

# Effectiveness of the Eutectic Mixture of Local Anaesthetics Cream in the Management of Arteriovenous Fistula Needle Insertion Pain in Patients Undergoing Haemodialysis

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**ABSTRACT:** This review aimed to assess the effectiveness of the eutectic mixture of local anaesthetics (EMLA) cream in the management of arteriovenous fistula (AVF) needle insertion pain in adult patients undergoing haemodialysis (HD) compared with other alternative interventions. The main search was conducted in November 2020 and updated in December 2021. In the search strategy, keywords and synonyms were used and multiple databases were searched with no date limitation to ensure a comprehensive search that would yield all studies relevant to the review and minimise location bias. A total of 209 studies were found in this search and filtered. After filtering through these studies, only five studies were finally included in the review. EMLA-cream was found to be effective in reducing AVF needle insertion pain among adult patients undergoing HD. Despite EMLA cream's effectiveness in reducing HD needle insertion pain and its fewer side effects, the findings of the included studies should be interpreted with caution, as there are some limitations, and further research is required.

**Keywords:** EMLA Cream; Pain; Dialysis; Arteriovenous Fistula.

ARTERIOVENOUS FISTULA (AVF) IS A MAJOR requirement for a good haemodialysis (HD) session. Aghbolagh *et al.* reported that 80% of HD patients experience moderate-to-severe pain during AVF needle insertion but do not receive pain relief.<sup>1</sup> These patients undergo AVF needle insertion two to three times per week, which is often their greatest concern during HD treatment.<sup>2</sup> This struggle with pain often causes patients despair and frustration and may cause them to abscond from treatment.<sup>3–5</sup>

The eutectic mixture of local anaesthetics (EMLA) cream is a mixture of lidocaine (25 mg/g) and prilocaine (25 mg/g). It is the preferred local anaesthetic and can be easily used by the patients themselves.<sup>6</sup> The EMLA cream blocks both active and inactive sodium channels, inhibiting the conduction of stimuli and reducing pain transmission.<sup>6</sup>

HD is a painful process for patients with renal failure. However, the ability to adapt to the pain psychologically varies among individuals. A study by Jeon *et al.* found that female patients experience a greater pain dimension than their male counterparts.<sup>7</sup> According to Brkovic *et al.*, the pain associated with AVF needle insertion should be considered a health issue.<sup>8</sup> Hence, the nephrology community needs to promote this as a clinical research priority to improve the HD patient's quality of life and pain-related disability.

Despite the diverse pain management and control methods developed in the past few decades, local anaesthetic therapy is the most adopted method due to patient perceptions, its ease of use and availability of several options. In addition to having chronic renal problems, HD patients also face some related health issues, including insomnia, anxiety and depression. According to a study by Davison and Jhangri, these three issues may increase the degree of pain sensation HD patients feel during AVF needle insertion.<sup>9</sup> Therefore, the practical implication of a local anaesthetic is to improve compliance despite the pain generated during the venipuncture process.<sup>7,9</sup>

The EMLA cream is a mixture of two substances (lidocaine and prilocaine) and was commercialised in 1984 as a non-invasive intervention. It is available as a cream, patch or spray and is widely used during medical procedures such as venipuncture, laser therapy, skin biopsy, lumbar puncture, vaccination, cryosurgery and intradermal testing.<sup>7,10</sup>

To date, no systematic review specifically addresses the effectiveness of EMLA cream in managing AVF needle puncture or insertion pain in adult HD patients. A study was conducted comparing the efficacy of EMLA cream with that of local infiltration anaesthesia in pain reduction during vaginal delivery. That study reviewed four studies, with a total of 348 patients (173 in the EMLA group and 175 in

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the conventional local infiltration anaesthesia group) undergoing perineal repair after vaginal delivery. They found that EMLA cream helped to reduce pain during perineal repair after vaginal delivery with a success rate of 95%.<sup>11</sup>

Regarding current interventions for pain management in HD, there are a few strategies, such as the EMLA cream, lidocaine spray or tape, vapocoolant spray and piroxicam cream, which may be used to reduce and relieve patients' pain during needle insertion and persuade them to continue HD treatment.<sup>4</sup> However, some studies have shown that without such pain relief intervention, HD patients' quality of life may be affected, resulting in the desire to withdraw from HD treatment.<sup>5,9</sup> Assessing the effectiveness of pain relief interventions is a highly important strategy to improve HD patients' quality of care and treatment adherence. This systematic review was conducted to primarily evaluate the effectiveness of EMLA cream in reducing AVF needle insertion pain; the secondary aim was to assess whether EMLA cream was safe to use in adult HD patients, with no adverse side-effects that may harm them.

