

Allergic contact dermatitis due to the liquid skin adhesive Dermabond predominantly occurs after the first exposure

Running head: ACD due to Dermabond after the first exposure

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ABSTRACT

Background: The clinical characteristics of patients with allergic contact dermatitis (ACD) due to a skin adhesive containing 2-octyl cyanoacrylate, Dermabond, have not yet been elucidated.

Objective: To investigate the clinical characteristics of patients with ACD caused by Dermabond application.

Methods: In this retrospective study, 577 patch tested patients were included. We identified patients with positive patch test results for Dermabond and evaluated their results concerning (meth)acrylates and ethyl cyanoacrylate adhesive.

Results: Nine patients had positive patch test results to Dermabond; six had developed secondary generalisation. Mean time between Dermabond application and ACD onset was 34 days (range, 27–44) in six patients with ACD after the first use, whereas, in the other three patients, it was 5.6 days (range, 4–8) after the second use. The time was significantly different between the two groups ($P<.01$). Positive reactions to ethyl cyanoacrylate adhesive (Aron Alpha) occurred in seven of nine patients, to ethyl cyanoacrylate 10% pet. in four of eight patients tested, and to 2-hydroxyethyl

methacrylate in one of eight patients tested.

Conclusions: Dermabond-induced ACD is apparently characterised by a high prevalence of primary sensitisation at first exposure to Dermabond, secondary generalisation is frequent, and most patients show cross-reactivity to ethyl cyanoacrylate.

Keywords: Allergic contact dermatitis, Dermabond, 2-octyl cyanoacrylate, ethyl cyanoacrylate, (meth)acrylate, tissue adhesive, gel nails

1. INTRODUCTION

Dermabond Advanced (Ethicon, Tokyo, Japan) is a liquid skin adhesive containing 2-octyl cyanoacrylate, used for closing surgical incisions. Currently, the use of cyanoacrylates, such as 2-octyl-, 2-butyl, and 2-ethyl-cyanoacrylates, has been increasing in the surgical field as an alternative to standard wound closure because of their rapid polymerisation and easy handling.^{1,2} Of note, the rapid polymerisation after the application of Dermabond is expected to prevent antigen-presenting cells from inducing sensitisation, because antigen-presenting cells are only capable of recognizing monomers of cyanoacrylates, but not polymers.³ The number of reported cases of allergic contact dermatitis (ACD) due to Dermabond has recently been increasing. However, the clinical characteristics of patients with ACD due to Dermabond have not yet been clarified.

In this study, we aimed to investigate the clinical characteristics of patients with ACD due to Dermabond and to evaluate concomitant sensitisation to (meth)acrylates and ethyl cyanoacrylate based on patch test (PT) results.

2. METHODS

In this retrospective observational study, the data of 577 consecutive patients (152 men and 425 women) who were patch tested between April 2015 and March 2019 in the Department of Dermatology of Yokohama City University Hospital were reviewed. Those patients who developed allergic skin reactions (more than + according to ESCD guidelines) at the site of application of agents were included in the study.⁴

We identified patients with a clinical history of allergic reaction due to Dermabond and positive PT results with Dermabond, and investigated the clinical characteristics of ACD induced by Dermabond. In addition, we evaluated the PT results obtained with the Japanese baseline series, as well as a metal, and a (meth)acrylates series (Chemotechnique Diagnostics, Vellinge, Sweden) (Table 1); ethyl cyanoacrylate 10.0% pet. (Chemotechnique Diagnostics); and ethyl cyanoacrylate adhesive, Aron Alpha (Toagosei, Tokyo, Japan). If the patients had a history of ACD caused by other products containing (meth)acrylates, such as eyelash glues, these products were additionally tested as allergens during PT. One patient (case 9) in this series has been reported on previously.⁵

All study patients provided informed consent, and the study was approved by the appropriate ethics review boards at Yokohama City University (B191000006). The study

conforms to the standards laid out in the Declaration of Helsinki.

