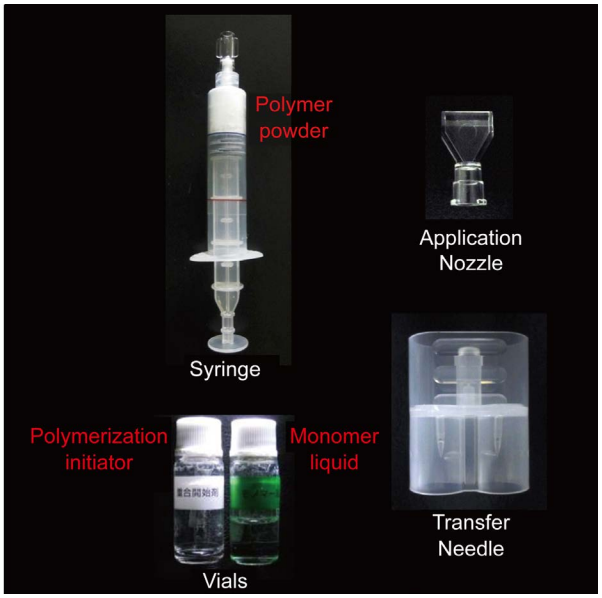


Figure 1. A photograph of the product.

Table 1. Manchester scar scale.

Visual Analogue Scale				
←Excellent				Poor→
Lighter or darker	A	Color (cf.to surrounding skin)	Perfect	1
			Slight mismatch	2
			Obvious mismatch	3
			Gross mismatch	4
	B	Matte vs shiny	Matte	1
			Shiny	2
	C	Contour	Flush with surrounding skin	1
			Slightly proud/indented	2
			Hypertrophic	3
			Keloid	4
	D	Distortion	None	1
			Mild	2
			Moderate	3
			Severe	4
	E	Texture	Normal	1
			Just palpable	2
			Firm	3
			Hard	4

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 our hospital in advance (approval code No. 20140141). The subjects were given sufficient explanation using the informed consent form and voluntarily submitted a written consent at least 2 days prior to the surgery. Careful consideration was paid to the protection of the privacy and personal information of the subjects.

2.2. Statistics

The Full Analysis Set (FAS) was defined as enrolled subjects except those who did not use Epinexus™ or whose data were not available for endpoints and the Per Protocol Set (PPS) as 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 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 efficacy analysis. The number of subjects with or without a wound dehiscence and their percentages were calculated, respectively. The cosmetic outcomes at 4 weeks ± 7 days and 24 weeks ± 14 days were evaluated using the Manchester Scar Scale by 2 sub-investigators. For the comprehensive evaluation of the wound, the length to the mark on the Visual Analog Scale (VAS) of 10 cm long 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 timepoint, and endpoint, and then the mean, maximum, and minimum values for each endpoint for the PPS.

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

3. Results

Of the enrolled 7 subjects, 2 subjects were excluded because their application sites were found not to meet the inclusion criteria after enrollment (Table 2, Table 3). As a result, the number of subjects of the FAS and the PPS was both 5. The scores for the primary endpoint were all 0, which demonstrated the safety of Epinexus™. For the secondary endpoints, which were evaluated using the PPS, there was no wound dehiscence, or need for additional brace or re-treatment, which demonstrated that Epinexus™ has no problem in wound closure (Table 4), and the Manchester Scar Scale for the cosmetic outcome were 16.11 and 11.65 at 4 weeks ± 7 days and 24 weeks ± 14 days, respectively, which demonstrated that the level of the scar was about the same as the scar healed by the existing skin

Table 2. Patient demographics.

