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Influence of Skin Hydration on Anesthetic Effect of Lidocaine Tape in Hemodialysis Patients

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We surveyed the current use of lidocaine tape in hemodialysis (HD) patients and evaluated the condition of their skin. Nearly 80% of them complained of pain on needle insertion, and the evaluation of their skin condition indicated that the stratum corneum moisture content was significantly lower than that of healthy volunteers. In view of this, we investigated skin hydration as a simple method of enhancing lidocaine absorption in HD patients. Skin hydration reduced the amount of pain on needle insertion in half of the 16 HD patients. It stayed about the same or increased slightly in the other half.

To examine the effect of skin hydration in more detail, we investigated lidocaine concentrations in porcine ear skin and found that the skin lidocaine concentrations were significantly increased ($8.97\pm2.44\mu g/cm^2$ vs. $24.51\pm12.26\mu g/cm^2$ after 30 min of application) by skin hydration. We feel that it could be an effective means of alleviating the pain experienced by HD patients.

Key words —— electric capacitance, hemodialysis, lidocaine, pain, skin

Introduction

Many hemodialysis (HD) patients experience much physical and mental pain associated with needle insertion before dialysis. To alleviate this, tape-type lidocaine-containing local anesthetic patches (Penles®, Wyeth K.K.) are widely used in Japan[1]. Lidocaine tape consists of a thin layer of a lidocaine-containing hypoallergenic polymer adhesive. This polymer adhesive contains a crystalline lidocaine base (18 mg per 12mg polymer) at a concentration of 60%. Although the manufacturer's recommendation is to apply the lidocaine tape to the needle insertion site for 30 min, some reports have indicated that 30 min is insufficient and it is common practice to apply the tape for longer[1,2]. Generally, the rate of transdermal drug absorption is modulated by permeation of the stratum corneum[3], and many reports have shown that HD patients exhibit a variety of dermatological symptoms, such as pruritus, xerosis, pigmentation, and erythema[4—8]. These symptoms may affect the transdermal lidocaine absorption by HD patients, but this remains unclear.

In this study, we surveyed the current use of lidocaine tape and evaluated the skin conditions in HD patients, and we also examined a method to enhance the absorption of lidocaine from the tape.

Methods

Experiment I：Hemodialysis Patients

These studies were carried out at Yokkaichi Social Insurance Hospital in Mie, Japan. All patients and healthy volunteers were recruited after local ethics committee approval and they had given their written informed consent.

1. Survey of the current use of lidocaine tape

Forty HD patients were recruited, ranging from 35 to 83 years of age (mean age ; 65.3 ± 11.2 years)；21 were male and 19 were female. Their mean duration of HD was 7.10 ± 5.60 years. The authors asked them questions about the current use of lidocaine tape. The questions involved the application time of lidocaine tape, the pain associated with needle insertion, and their complaints about skin problems due to the lidocaine tape. The pain was categorized as follows : (i)

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no pain ; (ii) slight pain ; (iii) moderate pain ; (iv) severe pain ; and (v) worst pain.

2. Evaluation of skin conditions

The skin conditions of the 40 HD patients recruited above were evaluated. The transepidermal water loss (TEWL), electrical capacitance of the skin surface, and skin surface pH were measured at the site where lidocaine tape was applied on the forearm. All measurements were performed in the following order : TEWL, capacitance, and skin surface pH. As a control group, 32 healthy adult volunteers were recruited. The characteristics of the volunteers were as follows : male : 22, female : 10, mean age : 36.7±16.0 years. They had no skin problems when these measurements were performed. TEWL, capacitance, and skin surface pH were measured at the same site as for HD patients. Subjects stayed in a room maintained at a temperature of 24−26°C and a humidity of 50−55% for 30 min, and then all evaluations were performed in the reclining position.

TEWL, which characterizes the skin water barrier function, was registered using a tewameter TM 210 (Courage+ Khazaka Electronic GmbH). A corneometer CM 825 (Courage+Khazaka Electronic GmbH) was used to register the electrical capacitance of the skin surface as an indicator of stratum corneum moisture, which is dependent on the water content and the high dielectric constant of water relative to other skin components. The skin surface pH was measured with a skin-pH-meter PH 905 (Courage+ Khazaka Electronic GmbH). All measurements were performed according to the manufacturers ' instructions.