PTs were applied to the patient's upper back with Finn Chambers (SmartPractice, Phoenix, Arizona) and PT panel (Sato, Tokyo, Japan) on a Medipore tape (3M, St Paul, Minnesota) and were occluded for 48 hours. Readings were performed on day (D) 2, D3, and D7 and a reaction stronger than + was considered positive according to ESCD guidelines.⁴ ACD was diagnosed based on a relevant history and positive PT results using products that were suspected to induce ACD. Dermabond, false eyelash glue, and Aron Alpha were applied "as is" during the open test. In the open test, these products dripped onto the skin were dried and left open ESCD guidelines.⁴

The patients with Dermabond-induced ACD were divided into two groups: one group who developed ACD after the first application and the other group who developed ACD after the second application. The mean duration of the onset of ACD following Dermabond application in the two groups was analyzed using the Student's t-test. A *P*-value < .05 suggests that the mean duration in the two groups is significantly different.

JMP version Pro 15 software (SAS Institute, Cary, North Carolina) was used for the analysis.

3. RESULTS

Of the 577 patients included in the study, nine patients (1.5%) (7 women, 2 men, mean age of 50 years) were diagnosed with ACD due to Dermabond (Table 1). In terms of a history of other allergies, four of the nine patients experienced ACD due to cosmetic products, hair dye, cold compress for pain and diphenhydramine ointment. Two patients had a history of bronchial asthma, one patient had atopic dermatitis, and one patient had hay fever.

All nine patients had developed allergic skin reactions after orthopaedic surgeries (Table 2, Online supplemental Figure 1). Six of the nine patients had undergone hip joint surgery (artificial hip replacement surgery and acetabular rotational osteomy), whereas two and one patients had undergone a proximal femur osteotomy and splint removal, respectively.

All nine patients developed allergic skin reactions after the first and/or second

application of Dermabond. Six of the nine patients experienced ACD after the first application of Dermabond. The other three patients developed ACD after the second application. The mean time between the Dermabond application and the onset of ACD was 34.1 days (range, 27–44 days) in the six patients with ACD induced by the first application of Dermabond; of these, two patients had experienced another episode of ACD due to Dermabond 2 days after a second application, which took place during a similar orthopaedic surgery 2 years later. Thus, the duration between the application of Dermabond and the onset of ACD was much shorter following the second application compared to that following the first application. On the other hand, in the three patients who developed ACD for the first time following the second application of Dermabond, the mean duration was 5.6 days (range, 4–8 days). The duration between Dermabond application and the onset of ACD was significantly different between the group who developed ACD after the first application and those who developed ACD after the second application ($P<.01$).

Regarding the anatomical site of ACD, three of the nine patients had the allergic skin reactions localized to the surgical wound on their thigh (Table 2). In the other six patients

(66.7%), the skin eruption spread beyond the sites applied with Dermabond. Three of the six patients with secondary generalised eruption developed allergic reactions over the application site and the surrounding area. In the other three patients, the allergic eruption was distributed throughout the body areas apart from the application sites, such as the neck and upper extremities. In one of the three patients, cervical lymphadenopathy were observed after Dermabond application on the thigh. Two cases (cases 4 and 6) had used eyelash glue prior ACD due to Dermabond®, but there was no case with prior exposure to nail glue or Superglue.

PT were positivity for Dermabond in nine patients and positive to ethyl cyanoacrylate 10.0% pet. in four of the eight patients tested for it, and to 2-hydroxyethyl methacrylate (2-HEMA) 10.0% pet. in one (case 4) of the eight patients tested. In addition, seven of the nine patients (78%) had positive PT results to Aron Alpha. Furthermore, as one patient (case 4) developed a reaction to n-butyl cyanoacrylate-containing eyelash glue 1.5 years after Dermabond-induced ACD, she underwent additional PT using the eyelash glue. Consequently, she had positive PT results to the n-butyl cyanoacrylate-containing eyelash glue (D2+, D3+).

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All nine patients were patch tested with the Japanese baseline series, and six patients (cases 1, 2, 3, 4, 6, and 8) with the metal series. PT showed positive results for gold sodium thiosulfate in one patient (case 8, D2 +, D3+, D7 –), potassium dichromate in one patient (case 9, D2 +, D3++, D7 –), and nickel sulfate in one (case 3, D2 +, D3+, D7 –).

