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Original Article

Randomized controlled study evaluating the efficacy of different lidocaine preparations to manage arteriovenous fistula puncture site pain in patients undergoing hemodialysis

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Abstract: Objective: We aimed to observe the analgesic efficacy of lidocaine to manage arteriovenous fistula (AVF) puncture site pain. Methods: We studied 120 patients with AVF puncture site pain who were randomly divided into 4 groups: the cream group (A), the spray group (B), the wet compression dressing group (C), and the control group (D). The visual analogue scale (VAS) pain score, puncture success rate, analgesic onset time, degree of patient satisfaction, and adverse reactions were compared between the 4 groups. Results: The percentage of the VAS pain score in group A (26.67%) was lower than in group B (33.33%) and group C (40.00%), and the values observed in all 3 groups were lower than in group D (100%). A significant difference in the degree of pain was observed between the 4 groups (χ^2 = 25.595, P < 0.001). Results in group A were better than in group B, C, and D; however, there was no significant difference observed in the post-intervention AVF puncture success rate between the 4 groups (χ^2 = 3.00, P = 0.392 > 0.05). The analgesic onset time in group B (6.90±2.54 min) was statistically shorter than in group C (10.00±2.58 min) and group A (55.78±19.98 min). The degrees of patient satisfaction in group A (96.67%), B (90.00%), and C (90.00%) were higher than in group D (63.33%) (Fisher exact test = 13.053, P = 0.003), and the value observed in group A was significantly higher than that observed in group D (χ^2 = 10.417, P = 0.002 < 0.0083). Conclusions: We observed that the 3 dosage forms of lidocaine studied can be effectively used to manage AVF puncture site pain. We observed that the cream preparation showed a slower onset of action, but a better analgesic effect, and the spray preparation showed a much more rapid onset of action.

Keywords: Lidocaine, hemodialysis, arteriovenous fistula, puncture pain

Introduction

Hemodialysis (HD) is one of the major renal replacement therapies used for the management of patients with end-stage renal disease (ESRD) [1]. Establishment of an ideal vascular pathway is a prerequisite for successful HD, which forms the "lifeline" of HD patients. Relatively simple to operate, with a long-term patency rate, and fewer complications, an arteriovenous fistula (AVF) is a low-cost option that has gained wide clinical acceptance [2]. The Kidney Disease Outcomes Quality Initiative issued by the National Kidney Foundation, USA strongly recommends the use of long-term HD vascular access [3]. However, to ensure adequate blood flow in patients, AVF puncture requires use of specific intravenous puncture needles (16G-18G), which are several times thicker than needles routinely used for intravenous injections. Moreover, such patients need to undergo HD twice or thrice a week, or approximately 300 times a year, which can seriously affect their physical and mental health [4]. The

physiological-psychological stress associated with this regular puncture affects patients' comfort levels leading to fear, anxiety and/or depression [5], can reduce treatment compliance [6], and is negatively correlated with patients' quality of life [7]. Therefore, the physical and psychological pain and stress related to AVF puncture in HD patients needs urgent attention for better intervention and management.

Reportedly, current interventional studies pertaining to AVF puncture-related pain primarily describe 2 approaches: use of drug-intervention and non-drug intervention modalities. Because AVF puncture is a highly aggressive invasive technique, use of drug analgesia remains an important pain management approach in patients with severe degrees of pain or those with greater pain sensitivity (lower pain thresholds). Clinically, topical analgesics commonly used for AVF puncture site pain are lidocaine and its preparations, tetracaine, and benoxinate gel, among others. Of these, lidocaine and its preparations are more commonly used. A review of Chinese and English literature databases has revealed that commonly used lidocaine preparations and other medications are primarily used as topical preparations such as compound lidocaine cream [8] or Emla cream [9], 7% lidocaine spray [10], application of a wet warm dressing of 2% lidocaine [11], and lidocaine cream combined with other non-drug therapies such as relaxation training [12-14]-all modalities demonstrating variable efficacy against AVF puncture site pain.