3. Skin hydration

The influence of skin hydration on the anesthetic effect of lidocaine tape in HD patients was examined. Sixteen of 40 HD patients consented to participate in the study. The 16 HD patients recruited ranged in age from 36 to 81 years (mean age ; 60.1±13.9 years), with 8 males and 8 females, respectively. Their mean duration of HD was 5.5±4.4 years. Initially, HD patients applied lidocaine tape as usual. All of them applied the tape at home, then went to the hospital, and the pain associated with needle insertion was evaluated. One week later, they were subjected to the skin hydration method. At first, the electrical capacitance of the skin surface was measured as described above. After that, absorbent cotton soaked in distilled water at 37°C was applied for 5 min, and the electrical capacitance was registered 5 seconds after removal of the cotton. The reason why we used 37°C distilled water is that it does not irritate the skin because the water temperature is almost the same as the body temperature. Following this treatment, lidocaine tape was applied for 30 min, and then the pain was then evaluated using a numerical rating scale (NRS) (0=no pain, 10=worst painimaginable).

Experiment II : Lidocaine concentration in porcine ear skin

It is well known that there are significant similarities between porcine ear skin and human skin[9]. Porcine ears were obtained immediately post-sacrifice from a local abattoir. The skin was gently cleaned and shaved. Porcine ears were left for 30 min to stabilize, and then used for the experiment. All experiments were performed in a room at a temperature of 24−26°C and a humidity of 50−55%.

After recording the electrical capacitance of the skin surface, the porcine ears were treated with absorbent cotton soaked in distilled water at 37°C for 5 min. The capacitance was registered 5 seconds after removal of the cotton, and lidocaine tape was applied for 30 min or 120 min. As a control, the capacitance of the porcine ears was registered, and lidocaine tape was applied for 30 min or 120 min without skin hydration. After the application of lidocaine tape, all layers of skin (0.95 cm^2) were obtained from the site where lidocaine tape was applied. Skin was homogenized on ice in methanol containing methyl *p*-hydroxybenzoate as an internal standard, and centrifuged at 10,000×g for 10 min at 4 °C. The lidocaine concentration in the supernatant was measured using high performance liquid chromatography (HPLC). The HPLC system consisted of an LC−10 AS pump, and an SPD−10 Avp UV detector (Shimadzu Corp.). Separation was accomplished using a 150 mm×4.6 mm Luna 5 u C18(2) 100 Å column (Phenomenex,) and the mobile phase consisted of methanol and 10 mM phosphate buffer (pH 4.1) (35/65, v/v). The detection wavelength was 230 nm.

Statistical analysis

All results, except NRS data, were expressed as the mean ±SD, and statistical comparisons between two groups were made using Student's *t*-test. NRS data were compared using Wilcoxon's signed-ranks test. A *P* value of 0.05 or less was considered statistically significant.

Results

1. Survey of the current use of lidocaine tape

The results of the survey of the current use of lidocaine tape by HD patients are shown in **Table 1**. More than half of the patients applied lidocaine tape for 120 min or more. No one applied it only for 30 min, as recommended by the manufacturer. The median application time of lidocaine tape was 120 min. As for the pain associated with needle insertion, 21% of HD patients answered " no pain, " while the other 79% complained about pain. More than half of the patients complained about skin problems due to the lidocaine tape, such as itching, skin redness, and irritation.

2. Evaluation of skin conditions

The results of the measurements of TEWL, capacitance, and skin surface pH are shown in **Fig. 1**. The TEWL in HD patients was 10.21±3.85 g/m^2 h, and 9.34±3.11 g/m^2 h in

Table 1. Current use of lidocaine tape by hemodialysis patients

Question		Number
Application time of lidocaine tape (min)	30	0
	60	9
	90	9
	120	18
	150	3
	180	1
Pain associated with needle insertion	No pain	8
	Slight pain	22
	Pain	7
	Severe pain	2
	Worst pain	1
Complaints of patients about skin problems caused by lidocaine tape application	Itching	20
	Skin redness	11
	Irritation	1
	Skin thickening	1
	No change	18

(n=40)