4. DISCUSSION

We identified the clinical characteristics of patients with ACD due to Dermabond® in our cohort. Among these selected cases, two-thirds had been sensitised at the first exposure to Dermabond. In these cases, the onset of dermatitis was frequently delayed to approximately 1 month after the application. In addition, more than half of the patients with Dermabond-induced ACD secondarily developed generalised eruption. In 2008, Hivnor et al reported the first case of Dermabond-induced ACD,⁶ and 11 other patients diagnosed with ACD based on positive PT results for Dermabond from other institutes have been reported (Online Supplemental Table 3).⁶⁻¹⁶ Except for one patient whose sex was not described, eleven patients were female. The age of the patients ranged from 15 to 72 years (mean, 41.4 years). Six patients underwent orthopaedic surgery; two patients

abdominal surgery; one patient breast surgery; one patient thyroid surgery; one patient varicose vein surgery; and one patient lipoma surgery. Six of the previous 12 cases developed a secondary generalised eruption (Online supplemental Figure 1). When taking into consideration the findings of the present study, Dermabond could be considered to often cause secondary generalisation. Interestingly, in all of our cases, ACD due to Dermabond occurred after the first or second application of Dermabond. In particular, the first application more frequently triggered ACD compared to the second application (Online supplemental Figure 1). Likewise, in the seven of 12 previously reported cases for whom a detailed surgical history was given, five patients experienced ACD after the first application of Dermabond; two patients after the second application. In general, an allergic skin eruption usually appears 1 to 3 days after exposure to the causative agent in those who are sensitised. ACD recurs faster (in a few days) when exposure is repeated.¹⁷ However, in our cases with Dermabond-ACD, the time between the first application and ACD onset was approximately 1 month, which was longer than that of typical ACD. When the patients experienced dermatitis again after the second operation using Dermabond, the duration was shortened to approximately 2 days, which was comparable

to the duration of typical ACD. These results indicated that monomers in Dermabond might remain unpolymerised in the dermis for approximately 1 month and consequently have the capacity to sensitise the hosts, even though Dermabond has been considered as relatively less frequently sensitising due to the rapid polymerisation immediately after contact with liquid, such as water. On the other hand, in the other two patients who only experienced Dermabond-induced ACD after the second application, the time between application and onset of ACD (mean, 5.6 days) was shorter than that in patients with ACD after the first application, but was longer than that in typical ACD. The findings suggested that, in patients who experienced ACD only after the second application, sensitisation after the first application was incomplete, and more applications would be needed to complete the sensitisation to Dermabond and induce ACD. Similarly, in the five patients in the literature for whom data were available, three developed ACD for the first time 18.7 days (range, 7–28) after the first application and two developed ACD 2.5 days (range, 2–3) after the second application.

ACD due to Dermabond was more common in women in this study and previous reports. In our study, case 4 developed dermatitis due to eyelash glue containing n-butyl

cyanoacrylate 1.5 years after the Dermabond-induced ACD. Recently, acrylate allergy has been thought to have a female predominance.¹⁸ A retrospective observational study on 241 consecutive patients who underwent PT with meth(acrylates) and cyanoacrylates showed that 16 patients (aged 14-62 years; male/female ratio of 1:15) had a positive PT reaction to a (meth)acrylate or a cyanoacrylate. Women are more likely to encounter (meth)acrylates contained in cosmetics and nail products, such as gel and acrylic nails, and consequently might co-react to (meth)acrylates. Another possible reason for the female predominance in ACD due to Dermabond might be related to the types of operative procedures they undergo. Most of our patients underwent artificial hip replacement for hip osteoarthritis, which is more common in women (male/female ratio of 1:7).¹⁹ (Meth)acrylates and cyanoacrylates do not cross-react, but there may be co-sensitisation. Female predominance is more likely due to the fact that hip replacement is more common in women, but could be due to exposure to eyelash or nail glue. Therefore, it is worthwhile to check previous use of eyelash glue. However, if the eruption after exposure to the causative reagent is late-onset, this would suggest primary sensitisation rather than elicitation.