In summary, different preparations and application methods of lidocaine in China and abroad have demonstrated varying efficacy in reducing AVF puncture site pain in patients undergoing HD. Following extensive literature review and analysis, we observed that 60-min application of compound lidocaine cream, wet-dressing using 2% lidocaine HCl, and the use of 7% lidocaine HCl spray are the more commonly used modalities in current domestic clinical practice. However, such methods have their own advantages and disadvantages. For example, although compound lidocaine cream shows positive effects, it shows a slow onset of action, 2% lidocaine combined with other drugs shows a rapid onset of action, although some researchers have reported cases without the desired effects due to the possible role of the skin barrier [15]. Related research designs have not been randomized and blinded. Additionally, these studies have involved small sample sizes and used variable evaluation tools; thus, the efficacy of various methods cannot be conclusively validated, and these studies cannot provide a reliable basis for the use of these agents in clinical practice. Our study aimed to investigate the following: A) Which among the 3 types of lidocaine preparations provides the best analgesia for the management of AVF puncture site pain? B) Which among the 3 types of lidocaine preparations provides the most rapid onset of analgesia? C) How do the 3 lidocaine preparations compare with each other in terms of their success rate in relieving AVF puncture site pain? D) How do the 3 lidocaine preparations compare with each other in terms of patient satisfaction with respect to their analgesic effect?

Therefore, based on a comprehensive balance, sampling convenience, economics, and application safety, this study used a multi-center randomized controlled trial to observe and compare the effects of the 3 methods of lidocaine use mentioned above, for the management of AVF puncture site pain. Moreover, we studied the differences between these approaches with respect to the time of onset of action, safety profile, puncture success rate, and nurse satisfaction, aiming to identify an optimal drug for the management of AVF puncture site analgesia, which requires urgent attention to alleviate AVF puncture site pain in patients undergoing HD.

The specific analysis is as follows:

Materials and methods

Subjects

We selected 120 patients who underwent an AVF procedure prior to HD at the Blood Purification Center of a Level 3 Grade-A hospital between July 2015 and June 2016. Inclusion criteria: ① patients who could undergo regular AVF puncture for maintenance HD thrice per week, ② patients who did not undergo a change in the dialysis pattern in the previous 3 months, ③ patients aged 18-78 years, ④ those without skin lesions, scars, or allergy at the puncture site, ⑤ those without concomitant ongoing pains, those who did not use other related anal-

Table 1. Comparison of general info among the four groups (n, $\bar{x}\pm s$, n = 90)

Group	Gender		Age (years)	Dialysis duration (moth)	AVF application time (month)				VAS (n)			
	M	F			< 6	6~12	13~36	> 36	Mild	Moderate	Severe	Intense
A	22	8	55.00±12.81	20.10±10.08	9	7	12	2	2	11	15	2
B	23	7	52.07±13.36	22.38±11.12	9	7	9	5	3	12	12	3
C	21	9	53.40±14.39	27.27±13.84	8	8	7	7	2	11	16	1
D	22	8	53.52±13.27	21.70±10.35	9	7	7	7	2	13	13	2

gesics or participate in other related experimental studies, ⑥ those without history of allergy to the test drugs, ⑦ and those patients who voluntarily signed the informed consent and participated in the test. Exclusion criteria: ① patients who demonstrated pain other than puncture-site pain, ② critically ill patients, ③ those using other related analgesics or participating in other experimental studies, ④ those allergic to the test drugs, ⑤ those with skin scars, injuries, or skin allergy at the puncture site, or hyperalgesia, ⑥ those who could not communicate properly, ⑦ and those who did not participate voluntarily and/or provide informed consent. Withdrawal criteria: patients who died during the study, those who switched the treatment methods used, those who demonstrated very strong drug responses and could therefore no longer continue participating in the study, those transferred to other hospitals, or initiatively required withdrawal during the study. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan provincial hospital of traditional Chinese medicine. Written informed consent was obtained from all participants.

Grouping

Patients enrolled in the study were randomly divided into 4 groups-group A: those in whom compound lidocaine cream was applied for 60 min, group B: those in whom 7% lidocaine hydrochloride spray was used, group C: those in whom 2% lidocaine hydrochloride wet compression dressing was applied, and group D: those in whom a saline wet compression dressing was applied (the control group). Each group comprised 30 patients, and there was no statistically significant difference between the groups in terms of baseline data such as age, gender, degree of pain, dialysis duration, or AVF application time ($P > 0.05$) (**Table 1**).