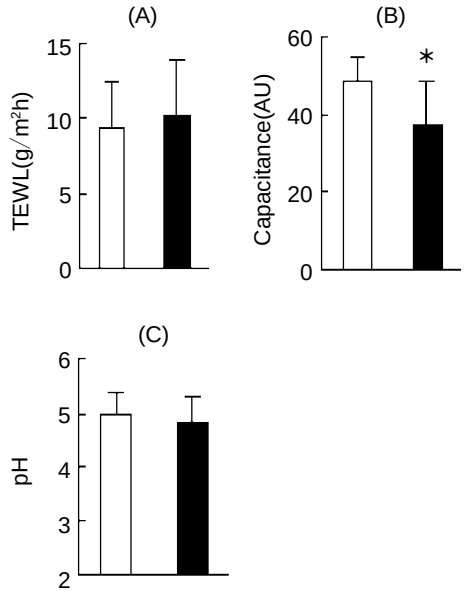

Fig. 1. Comparison of TEWL (A), the electrical capacitance of the skin surface (B) and skin surface pH (C) between healthy volunteers and HD patients. Open and filled bars represent healthy volunteers and HD patients, respectively. Each bar is a mean±SD. $^{*}P<0.05$ (*t*-test). ($n=40$)

healthy volunteers. The skin surface pH of HD patients was 4.84±0.46, compared with 4.96±0.42 for healthy volunteers. Regarding these results, there was no significant difference between HD patients and healthy volunteers. However, the capacitance was significantly lower in HD patients (37.18±11.33 AU) than in healthy volunteers (48.81±6.53 AU).

3. Influence of the skin hydration before lidocaine tape application in HD patients

The skin hydration method, application of absorbent cotton soaked in distilled water at 37°C for 5 min, was examined in HD patients. The electrical capacitance of the skin surface was registered before and after skin hydration (**Fig. 2**). The capacitance increased significantly with skin hydration (before hydration ; 32.32±7.18 AU, and after hydration ; 94.61±14.38 AU). The pain after application of lido-

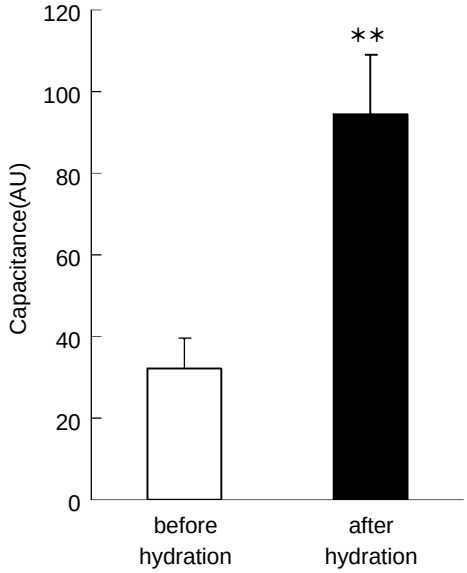

Fig. 2. Changes in the electrical capacitance in hemodialysis patients. Open and filled bars represent before and after skin hydration, respectively. Each bar is a mean±SD. $^{**}P<0.01$ (*t*-test). ($n=16$)

caine tape for 30 min with skin hydration was compared with that after the normal procedure (**Fig. 3**). The median of the NRS was 2 for the normal procedure, and 3.5 for the 30 min application with skin hydration, and a comparison showed no significant differences between them. Half of the patients reported an improvement when the tape was applied for 30 min with skin hydration compared with the normal procedure, and the remaining half of them reported no change or a slight increase.

4. Lidocaine concentration in porcine ear skin

The skin hydration method was examined using porcine ear skin. The electrical capacitance of the skin surface was registered before and after skin hydration (**Fig. 4**). The capacitance increased significantly with skin hydration (before hydration ; 40.52±8.01 AU, and after hydration ; 83.32±13.07 AU). **Fig. 5 a** shows the lidocaine concentration, with or without skin hydration, at each lidocaine application time in porcine ear skin. When lidocaine tape was applied for 30 min without hydration, the lidocaine concentration in skin was 8.97±2.44μg/cm^2, against 24.51±12.26μg/cm^2 with hydration. When lidocaine tape was applied for 120 min without hydration, the lidocaine concentration in skin was 22.78±6.71μg/cm^2, and it was 32.78±5.20μg/cm^2 with hydration. The lidocaine concentration in skin increased significantly with skin hydration for each application time. Furthermore, the capacitance before application of lidocaine tape correlated with the lidocaine concentration in skin. For the 30 min and 120 min application of lidocaine tape, the correlation coefficient was 0.758 (data not shown), and 0.810, respectively (**Fig. 5 b**).