## Methods

### SEARCH APPROACH

A systematic literature review was conducted in December 2020 in multiple databases. The study design, search strategy and data abstraction were determined using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [Figure 1]. The search was restricted to articles published in the English language.

Since the research aimed to investigate the effectiveness of EMLA cream in clinical practice, only a few experimental studies addressing EMLA cream as an intervention for pain management were found. Thus, the Population, Intervention, Comparison and Outcome framework was used to explain the research question and set up the inclusion criteria. This framework ensured that the key concept was addressed and that the retrieved articles were relevant to the aims and objectives of the current research. The population was adult HD patients (>18 years old); the intervention was ELMA cream (a mixture of lidocaine and prilocaine); comparison was an alternative intervention (e.g. lidocaine, vapocoolant and piroxicam); and the outcome was either primary (reduce and relieve pain during AVF needle insertion) or secondary (no side effects on the patients' skin or safety risk). The inclusion and exclusion criteria are shown in Table 1.

An initial scoping search was conducted to determine the keywords to be used for the search and ensure the availability of relevant papers. In addition, the search facilitated the creation of other keywords, synonyms and abbreviations related to the search.

To ensure that no comparable systematic reviews had been conducted or proposed, the following databases were explored: the Joanna Briggs Institute (JBI), the International Prospective Register of Systematic Reviews (PROSPERO), the Cochrane Library and the Campbell Collaboration Library of Systematic Reviews.

'EMLA cream', 'Arteriovenous Fistula needle pain' and 'hemodialysis patients' or 'haemodialysis patient' were the keywords used during the scoping search

**Table 1:** The inclusion and exclusion criteria for selecting studies for this review.

	Inclusion Criteria	Exclusion Criteria
<b>Population</b>	Fully conscious adult haemodialysis patients age >18 years old Male or female patients with AVF for >2 months	Haemodialysis patients <18 years old Patients who underwent AVF surgery less than 2 months ago Unconscious or mentally challenged patients Patients with a known history of neuropathy disease and skin allergies or eczema
<b>Intervention</b>	EMLA cream (a mixture of lidocaine and prilocaine)	Pain relief and medicine Pharmaceutical intervention
<b>Comparison</b>	Alternative interventions (e.g. lidocaine, vapocoolant and piroxicam)	-
<b>Outcome</b>	The effectiveness of EMLA cream in pain management during AVF needle insertion	Outcome not reported
<b>Study design</b>	Quantitative research including RCTs and quasi-experimental studies Grey literature	Qualitative studies Case report Expert opinion
<b>Setting</b>	In-centre haemodialysis unit (hospital)	Home dialysis Not in hospital
<b>Time-span</b>	No time limit	
<b>Language</b>	Studies published in the English language	Studies with only title and abstract in English but the remainder in a different language Other languages