Medication methods

Based on the HD procedures used, each patient was explained the purpose and significance of the puncture prior to initiating treatment, and a good nurse-patient relationship was simultaneously established. Each patient was placed in a comfortable position prior to the puncture and carefully assessed to select an appropriate blood vessel to obtain vascular access. The 4 groups were treated in the following manner. Group A: Lidocaine cream was applied to the puncture site approximately 60 min prior to HD. The amount of cream application was approximately 5 cmm in diameter, and the thickness of the cream application was approximately 2 cm (equal to the thickness of ¥1 coin). The dosage used was 1.5-2.0 g/10 cm^2, and the site was covered using a thin film after the application. The skin at the site of application was firstly thoroughly cleaned prior to the puncture, followed by routine procedures used for the creation of an AVF for HD. Group B: the 7% lidocaine aerosol spray was sprayed onto the puncture site twice consecutively such that the total dose delivered was 9 mg (4.5 mg each spray), and the site was disinfected and punctured 7 min later based on the procedures used in group D patients. Group C: A 2% lidocaine HCl wet dressing (8 × 10 cm, at 40°C, the whole dressing was completely soaked but not dripping) was placed on the puncture site, followed by maintaining warmth over the site and fixation using an extra towel. The site was disinfected and punctured 7 min later based on the procedures used in group D patients. Group D: a saline wet dressing of an appropriate size was placed on the puncture site 10 min prior to the puncture (8 × 10 cm, the whole dressing was completely soaked but not dripping), and the patients underwent a puncture using the conventional method 5 min later. An electrocardiogram, blood pressure, and blood oxygen saturation prior to dialysis were continually

monitored in all patients to identify possible adverse effects. All patients were trained regarding the method of pain assessment. The skin over the puncture site was prepared and disinfected in a routine manner, and the puncture was completed by specifically trained staff using the rope ladder method, which was the only puncture method used in all patients after which the cannulation site resembled a rope ladder. The site should be changed for each AVF puncture to avoid repeated needling at the same site. The puncture angle was > 40° and the needle was fixed after puncturing the skin. During the puncture procedure, attention was paid to patients' complaints for psychological comfort. The degree of pain reported by patients and local skin reactions were assessed 30 min later with simultaneous attention to the general condition of patients. We avoided bias in the study by assigning one staff member to prepare all the drugs in this study, assigning another for the administration of drugs, and one nurse for pain and adverse reaction assessment. These 3 staff members were blinded to patient information, and only the study designer was aware of the groupings. The 2% lidocaine used for our study was manufactured by Chongqing Taiji Pharmaceutical Co., Ltd. China, and the compound lidocaine cream used was manufactured by Tsinghua Unispharm Co. Ltd. China, State Medical Approval No: H20063466.

Observation indices

The visual analogue scale (VAS) score, AVF puncture success rate, the degree of patient satisfaction, as well as adverse reactions observed among the patients from the 4 groups were recorded and compared at the end of the AVF puncture. ① VAS scoring criteria used were [16]: 0 points, no pain; 1-3 points, mild pain; 4-6 points, moderate pain; 7-9 points, severe pain; and 10 points, intense pain. The proportion of patients with pain = (total number of patients-number of patients without pain)/total number of patients. ② Criteria for successful AVF puncture were [17]: no subcutaneous congestion or hematoma at the puncture site, no pain or discomfort reported by the patient, a satisfactory arterial blood flow meeting the requirements of HD (180-250 mL/min), and smooth functioning of the dialysis machine (no sounding of the dialysis machine alarm). The AVF puncture success rate was defined as the ratio of patients with successful AVF puncture to the total patients in each group, respectively. ③ Safety indices evaluated were skin manifestations of pallor, erythema, edema and pimples, blisters, or erosion. Patients were also assessed for a subjective feeling of burning, tingling, or other sensations in addition to systemic adverse reactions or related signs and symptoms [18]. ④ The best analgesic onset time was defined as the period from the time of puncture to the time of complete disappearance of pain. ⑤ The degree of patient satisfaction was designed by the researchers to include such parameters as patients' satisfaction with analgesia, analgesic onset time (rapidity of analgesic action), ease of operation, and economics. These were graded as unsatisfactory, basically unsatisfactory, basically satisfactory, satisfactory, and very satisfactory. This study assessed and described the overall evaluation of analgesic effects described by patients.

Medical ethics:

(1) Informed consent from patients: all patients were explained in detail the purpose of the trial and possible adverse reactions, and other issues prior to their participation in the trial. All patients were required to sign informed consent prior to proceeding with the further steps in the study.

(2) This study was approved by the hospital ethics committee.

(3) Safety of medications used: We confirmed that no serious adverse reactions have been reported with use of compound lidocaine cream based on our review of a large volume of related literature and clinical pre-testing results shown by different studies.

(4) Patient rights: All patients could terminate the trial at any stage. We declare that the relevant case data obtained from this study will be maintained by an authorized person (the person in charge).