Patient background		
		n = 7
Height (cm)	Average	160.7
Weight (kg)	Average	55.5
Gender	Male	1
	Female	6
Primary disease	Right breast cancer	3
	Multiple mole	1
	Subcutaneous tumor on the left back (Suspected lipoma)	1
	Bilateral breast cancer	1
	Left breast cancer	1
Complications	No	2
	Yes	5
Disease name		n = 13
	Epilepsy	1
	Rhinitis allergic	1
	Hypertension	1
	Dyslipidaemia	1
	Shoulder muscle stiffness	1
	Low back ache	1
	Coronary spastic angina	1
	Osteoporosis	1
	Peripheral nerve disorders	1
	Seborrhoeic eczema	1
	Glaucomas	1
	Gonarthrosis	1
	Asthma	1
Treatment		n = 13
	No	4
	Yes	9
Medical history	No	7
	Yes	0
History of allergy	No	7
	Yes	0
Concomitant medications	No	2
	Yes	5

Table 3. Patient background (application site).

Diagnosis (day applied)		n = 7
Systemic symptoms, etc.	Neurocutaneous melanosis, multiple mole	1
	Lipoma on the left back	1
	No problem	5
Application site	Right breast	3
	Right front chest	1
	Left back	1
	Over 6 cm, but not meeting Criterion 3	2

Table 4. Wound closure evaluation.

Wound closure evaluation				
Day 0 (day applied)		n = 5		
Wound dehiscence	No (0)	5	Total average	0
Need for additional brace or re-treatment	No (0)	5	Total average	0
Day 1 (next day)		n = 5		
Wound dehiscence	No (0)	5	Total average	0
Need for additional brace or re-treatment	No (0)	5	Total average	0
Day 3 ± 1 day		n = 5		
Wound dehiscence	No (0)	5	Total average	0
Need for additional brace or re-treatment	No (0)	5	Total average	0
Day 7 ± 2 days		n = 5		
Wound dehiscence	No (0)	5	Total average	0
Need for additional brace or re-treatment	No (0)	5	Total average	0
Day removed (5 days after application or later)		n = 5		
Wound dehiscence	No (0)	5	Total average	0
Need for additional brace or re-treatment	No (0)	5	Total average	0

*: Described in the Day removed (5 days after application or later) column of the CRF.

adhesives (Figure 2, Table 5), and the usability evaluation result demonstrated that there is no problem in use of Epinexus™.

There were no adverse events among the FAS for which a causal relationship cannot be ruled out or failures. There was 1 adverse event of a mild vertigo, which was attributed to the concomitant medication, but there were no inflammatory findings, etc., which are risks of the existing similar products.

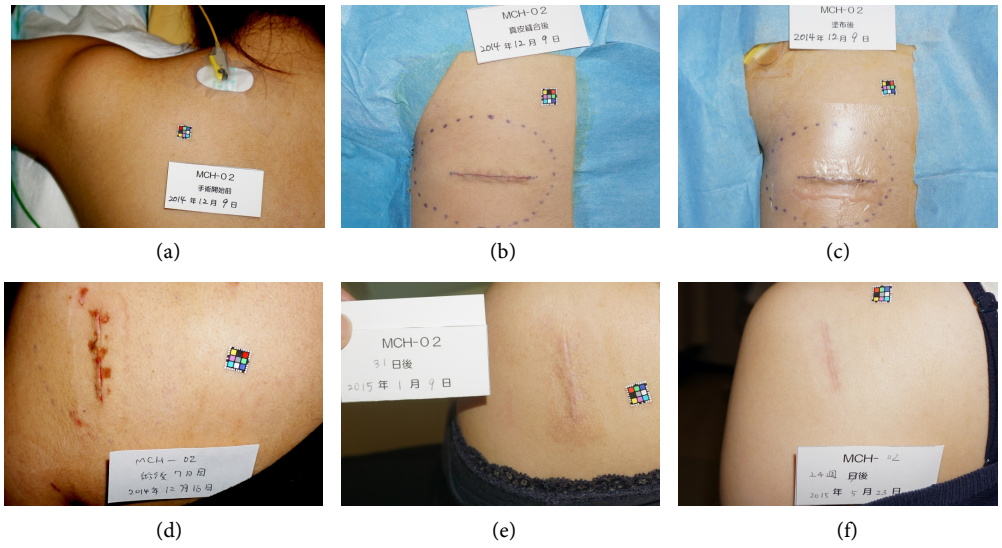
4. Discussion

The purpose of this study was to evaluate the efficacy and safety of Epinexus™

Table 5. Cosmetic outcome evaluation (Manchester Scar Scale).