AVF = arteriovenous fistula; RCT = randomized controlled trial

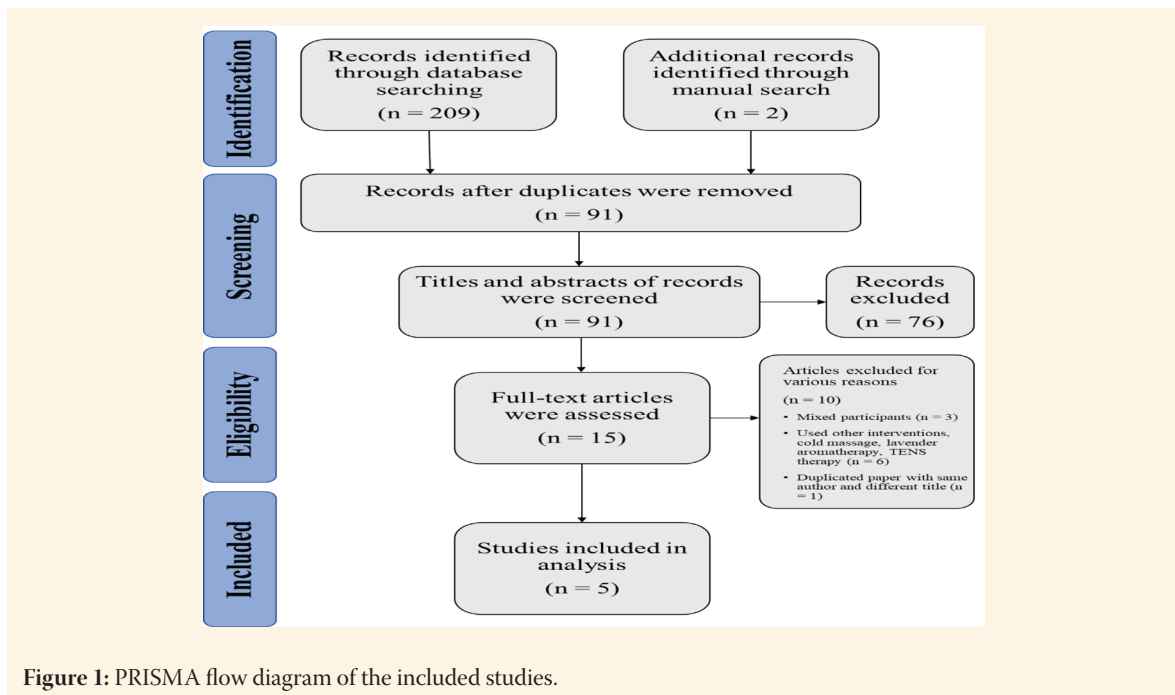


Figure 1: PRISMA flow diagram of the included studies.

on Google Scholar, whereas ([‘EMLA’] OR [‘eutectic mixture of local anesthetic\*’] AND Arteriovenous\*) OR ‘fistula needle\* fistula cannula\* and (‘hemodialysis patient’ OR \* dialysis patient) were used in the other databases.

Truncation was used to ensure the variations of word stems. Furthermore, quotation marks allowed the researcher to keep the terms in order and look for every phrase relevant to the search. In addition, parentheses were used to allow for the combination of various concepts within the search, while Boolean operators were used to connect and define the search terms.

The main systematic search was conducted on the following databases: CINIL, BNI, EMBASE, Medline, PubMed, Cochrane Library, AMED, JBI, SIGN, NICE, Center for Evidence-Based Medicine and PROSPERO. In addition, hand-searching and citation chaining (backward and forward chaining) were utilised to ensure that all relevant studies were found and considered in this review. Also, grey literature was utilised in this review to limit publication bias.

The main search was conducted in November 2020 and updated in December 2021. In the search strategy, keywords and synonyms were used and multiple databases were searched, with no date limitation to ensure a comprehensive search that would retrieve all studies relevant to the review and minimise location bias. The search was limited to studies published in English, which might be considered a limitation of the review due to language bias. However, the lack of available study translations was an issue; therefore, this

limitation was considered acceptable by the authors. Also, truncation, quotation marks, parenthesis and Boolean operators were utilised and the number of references for each of them was identified.

## STUDY SELECTION

Original research articles reporting on the use of pain management during AVF needle insertion for HD patients were included. Conference abstracts were not included because they lacked detail and had not undergone rigorous peer review. The level of evidence of the studies included was rated according to the criteria of the Center for Evidence-Based Medicine (<http://www.cebm.net>). The methodological quality of the studies was assessed using the JBI critical appraisal tool.

Two reviewers independently appraised the chosen studies and the lists of essential questions in the tools were scored. Any variation was discussed by the reviewers, looking for any inconsistency between individual scores of the studies, with a third reviewer available to adjudicate if there was any disagreement. This ensured that bias was minimised, enhancing the review’s trustworthiness. Subsequently, the studies that met the essential criteria were moved to the next stage, which was data extraction.

## DATA EXTRACTION AND SYNTHESIS

After using the critical appraisal tool to filter the studies, the relevant data were extracted using a valid extraction tool. This step was crucial to enhance the validity of the findings and allow conclusions to be

**Table 2:** The setting, country, sample size, gender, age range and haemodialysis experience of participants in the five studies.