Statistical analysis

The SPSS 19.0 software was used to establish the database for analysis. General data were analyzed using descriptive statistical analysis such as ratios and percentages with countable data, and the mean ± standard deviation was used to obtain the mean value for measure-

Table 2. Comparison of post-intervention VAS pain degrees among the four groups (n/%, n = 90)

Group	n	Painless	Mild pain6	Moderate pain	Severe pain	Intense pain	Pain ratio	χ^2	*P*
A	30	22	8	0	0	0	26.67%	25.595	0.000
B	30	20	10	0	0	0	33.33%		
C	30	18	12	0	0	0	40.00%		
D	30	0	3	15	11	1	100%		

Table 3. Comparison of AVFP success rate among the four groups (n = 90)

Group	n	One-step success	Multi-step success	Success rate (%)	χ^2	P
A	360	350	10	97.22	3.00	0.392
B	360	342	18	95.00		
C	360	338	22	93.88		
D	360	337	23	93.61		

Table 4. Comparison of puncture satisfaction among the four groups (n/%, n = 90)

Group	n	Satisfactory	Unsatisfactory	Satisfactory degree	Fisher	*P*
A	30	29	1	96.67%	13.053	0.003
B	30	27	3	90.00%		
C	30	27	3	90.00%		
D	30	19	11	63.33%		

ment data. The χ^2 test was used for analysis of the general data, AVF puncture success rate, and comparison of post-intervention VAS pain scores between the 4 groups. Puncture satisfaction between the 4 groups was compared using the Fisher exact test. The one-factor analysis of variance (ANOVA) test was used to compare the analgesic onset time between the 3 groups and identify the medication with the best (most rapid) analgesic onset time. P < 0.05/0.0083 was considered a statistically significant value.

Results

Comparison of post-intervention pain

No patient was lost to follow-up after the intervention. We observed a significant difference in the degree of pain reported by patients among the 4 groups (χ^2 = 25.595, *P* < 0.001). Pairwise comparison, one-factor ANOVA, and Student-Newman-Keuls (SNK) analysis revealed statistically significant differences between the 4 groups (Fisher test [*F*] = 10.596, *P* < 0.001). Furthermore, group A, B, and C were observed to show better results than those observed in group D, and the results observed in group A were better than those observed in group B, C, and D. We observed no statistically significant difference between group B and C (**Table 2**).

Intergroup comparison of arteriovenous fistula puncture success rate

We observed no significant difference in the post-intervention AVF puncture success rate between the 4 groups (χ^2 = 3.00, *P* = 0.392 > 0.05) (**Table 3**).

Intergroup comparison of puncture satisfaction

To facilitate the intergroup comparison, this study unified "unsatisfactory" and "basically unsatisfactory" as "unsatisfactory", and "basically satisfactory", "satisfactory", and "very satisfactory" as "satisfactory". We observed statistically significant differences in the degrees of overall satisfaction between the 4 groups (Fisher = 13.053, *P* = 0.003). Further pairwise comparison revealed that the degree of satisfaction observed in group A was significantly higher than that in group D (χ^2 = 10.417, *P* = 0.002 < 0.0083) (**Table 4**).

Intergroup comparison of the best analgesic onset time (analgesic showing the most rapid onset of action)

The one-factor ANOVA test showed overall statistically significant differences between the A, B, and C groups in terms of the analgesic onset time (*F* = 163.519, *P* < 0.001). The SNK pairwise comparison revealed that the analgesic onset time in group B was better than that observed in other groups (*P* < 0.001) (**Table 5**).

Adverse reactions

No patient in this study showed any local pallor, erythema, pimples, or other adverse reactions.

Table 5. Comparison of the best analgesic onset time among the three groups (min, $\bar{x}$ ±s, n = 90)

Group	n	Time	*F*	*P*
A	30	55.78±19.98		
B	30	6.90±2.54	163.519	0.000
C	30	10.00±2.58		

Additionally, no patient complained of burning, tingling, or itching, and no systemic adverse reactions were observed in any patient.

Discussion

Iatrogenic pain in patients undergoing HD is primarily attributable to AVF puncture site pain. These patients frequently report pain and discomfort during the AVF puncture procedure; thus, attempts to alleviate such pain can improve their acceptance of the procedure and their quality of life [19]. Therefore, expanding efforts directed toward better pain management in these patients will be conducive to improving their overall quality of life, and also constitute an important aspect of people-oriented nursing work. Although presently, several interventions have been used to manage AVF puncture site pain, greater efforts would be needed to adopt painless approaches directed toward achieving humanistic patient care, and drug intervention plays a key role in this regard in clinical practice. Several previous studies have shown that lidocaine demonstrates a wide range of applications in AVF puncture site analgesia. Therefore, researching and exploring the efficacy and suitability of individual drugs with better analgesic effects and easier modes of application/administration is the focus of current research.