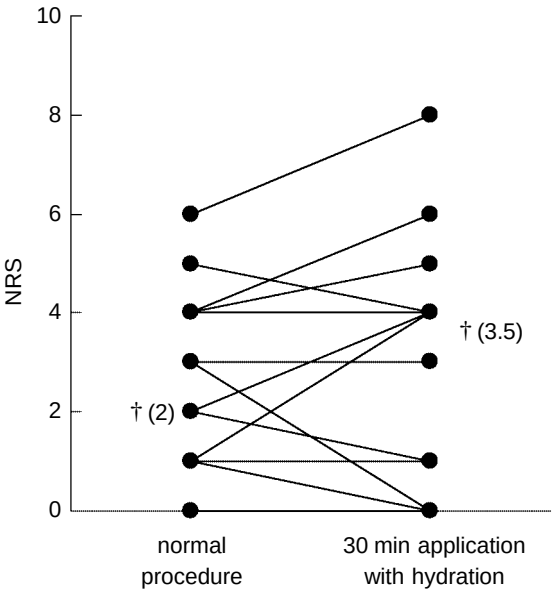

Fig. 3. Numerical rating scale of pain associated with needle insertion, with the normal application of lidocaine tape and a 30-min application with skin hydration. Individual data (●) are linked by the line. $^*P<0.05$ (Wilcoxon's signed-rank test). (n=16)

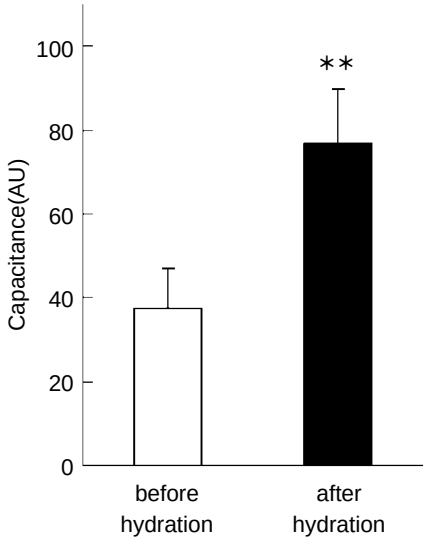

Fig. 4. Changes in the electrical capacitance of porcine ear skin. Open and filled bars represent before and after skin hydration, respectively. Each bar is a mean±SD. $^{**}P<0.01$ (*t*-test). ($n=10$)

Discussion

In our survey of the current use of lidocaine tape, HD patients applied it for about 120 min, and other reports showed the same results[1, 2]. In addition, nearly 80% of them complained about pain associated with needle insertion, and more than half of them complained about skin problems due to the tape. These complaints about skin problems were not diagnoses made by a doctor but subjectively-assessed symptoms by patients, and may include chronic reactions attributable to lidocaine tape (for example, skin thickening) or problems which are not attributable to the tape. However, it has been reported that application of lidocaine tape for a long period leads to skin problems such as pruritus and erythema[10]. In consideration of these results, methods are needed to increase the anesthetic effect of lidocaine tape over a short period. Many methods have been investigated to enhance the transdermal delivery of lidocaine, for example, skin pretreatment by tape stripping or benzene, ultrasound, electroporation, and iontophoresis[11–14]. We focused on the particular skin condition HD patients to enhance the transdermal delivery of lidocaine, because the rate of transdermal drug absorption is modulated by permeation of the stratum corneum[3] and HD patients exhibit a variety of dermatological symptoms[4–8]. As a result, the electrical capacitance of the skin surface was found to be significantly lower in HD patients than in healthy volunteers. The group of healthy volunteers was much younger than the HD patients (36.7±16.0 years vs. 65.3±11.2 years) in our study, and the electrical capacitance is known to be generally affected by age. However it did not correlate well with age in our study, and the same trend has been observed in another report[15]. The dry skin exhibited by HD patients may be caused by not only age but also other factors which are specific to HD