Author and year of publication.	Setting	Design	Sample Size	Gender	Age Range	HD Experience
Mirzaei <i>et al.</i> <sup>6</sup> (2018)	S.R. Hospital, Iran	Quasi-experimental study	40 Patients Pre-/post-test similar	Male:25 (62.5%) Female:15 (37.5%)	>18 years (Mean age SD: 55.25 years).	More than 3 months on haemodialysis treatment, (Mean HD time: 4.98 years) With easy AVF access
Fujimoto <i>et al.</i> <sup>12</sup> (2020)	Six Japanese HD facilities, Japan	Multi-centre randomised crossover study (RCT)	66 Patients Group EL: 32 patients Group LE: 34 patients	Group EL: Males 20 (62.5%), Females 12 (37.5%). Group LE: Males 18 (52.9%) Females 16 (47.1%).	>20 years (Mean age SD: 65.8 years). Group EL: 65.5 ± 10.6 Group LE: 66.2 ± 10.7	With forearm AVF access (radio-cephalic fistula)
Malekshahi <i>et al.</i> <sup>13</sup> (2017)	S.A. Hospital, Iran	Double-blind clinical trial (RCT)	75 Patients Piroxicam Group A: 25 patients EMLA Group B: 25 patients Placebo Group C: 25 patients	Male: 67% Female: 36% The three same groups with: Male 16 Female 9	>18 years 3 patients (4%) younger than 30 years; 18 patients (24%) between 30 and 49 years; 54 patients (72%) older than 50 years	More than 3 months on HD treatment Less than 1 year: 7 patients (9.3%) Between 1 to 3 years: 27 patients (34.7%) More than 3 years: 42 patients (56%) With HD vascular access
Çelik <i>et al.</i> <sup>16</sup> (2011)	S. University Hospital, Turkey	Randomised, placebo-controlled, crossover study (RCT)	41 Patients All patients randomly received three different interventions during three consecutive HD treatments	Male: 21 (51.2%) Female:20 (48.8%) No specific data reported for the groups	Between 32 to 82 years (57.5 ± 13.3)	10 Persons with diabetes (24.4%) Seven smoking patients (17.1%) Fistula age between 3 to 180 months (0.3 to 15 years) Radio-cephalic fistula: 53.7% Brachiocephalic fistula: 46.3% (upper and lower arm AVF area) Fistula site: Right arm 48.8%, Left arm 51.2%
George <i>et al.</i> <sup>14</sup> (2014)	C.M.C. Hospital, India	Single-centre, crossover study (RCT)	50 Patients -EMLA group -Lidocaine -Infiltration group	Male: 35 (70%) Female: 15 (30%)	Between 12 to 82 years (Mean SD: 57.5) One patient was only 12 years old	22 Hypertensive patients (44%) 19 diabetic patients (38%) 27 patients with radio-cephalic fistula (54%) 23 patients with brachiocephalic fistula (46%)

HD = haemodialysis; SD = standard deviation; AVF = arteriovenous fistula; RCT = randomised controlled trials; EMLA = eutectic mixture of local anaesthetics.

drawn clearly for extraction. The JBI data extraction tool was used. Due to the heterogeneity of the included studies, a meta-analysis was not possible. Thus, the extracted data were synthesised by the authors as a narrative synthesis.

## Results

### FILTRATION

The search yielded a total of 209 studies, which were filtered and any duplicate studies removed, leaving

**Table 3:** The intervention, its manufacture, period, haemodialysis access/technique and needle size and the washout period.

Author and year of publication	Intervention	Medicine (Drug) manufacture	Period	HD access area/ technique	HD needle size/ diameter	Wash-out	Follow-up
Mirzaei <i>et al.</i> <sup>6</sup> (2018)	EMLA cream (1.5g) applied on fistula site 20 mins before cannulation. Lidocaine spray (20mg) applied on fistula site 5 mins before cannulation. Ice pack (five pieces) applied on fistula site 2 mins before cannulation.	Not reported	Total of four weeks Each intervention repeated three times for each patient Three weeks intervention + one week wash-out	Not reported	16 gauge for all patients	One week (Last week) wash-out for all patients	Successful monitoring of intervention process by the assessors Last week considered as wash-out to assess any interferences in the medicines used (researchers).
Fujimoto <i>et al.</i> <sup>12</sup> (2020)	EMLA cream 1g, applied 1 hour before AVF puncture Lidocaine tape 18mg, applied 30 mins before AVF puncture	Reported	Total of four weeks Week 1: no intervention Week 2: EMLA and Lidocaine Week 3: wash-out Week 4: Lidocaine and EMLA	Area: forearm AVF	16 gauge for all patients	One week (Week three) wash-out for each patient	Regular follow-up provided. Intervention drugs safety (side-effects) monitored
Malekshahi <i>et al.</i> <sup>13</sup> (2017)	EMLA cream (2g) Piroxicam cream (2g) Placebo (Vitamin A+D) cream (2g) Distributed to patients (25+25+25), who were instructed to apply 2g of each on the fistula area and cover with a transparent tape for 1 hour before HD session	Not reported	Two stages in two days Before and after HD session One session with no intervention + one session with intervention	Not reported	16 gauge for all patients	Not reported	Follow-up measurement during intervention provided. Short-term side-effect checklist provided for assessing the intervention medications used
Çelik <i>et al.</i> <sup>16</sup> (2011)	Ethyl chloride vapocoolant spray: Use at a 10-cm distance for 2 seconds. EMLA cream (5%): 2ml applied for 45 to 60 mins before fistula needle insertion Placebo cream: 2 ml applied 45 to 60 mins before fistula needle insertion	Reported	Four HD sessions 1st: no intervention 2nd, 3rd and 4th: with intervention	Not reported	18 gauge for all patients	Not reported	Intervention process and tolerability assessed by the researchers Safety of interventions used monitored before and 2 hours after needle puncture
George <i>et al.</i> <sup>14</sup> (2014)	EMLA cream: A thick layer applied for 1 hour before cannulation. Subcutaneous infiltration of lidocaine performed with 26-gauge needle.	Not reported	Four HD sessions (4 days) 50 patients randomised into two groups, each started with either EMLA or injectable lidocaine infiltration.	Traditional area technique	16 gauge for all patients	Not reported	Regular follow-up provided

HD = haemodialysis; EMLA = eutectic mixture of local anaesthetics; AVF = arteriovenous fistula.