Our study showed a potential cross-reactivity between 2-octyl cyanoacrylate and other cyanoacrylates in these patients. Ethyl cyanoacrylate was the reagent that patients most commonly reacted to, although our reagents did not include 2-octyl cyanoacrylate. Octyl cyanoacrylate is not commercially available as a patch test preparation. Cross-sensitisation between 2-octyl cyanoacrylate and ethyl cyanoacrylate is commonly recognized.^{9,16,19,20} Gonzalo-Garijo et al reported a case of Dermabond-induced ACD two days after orthopaedic surgery with sensitisation to Dermabond and ethyl-cyanoacrylate.²⁰ According to the report by El-Dars et al, a case developed Dermabond-induced ACD four weeks after the first orthopaedic surgery and had positive PT results to Dermabond and ethyl-cyanoacrylate.⁹ Liu et al presented a case of Dermabond-induced ACD, followed by ACD due to Krazy Glue (Elmers Products, Westerville, Ohio), which contains ethyl cyanoacrylate and was used in the setting of making a craft project in school.¹⁶ According to the study conducted by Cook, 13 (37%) of the 35 cyanoacrylate-allergic patients who used cyanoacrylate adhesives including Dermabond were also allergic to (meth)acrylates or acrylates.²¹ The proportion of Dermabond-allergic patients with positive PT results for octyl cyanoacrylate and ethyl cyanoacrylate was 50% and

29%, respectively.²¹ One of our patients (case 4, 12.5%) also reacted to 2-HEMA. The 2-HEMA reaction is probably due to co-sensitisation, but not cross-reaction.²²

In our patients with Dermabond-induced ACD, the prevalence of sensitisation to Aron Alpha, containing ethyl cyanoacrylate, was high (77.8%). These results confirm frequent cross-reactivity to ethyl cyanoacrylate among Dermabond-allergic patients. Case 6 had a history of ACD to Aron Alpha before the onset of ACD after the first Dermabond application. We considered that she might primarily be sensitised to the ethyl-cyanoacrylate in Aron Alpha. However, in that case, Dermabond-induced ACD occurred after a long duration (44 days) following exposure to the causative agent. Therefore, in case 6, Dermabond-induced ACD might have been due to the primary sensitisation to 2-octyl cyanoacrylate rather than the cross-reactivity to ethyl cyanoacrylate in Aron Alpha. In contrast, case 4 experienced ACD for the first time 32 days after the first application of Dermabond. Three months later, the patient had a generalized eruption one day after using Aron Alpha while crafting. Six months later, she developed dermatitis on her upper eyelids one day after her first use of a false eyelash glue containing n-butyl cyanoacrylate and acrylic resin. We suspected that in case 4 the primary sensitizer was 2-octyl

cyanoacrylate in Dermabond, and the subsequent ACD after the first use of Aron Alpha and the false eyelash glue might be due to the cross-reactivity between cyanoacrylates. Therefore, patients should be advised to avoid all cyanoacrylates.

In conclusion, our study indicated that Dermabond can lead to severe postoperative ACD, even after its first application. Even if eruptions are found approximately onemonth after the first application, Dermabond should be screened for as a causative agent of ACD. Moreover, patients with Dermabond-induced ACD should be instructed to pay attention to the possible cross-reactivity to cyanoacrylates in a wide range of products, especially, adhesives such as Aron Alpha and glue-on nail cosmetics.

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Tables

Table 1. (Meth)acrylate series and ethyl cyanoacrylate utilized in the present study

Allergen	Concentration
Methyl methacrylate	2% pet.
Butyl methacrylate	2% pet.
2-Hydroxyethyl methacrylate	2% pet.
Hydroxypropyl methacrylate	2% pet.
Ethylene glycol dimethacrylate	2% pet.
Triethylene glycol dimethacrylate	2% pet.
1,4-Butanediol dimethacrylate	2% pet.
Urethane dimethacrylate	2% pet.
Bisphenol A dimethacrylate	2% pet.
Bisphenol A glycerolate dimethacrylate	2% pet.
1,6-Hexanediol diacrylate	0.1% pet.
Tetrahydrofurfuryl methacrylate	2% pet.
Tetraethylene glycol	2% pet.
Dimethylaminoethyl methacrylate	0.2% pet.
Ethyl cyanoacrylate	10.0% pet.

Table 2. Demographic and clinical characteristics of the patients in our study

*Number of Dermabond ® application
ACD, allergic contact dermatitis; SG, secondary generalisation; Lt, left; ND, not done; Rt, right.