This study achieved its purpose in that it confirmed the efficacy of lidocaine spray, lidocaine solution dressing, and compound lidocaine cream application as a therapeutic option for AVF puncture analgesia. Compound lidocaine cream was observed to show better analgesic effects, lidocaine spray is easier to apply, acts faster, and demonstrates definite beneficial analgesic effects, leading to better acceptance by nurses and patients. Additionally, the difference in the puncture success rate between the 3 methods was not observed to be statistically significant.

The specific analysis is as follows:

Compound lidocaine cream is an amide-type local anesthetic. It contains the short-acting anesthetic 2.5% lidocaine with its rapid onset of action and the intermediate-acting anesthetic 2.5% pramoxine that lasts longer. Thus, this drug is a compound containing a short- and an intermediate-acting anesthetic such that both components can achieve synergistic effects and thereby offers the advantage of a rapid onset and longer duration of action. This product containing a combination of these 2 drugs can be quickly absorbed by the skin and is released 5 mm under the skin through the base form, thereby acting on the cutaneous pain receptors and nerve endings to achieve anesthesia [20]. Reportedly, the analgesic effect of this drug is better 1 h after administration, and the analgesic effect achieved after 2 h of application can be maintained over 4-5 h. Compared to an injectable formulation, the cream is more convenient to apply, painless, and therefore associated with a higher compliance rate. Presently, this drug has shown increasingly wide application and acceptance in patients undergoing various invasive operations [21] and has also demonstrated beneficial effects in providing AVF puncture analgesia in patients undergoing HD [22]. This study showed that the analgesic effect of compound lidocaine cream is more effective in preventing AVF puncture pain, although no statistical significance was observed when compared with 7% lidocaine spray and 2% lidocaine wet compression dressing, similar to results of previous studies [10].

The results of this study showed that no statistically significant difference was observed in the degree of satisfaction reported with use of the four preparations. A possible explanation could be that the degree of satisfaction is based on a comprehensive evaluation that combines multiple indices such as analgesic effect, analgesic onset time (rapidity of onset), ease of operation/use, and economics. Combined with the clinical and experimental results, as well as the convenience of operation and economic considerations [23], most patients will choose to use a spray. Usually, a lidocaine spray is used to reduce the incidence and severity of postoperative sore throat because reportedly, local anesthetics can significantly

reduce inflammation and tissue damage and are frequently used in patients experiencing difficult esophageal intubation [20]. The lidocaine spray is directly sprayed locally on the skin and/or mucous membrane. It generates a local anesthetic effect by inhibiting the ionic waves required for the generation and conduction of excitement. This dosage form is easy to use, non-invasive, diffuses widely and easily with strong permeability, and causes no stimulation of local tissue [24]. The dosage delivered through one spray is 4.5 mg, and the drug is sprayed in the form of a mist to ensure that the amount of medication delivered per spray is accurate and easy to control, which ensures higher safety than is associated with lidocaine cream and lidocaine wet (Mace, 2017 #65) dressing [25]. This study showed that in terms of AVF puncture success rate, no statistically significant differences were observed between the 4 groups, which may be related to various factors that are known to cause puncture-related pain. Although this study unified the puncture operator and used the rope ladder method of puncture to avoid bias, several factors affect puncture-related pain, combined with large individual differences in pain [12]. We reckon that further studies comprising a larger sample size are needed to validate results.

In terms of the analgesic onset time, our results showed that the analgesic onset time in the spray and wet dressing groups was significantly shorter than in the compound cream group indicating that these 2 preparations demonstrate a more rapid onset of action in clinical practice. A lidocaine spray is easy to use and is more convenient; therefore, it is more easily and widely accepted by patients and nurses, which is also suitable in situations of nursing staff shortage.

In conclusion, our study showed that lidocaine and its various preparations demonstrate positive effects in managing AVF puncture site pain. Compound lidocaine cream shows better analgesic effects, lidocaine spray is easier to use, acts faster, and also shows positive analgesic effects, leading to wider acceptance by nurses and patients. Additionally, the difference in the puncture success rate between the 3 methods evaluated was not statistically significant. The study achieved its purpose in that it confirmed that lidocaine spray, lidocaine solution dressing, and compound lidocaine cream can be used for local application to manage AVF puncture site analgesia. It provides a clinical basis for effective pain management in patients with AVF puncture site pain and focuses on a humane approach to the management of HD patients. Comprehensive evaluation suggests that individualized analgesic measures and drugs should be rationally selected based on not only their analgesic effects but also considering patients' individual feelings and opinions to minimize patients' suffering and maximize their comfort. This can conform to the current concept of multi-modal analgesia and individualized analgesia, which represent the best embodiment of humanistic services.

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Disclosure of conflict of interest

None.

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