**Table 4:** The clinical outcomes, measure/scale and results/findings of the five studies.

Author and year of publication	Clinical outcomes	Measure/scale	Results/findings
Mirzaei <i>et al.</i> <sup>6</sup> (2018)	EMLA cream is the most effective, easy and safe method	During the first three HD sessions, there was no intervention (control group); therefore, patients were asked to report their pain level using the VAS. Then the numeric pain assessment scale (ranging from 0–10) was used for the intervention stage, 2 min after fistula needles insertion (three methods).	<ul style="list-style-type: none"> <li>• Patients were satisfied with the EMLA cream, as it was an easy and effective method of reducing pain during fistula needles insertion compared to lidocaine spray and ice pack.</li> <li>• The findings indicated that there were differences in mean pain intensity between the three methods, with the EMLA cream being significantly more effective than the lidocaine spray and ice pack.</li> </ul>
Fujimoto <i>et al.</i> <sup>12</sup> (2020)	This paper examined three hypotheses: 1. EMLA cream inhibits pain during AVF puncture  2. QOL of HD patients (Carryover/ period and treatment effect)  3. No drug- related adverse events reported	A 100-mm straight line VAS was used to measure the AVF puncture pain by asking the patients to draw a slash on the line based on their perceived pain. -Left end indicating minimal pain (or no pain at all) -Right end indicating maximum pain (worst pain I have ever experienced)  Patients were asked to fill out evaluation forms (Six subscales in the SF-36)  The side effect of each intervention (drug) was evaluated after the examination Rating (Worst) 0 – 100 (Best)	Overall Result: <ul style="list-style-type: none"> <li>• EMLA cream is better than lidocaine tape in reducing AVF puncture pain.</li> <li>• No significant differences in patients' QOL was observed between EMLA and lidocaine.</li> <li>• No side-effects were reported in both methods.</li> </ul>
Malekshahi <i>et al.</i> <sup>13</sup> (2017)	1. EMLA cream relieved pain caused by AVF cannulation  2. Some skin bleaching observed in the EMLA group	All patients were asked to indicate their amount of pain after cannulation using the visual analogue scale (0 [no pain] – 10 [most pain])  Short-term side effect checklist used for all three groups during and after medication use	<ul style="list-style-type: none"> <li>• Median pain reduction in the EMLA group was much higher in the piroxicam and placebo groups</li> <li>• EMLA cream is a more effective and easy method than piroxicam gel in reducing the pain during AVF cannulation</li> </ul> <p>One hour after the application of medications:</p> <ul style="list-style-type: none"> <li>• Skin bleaching observed in 16% of patients in the EMLA group</li> <li>• No side effect observed in the remaining groups (Piroxicam and vitamin A+D)</li> </ul>
Çelik <i>et al.</i> <sup>16</sup> (2011)	1. EMLA cream is more effective than ethyl chloride vapocoolant in preventing AVF needle pain  2. Safety and tolerability of EMLA cream	<p><b>Control Group</b></p> <p>Patients' pain assessed using VAS before and after the first intervention VAS (0–100) score</p> <p><b>Intervention Group</b></p> <p>Every patient received one of three interventions (EMLA, ethyl chloride vapocoolant and placebo cream) and pain was measured by VAS</p> <p>All patients' AVF sites were inspected 2 hours before and after cannulation for redness, swelling and local skin reactions</p>	<ul style="list-style-type: none"> <li>• EMLA cream resulted in significantly lower pain scores in the EMLA group compared to the ethyl chloride vapocoolant spray and control groups.</li> <li>• One patient who used EMLA cream had a transient skin rash</li> </ul>

Author and year of publication	Clinical outcomes	Measure/scale	Results/findings
George <i>et al.</i> <sup>14</sup> (2014)	1. EMLA cream is suitable for managing AVF cannulation pain	An hour before HD treatment, patients were asked to apply the medication. Then, VAS (1–10) was used to assess the pain, and the data were recorded	<ul style="list-style-type: none"> <li>• Pain score was significantly higher in the infiltration group, and the pain on cannulation was slightly higher in the EMLA group.</li> <li>• Patients felt more stressed during lidocaine infiltration than AVF cannulation, which made them prefer EMLA cream.</li> </ul>
	2. Side-effects of EMLA reported	Any patient who reported itching, irritation and erythema during or after the application of the medication.	<ul style="list-style-type: none"> <li>• No patients had side effects</li> </ul>

EMLA = eutectic mixture of local anaesthetics; HD = haemodialysis; VAS = visual analogue scale; AVF = arteriovenous fistula; QOL = quality of life.