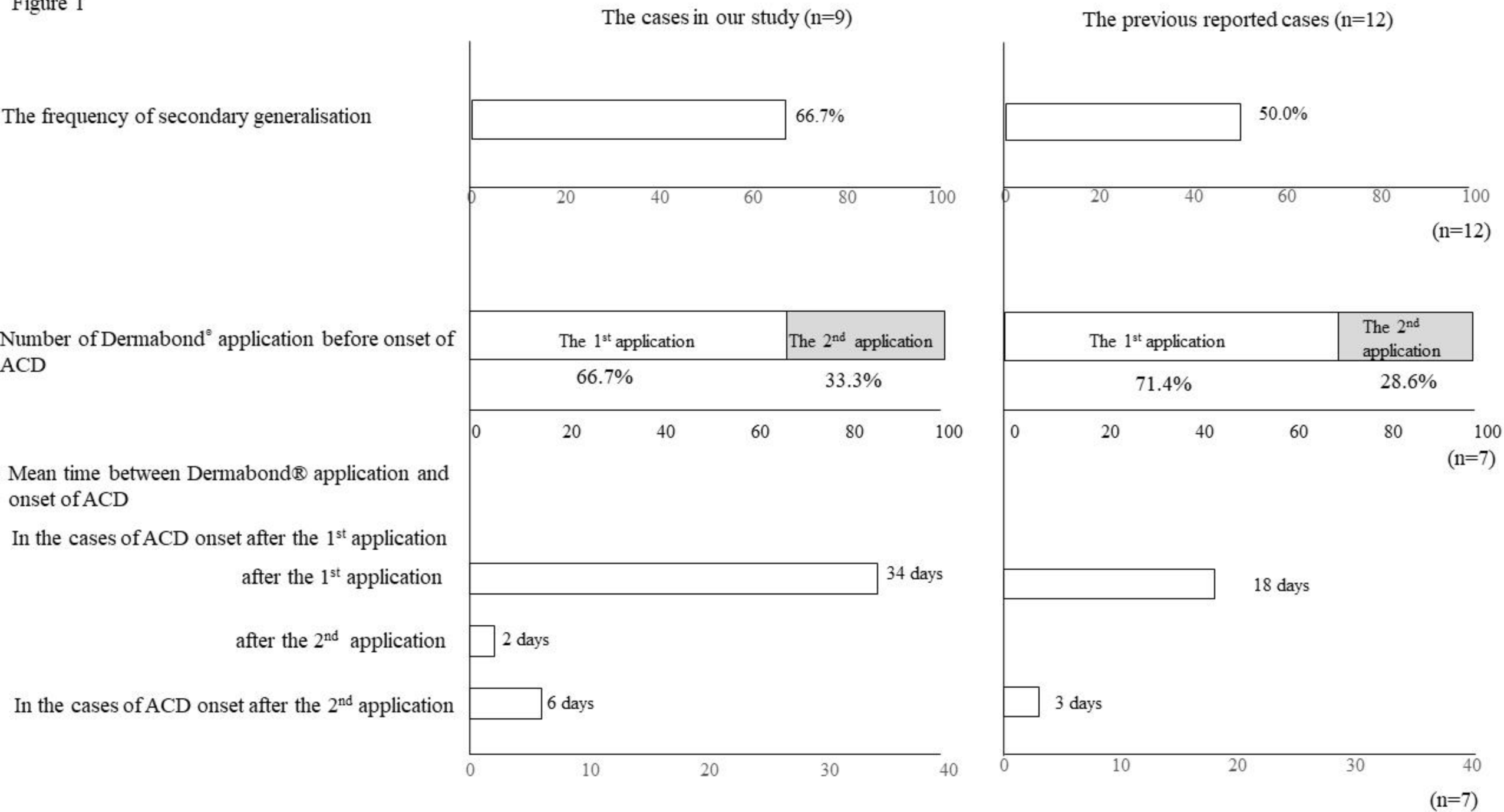
Patient No.	Sex	Age (years)	Time between application and ACD onset			Site of applied Dermabond®	Site(s) of ACD apart from applied site(s)	SG	Positive patch test results			Allergy history to products containing products acrylate
			Number of Dermabond® application before onset of ACD	Days	Dermabond®				Dermabond®	Acrylate series and ethyl cyanoacrylate	Aron Alpha®	
1	F	50	1	30	Not performed	Rt-thigh	Lower limbs Forearms	+	D2+++/D3+++	ND	-	ND
2	F	47	1	33	Not performed	Rt-thigh	Neck Lymph node	+	D2+/D3+	Ethyl cyanoacrylate	D2+/D3+	ND
3	F	23	2	Non-occurrence of ACD	8	Lt-thigh	Lower limbs Rt-hand	+	D2+/D3+	-	D2++/D3++	ND
4	F	24	1	32	2	1) † Lt-thigh 2) † Rt-thigh	None Rt-lower limb	- +	D2+++/D3+++	2-hydroxyethyl methacrylate D2-/D3-/D7+ Ethyl cyanoacrylate D2+/D3+	D2+++/ D3+++	Eyelash glue Alon Alpha + ®
5	M	16	2	Non-occurrence of ACD	5	Rt-Lt-thigh	Lower limbs	+	D2+/D3+	-	D2IR/D3++	ND
6	F	50	1	44	Not performed	Lt-thigh	Lt-lower limb	+	D2-/D3++	Ethyl cyanoacrylate D2+/?/D3+	D2+/D3++	ND
7	F	53	1	27	2	1) † Rt-thigh 2) † Lt-thigh	None None	- -	D2+/D3+	-	-	ND
8	F	76	1	39	Not performed	Lt-thigh	None	-	D2+/D3+	-	D2+/D3+	ND
9	M	71	2	Non-occurrence of ACD	4	Rt-thigh	None	-	D2+++/D3+++	Ethyl cyanoacrylate D2+/D3+	D2+++/ D3++	ND