Cosmetic outcome		
4 weeks ± 7 days		n = 5
	Total Average	16.11
	Patient number-01 Average	18.85
	Patient number-02 Average	12.85
	Patient number-03 Average	16.75
	Patient number-05 Average	16.75
	Patient number-07 Average	15.35
Lighter or dark	Lighter	5
	Dark	5
A. Color	Average	2.8
B. Matte or Shiny	Average	1.5
C. Contour	Average	1.7
D. Distortion	Average	2.5
E. Texture	Average	2.4
Visual Analogue Scale (cm)	Average	5.36
24 weeks ± 14 days		n = 5
	Total Average	11.65
	Patient number-01 Average	16.20
	Patient number-02 Average	10.30
	Patient number-03 Average	11.65
	Patient number-05 Average	11.00
	Patient number-07 Average	9.10
Lighter or dark	Lighter	7
	Dark	3
A. Color	Average	2.2
B. Matte or Shiny	Average	1.2
C. Contour r	Average	1.1
D. Distortion	Average	1.6
E. Texture	Average	1.9
Visual Analogue Scale (cm)	Average	3.69

Registration Number: Patient number -02



(a) (b) (c)

(d) (e) (f)

Figure 2. The photographs for cosmetic outcome. (a) Day 0 (Before surgery); (b) Day 0 (After dermal suture); (c) Day 0 (After applying Epinexus™); (d) Day Epinexus™ was Removed (5 Days after); (e) 4 weeks ± 7 days; (f) 24 weeks ± 14 days.

comprehensively and objectively. As a result, it was observed that Epinexus™ can be used with no particular problem in clinical practice. Wound closure and cosmetic outcome were evaluated as generally having no problem in its function as a skin adhesive. Usability was evaluated as generally having no problem except an impression of low viscosity reported from a few subjects. Safety in usage was demonstrated with only 1 adverse event of a mild vertigo for which causal relationship was denied, with no particular adverse events such as inflammatory findings. In conclusion, it was confirmed that Epinexus™ can be used with no problem in efficacy and safety as a skin adhesive. Comprehensive evaluation in clinical practice was that Epinexus™ is clinically useful because the potential risk of inflammatory response to toxicity of formaldehyde can be avoided.

References

[1] Toriumi, D.M., O'Grady, K., Desai, D., *et al.* (1998) Use of Octyl-2-Cyanoacrylate for Skin Closure in Facial Plastic Surgery. *Plastic and Reconstructive Surgery*, **102**, 2209-2219. https://doi.org/10.1097/00006534-199811000-00062

[2] Quinn, J., Wells, G., Sutcliffe, T., *et al.* (1997) A Randomized Trial Comparing Octylcyanoacrylate Tissue Adhesive and Sutures in the Management of Lacerations. *JAMA*, **277**, 1527-1530. https://doi.org/10.1001/jama.1997.03540430039030

[3] Singer, A., Arora, B., Dagum, A., *et al.* (2007) Development and Validation of a Novel Scar Evaluation Scale. *Plastic and Reconstructive Surgery*, **120**, 1892-1897. https://doi.org/10.1097/01.prs.0000287275.15511.10

[4] Beausang, E., Floyd, H., Dunn, K.W., *et al.* (1998) A New Quantitative Scale for Clinical Scar Assessment. *Plastic and Reconstructive Surgery*, **102**, 1954-1961. https://doi.org/10.1097/00006534-199811000-00022