89 studies that were relevant to the inclusion and exclusion criteria. Two studies were included from the hand search; however, no studies were identified in the grey literature and backward and forward chaining searches. Following the initial filtration, the titles and abstracts of the remaining studies were reviewed, and 76 were excluded. The full text of the remaining 15 studies were read in full and 10 were excluded for focusing on mixed participants (n = 3), using other interventions—cold massage, lavender aromatherapy and TENS therapy—(n = 6) and being a duplicate (n = 1). Finally, only five studies were used for the critical appraisal [Figure 1].

#### TYPE OF STUDIES

Four studies were randomised controlled trials (RCTs), while one was a quasi-experimental descriptive study [Table 2].

This heterogeneity necessitated the performance of a narrative synthesis rather than a meta-analysis. The included studies had a good methodology and the included participants were the same in all ramifications, both pre- and post-testing methodology; the studies were either blinded or double-blinded studies. Additionally, the assessors in all the included studies were expert and certified HD staff.

#### GEOGRAPHICAL LOCATION AND CLINICAL SETTING OF THE INCLUDED STUDIES

The geographical locations of the studies were as follow: two from Iran, one from Japan, one from Turkey and one from India [Table 2]. This explains the differences in the studies' clinical setting and range of findings, which is due to the diversity of the clinical environment and HD treatment methods used in the different countries. However, EMLA cream is used globally and in all HD settings due to its ease of use

and application. The main focus was the effectiveness of EMLA cream in reducing AVF needle insertion pain in different HD facilities.

Regarding clinical setting, all five studies were conducted in different clinical settings. However, four of them were single-centre studies conducted in one HD facility, while the one by Fujimoto *et al.* was conducted in six different HD centres.<sup>12</sup>

#### PARTICIPANTS

The number of participants in the included studies ranged from 40 to 75 [Table 2]. All included studies clearly stated the number of participants included. Malekshahi *et al.*'s study had the largest sample size (n = 75), as it examined three different intervention groups.<sup>13</sup>

The participants in all five studies were adult patients receiving regular HD and their age ranged from 18 to 82 years, except for George *et al.*'s study, which included one patient aged 12 years, a decision for which no clear rationale was given.<sup>14</sup> However, all the participants were on continuous HD treatment and had an AVF access, which usually meant they needed anaesthesia (for the pain) more often than others.

Regarding the gender of participants in the included studies, the majority were male. This is because the current review only considered HD patients with AVF and according to Weigert *et al.*, men are more likely to have an AVF than women during HD treatment.<sup>15</sup>

Patients' experiences during HD may have affected the studies' results, in terms of fistula area (site), AVF cannulation techniques and diabetes mellitus status. Çelik *et al.* and George *et al.* reported that 54% and 30% of patients with a radio-cephalic fistula in their study had diabetes mellitus, respectively.<sup>14,16</sup> The other included studies did not provide any data on these essential points.

## INTERVENTION

EMLA cream was the main intervention in all included studies and was compared with other interventions—lidocaine spray, piroxicam cream, ethyl chloride vapocoolant spray, placebo cream and lignocaine infiltration [Table 3]. The dose of each intervention was provided in four studies (apart from George *et al.*'s study).<sup>14</sup> The manufacturers of the interventions were only reported in two studies.<sup>12,16</sup>

## FACTORS AFFECTING EMLA CREAM'S EFFECTIVENESS

Certain factors, such as AVF needle size, cannulation technique, patients' experience in HD and the dose and duration of EMLA applied, might affect the effectiveness of EMLA cream in reducing and managing AVF needle insertion pain in adult HD patients. These were a key component of the included studies and were discussed in most of them [Table 3].

## DOSE OF EMLA CREAM AND TIME OF APPLICATION

The time between EMLA cream application and AVF cannulation was 60 minutes in four studies and 20 minutes in one.<sup>6</sup> This difference in the intervention dose (drug strength) and application time may have impacted on the effectiveness of the cream and led to insignificant findings. However, the strength of the EMLA cream was almost the same in all the included studies (1–2 gm), which could be explained by the fact that the manufacturing companies in the four geographical locations were following similar guidelines.