Figure legend

Online supplemental Figure 1. The features of allergic contact dermatitis (ACD) in our cases and the previously reported cases

The frequency of secondary generalisation is 66.7% and 50% in our cases and previously reported cases, respectively. Based on the available data, ACD following the first exposure to Dermabond occurs in 66.7% and 71.4% of patients in our cases and previously reported cases, respectively. The mean time between the first application of the agent and onset of ACD is 34 and 18 days in our cases and previously reported cases, respectively.

Figure 1



Online supplemental Table 3. The previously reported cases of ACD induced by Dermabond®

Author (published year)	Sex	Age (years)	Surgery	Number of Dermabond® application before onset of ACD	Time between application and ACD onset (days)	SG	Allergy history to products containing acrylate	The (meth)acrylates and cyanoacrylates showing positivity in the patch tests
Hinvor C (2008) (6)	F	32	Abdomen	The 1 st application	Not listed	+	-	None
Dunst (2010) (7)	F	44	Breast	ND	10	-	-	None
Howard BK (2010) (8)	F	55	Abdomen	ND	7	-	-	None
El-Dars LD (2010) (9)	F	66	Orthopaedic	The 1 st application	28	+	-	Ethyl cyanoacrylate
Sachse MM (2013) (10)	F	31	Lipoma	The 1 st application	Several weeks	+	-	None
McDonald BS (2014) (11)	F	50	Orthopaedic	The 1 st application	21	+	Artificial nail (before Dermabond®- induced ACD)	2-HEMA
	F	41	Varicose vein	The 2 nd application	2	-	-	N-2-butyl cyanoacrylate
Bowen C (2014) (12)	F	33	Orthopaedic	The 1 st application	7	+	-	None
Davis MD (2016) (13)	F	72	Orthopaedic	The 2 nd application	3	-	-	Tetraethylene glycol dimethylacrylate
Lefevre S (2016) (14)	ND	30	Orthopaedic	ND	1	+	-	None
Lefevre S (2017) (15)	F	28	Thyroid	ND	1	-	-	None
Liu T (2018) (16)	F	15	Orthopaedic	ND	7	-	Krazy Glue® (after Dermabond®- induced ACD)	Ethyl cyanoacrylate

ACD, allergic contact dermatitis; SG, secondary generalisation; HEMA, hydroxyethyl methacrylate; ND, not described.