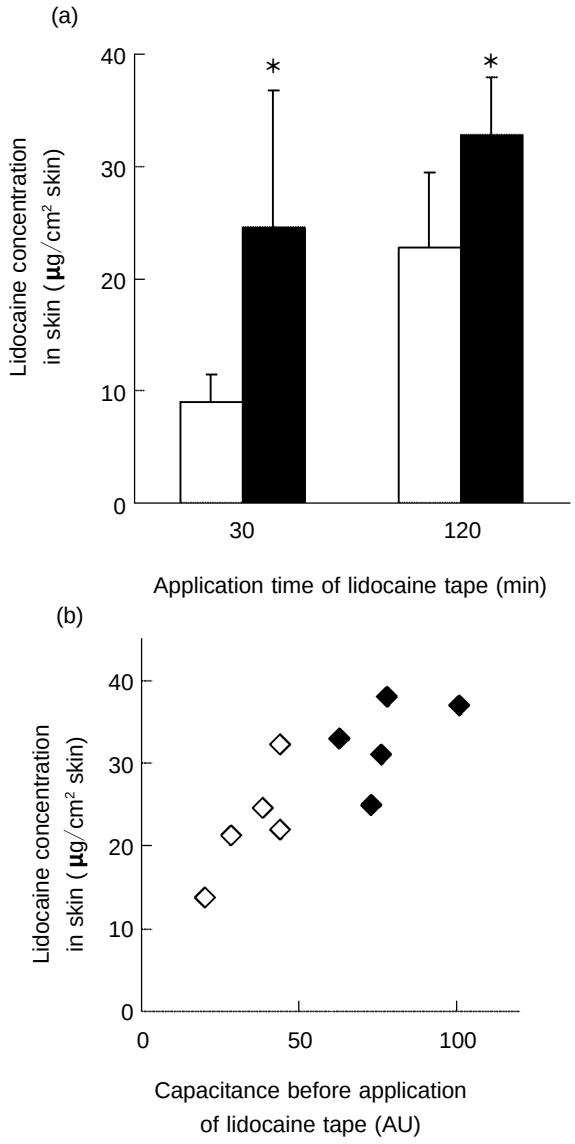

Fig. 5. (a) Influence of skin hydration on the lidocaine concentration in porcine ear skin after each application time of lidocaine tape. Open and filled bars represent the lidocaine concentration with no treatment and skin hydration, respectively. Each bar is a mean±SD. $^{*}P<0.05$ no treatment versus skin hydration (t-test) ($n=5$ in each)
(b) The relation between the capacitance before application of lidocaine tape and the lidocaine concentration in skin at 120 min. Open and filled squares represent the individual lidocaine concentration data with no treatment and skin hydration, respectively.

patients. It is conceivable that the low electrical capacitance of the skin surface in HD patients affects the transdermal absorption of lidocaine. Water is the most widely used and safest method to increase skin penetration[16–19], and previous reports have shown that the skin permeation of some drugs is enhanced by increasing the stratum corneum moisture. The skin permeation of steroids and salicylic acid was enhanced by increasing the stratum corneum moisture with vehicles[20], wet nicotine patches increased skin moisture in proportion to the exposure time, and the permeation of nicotine was increased for hydrated skin[21]. Arai et al. reported that applying a steamed towel for 5 min enhances the anesthetic effect of lidocaine in healthy adults[22]. We examined a 30 min application with the skin hydration method in HD patients expecting it to be at least as effective as the usual long application. In terms of the pain scale results, pain associated with needle insertion was reduced in half of the 16 HD patients, but remained unchanged slightly increased in the others. Some factors may contribute to these results. This study was not a double-blinded design, and so it is possible that the patients were biased, as pain is a subjective sensation. Also, the nurse who inserts the needle may make a difference. The influence of skin hydration on the anesthetic effect of lidocaine is not clear as far as these factors are concerned.

To examine the influence of skin hydration in more detail, we investigated the lidocaine concentration in porcine ear skin. We found that the lidocaine concentration in skin increased with skin hydration, and a good correlation was observed between the capacitance before the application of lidocaine tape and the lidocaine concentration in skin. There may be a number of factors responsible for the increased lidocaine concentration in skin. Some reports have described the effect of water on the intercellular membrane, such as an increase in the fluidity and extensive disruption of lipid lamellae[23]. This alteration in the intercellular membrane might enhance the permeability of the skin and the transdermal absorption of lidocaine.

In conclusion, the skin hydration method which is simple and easy, only applies water to the skin, and is non-invasive from the clinical point of view, is extremely useful to treat pain associated with needle insertion in HD patients. Further investigations are needed to obtain a more anesthetic effect of lidocaine tape using this method.

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