## HD NEEDLE SIZE

Four of the studies reported using a 16-gauge needle, while one reported using an 18-gauge needle.<sup>16</sup> This difference is because certain facilities choose the needle gauge based on patient preference and the blood pump. While there are no guidelines on the needle gauge to be used, the pain-relieving efficacy of EMLA cream in HD patients may be affected if a small gauge is used. However, the included studies showed that using the EMLA cream with either a 16- or 18-gauge HD needle resulted in the same level of reduction in AVF needle insertion pain. Moreover, there were no significant differences in the rate of complications, such as AVF site bleeding, due to the different needle sizes.

## DURATION

The study duration was stated in all the included studies. The longest study period was four weeks,<sup>6,12</sup> followed by four days,<sup>14,16</sup> and the shortest period was

two days.<sup>13</sup> However, Mirzaei *et al.*'s study repeated each intervention (three drugs) three times for everyone, whereas other studies assessed EMLA cream's efficacy for just two days.<sup>6,13</sup> Despite the differences in the studies' duration, the patients were satisfied with the EMLA cream during AVF cannulation.

## HD ACCESS AREA/TECHNIQUE

Different fistula areas or sites and cannulation techniques were reported in the included studies. Mirzaei *et al.* used the forearm as the AVF site for their participants, while George *et al.* reported that all patients were cannulated using the traditional AVF cannulation technique.<sup>6,14</sup> The remaining three studies did not provide any information on the cannulation area or technique used.<sup>12,13,16</sup>

## WASH-OUT

Two studies provided information about wash-out during their studies,<sup>6,12</sup> whereas the remaining three studies did not report if they had conducted a wash-out.<sup>13,14,16</sup>

## STATISTICS

Three studies utilised descriptive analysis for their data.<sup>13,14,16</sup> In contrast, Mirzaei *et al.* utilised both descriptive analysis and inferential statistics for their study baseline and continuous data, while Fujimoto *et al.* used inferential statistics.<sup>6,12</sup>

## OUTCOMES

Four studies measured their outcomes with the same tool—visual analogue scale; they measured the effectiveness of the interventions used before and after 1–2 minutes of AVF cannulation, whereas Fujimoto *et al.* measured their patients' pain experience immediately after AVF cannulation and used the SF-36 form to measure the quality of life of each patient.<sup>12</sup> However, all included studies measured three outcome: pain reduction, patients' quality of life and post medication side-effects [Table 4].

## ROBUSTNESS OF THE SYNTHESIS

The number, quality of evidence and trustworthiness of the included studies play an essential role in the robustness of the synthesis process.<sup>17</sup> In this systematic review, only five primary studies were included because of the difficulty involved in finding more studies that met the inclusion criteria. Despite this low number, four were level-two RCTs, according to the hierarchy of evidence, while the study by Mirzaei *et al.* was a quasi-experimental study.<sup>6,18</sup> Thus, the included studies were of moderate-to-high quality, according to the hierarchy of evidence.



All included studies had good methodology due to the nature of the interventions used; they all had the same type of participants (HD patients with AVF), pre- and post-test, with similar comparisons between the groups. Moreover, the researchers and assessors of each study conducted their study without any change, thus enhancing the trustworthiness of the studies.

According to the quality of the included studies, they would be an appropriate source for providing strong suggestions and recommendations for clinical practice regarding the effectiveness of EMLA cream in HD patients.

## Discussion

This systematic review found EMLA cream to be a highly effective, easy method of reducing or inhibiting AVF needle insertion pain in adult HD patients.

### EFFECTIVENESS OF EMLA CREAM AND THE SIZE OF THE HD NEEDLE USED

Four studies reportedly used the same AVF needle size (16-gauge) while one study utilised an 18-gauge needle for their patients. The studies showed that when compared with other interventions, EMLA cream performed well in achieving patients' desired outcome by reducing AVF needle pain, regardless of the difference in AVF needle size. According to Van Loon *et al.*, there are no current guidelines on HD needle size;<sup>19</sup> therefore, each HD facility could use the standard size of 14 to 18 gauge, based on patients' preferences, AVF vintage and expansion and patients' bleeding tendency. Since all the patients in the included studies were adults with mature AV fistulae (more than three months of HD AVF history), the size of the needle used had no effect the objective of the studies. Moreover, all studies using both needle sizes reported a statistically significant difference in the median pain reduction before and after the intervention. Thus, it can be concluded that the EMLA cream was effective despite the difference in needle size.

### TIME OF EMLA APPLICATION AND DOSE APPLIED

Although the studies reported some variation in the EMLA dose applied and time of application before AVF needle insertion, the results suggested that EMLA cream was significantly more effective in relieving the pain of AVF needle insertion compared to the other interventions. Moreover, the four RCT studies were considered high-quality papers according to the hierarchy of evidence. Tadicherla and Berman stated that the nerve endings in the skin are present in the dermis and to reach the dermis, topical anaesthetics

need to pass through the stratum corneum and be wrapped in oil droplet formulations to achieve their anaesthetic effect.<sup>20</sup>

EMLA cream is a combination of lidocaine and prilocaine, both of which exist as solids at room temperature but become liquid, oil droplets once mixed, due to a lowering of their melting point.<sup>21</sup> Therefore, based on this formulation, it appears that EMLA cream had a sufficient anaesthetic effect despite the small amount (1–2 gm) applied in the studies. Furthermore, many studies have recognised EMLA cream for its superior anaesthetic effect in clinical practice, especially in the field of dermatology and paediatric care.<sup>16,21,22</sup>

### EFFECTIVENESS OF EMLA CREAM AND AVF AREA AND CANNULATION TECHNIQUE

Drawing a conclusion regarding the effect of AVF cannulation techniques on the pain-reducing effect of EMLA cream in patients undergoing AVF needle insertion was challenging, as only one study reported using the rope ladder AVF cannulation technique on their patients;<sup>14</sup> the other studies did not provide any information in this regard. There are two main AVF cannulation techniques: the 'buttonhole technique', where the AVF needle is inserted at the same site and angle during every HD session (constant site), and the 'Rope Ladder technique' (also called the traditional cannulation technique), where the AVF needling sites are rotated before every session (different site).<sup>23</sup>

Many studies have highlighted and evaluated the impact of these techniques on HD patients regarding pain severity and needle site complications. These studies concluded that there was no difference in pain levels between the two techniques, but there was a higher risk of bacteraemia and AVF needle site infection associated with the 'buttonhole technique'.<sup>19,23–25</sup> This suggests that there is no association between the method of cannulation used and EMLA cream's effectiveness. Furthermore, researchers found that needle insertion pain severity was affected by the staff handling the procedure.<sup>19,23,24</sup> A cross-sectional survey by Parisotto *et al.*, conducted in nine countries, and a systematic review by Casey *et al.* found that clinicians skilled in vascular access make a difference with regard to patients' pain severity, increasing patients' confidence in receiving their HD treatment without fear and enhancing their quality of life.<sup>25,26</sup> This crucial point was clearly supported by Fujimoto *et al.*, Mirzaei *et al.*, Malekshahi *et al.* and George *et al.*<sup>6,11,12,14</sup> In all these studies, AVF needles were inserted and assessed by skilled HD nurses.

## HD PATIENTS' CHARACTERISTICS AND EXPERIENCE

Globally, significant differences in clinical treatment for both genders (men and women) and elderly patients exist; thus, the results of several studies may be affected.<sup>15</sup> However, the findings of Fujimoto *et al.*, Mirzaei *et al.*, Malekshahi *et al.* and George *et al.* reported significant differences in the gender of their studies' participants, with majority being men (the percentage of men included in the studies ranged from 62.5% to 70%).<sup>6,12-14</sup> Therefore, the findings might be affected negatively by the unequal gender proportion. Researchers investigated the tolerance of pain in male and female subjects and concluded that men have a higher tolerance for pain than women.<sup>27</sup>

While most studies considered adult patients aged between 18 and 82 years, the study by George *et al.* reported that one patient was aged 12 years.<sup>14</sup> Therefore, the generalisability of this review's findings could be affected because of the wide difference in the participants' ages.

These studies reported that many of the participants have been on maintenance HD treatment for more than 10 years. Hence, patients' needle insertion frequency experience, long history of HD treatment and mental status at the time of AVF cannulation might have affected their sensation of pain severity.<sup>28</sup> Therefore, EMLA cream (or other local anaesthetics) may not have significant effects on such patients. Thus, only HD patients who typically experience moderate-to-severe AVF needle insertion pain should be considered for EMLA cream. Heidari-Gorji *et al.* found that anxiety can cause pain, and pain can also cause anxiety.<sup>29</sup> They found that anxiety and pain sensation were lower among patients who have undergone HD for a long time compared to those who have only undergone dialysis for a short duration.

Çelik *et al.* and George *et al.* reported a significant effect of EMLA cream in their studies.<sup>14,16</sup> However, 24.4% and 38% of their study participants had diabetes mellitus, respectively. An RCT conducted by Heidari-Gorji *et al.* examined the perception of pain in 80 adult HD patients and found a relationship between pain sensation and diabetes status, but further research is needed to support this argument.<sup>29</sup>

## EMLA CREAM SAFETY

Four studies reported on the safety and tolerability of the EMLA cream. Çelik *et al.*<sup>16</sup> reported skin bleaching in 16% of patients in the EMLA group, when the cream was applied for 45–60 minutes;<sup>16</sup> however, Malekshahi *et al.* reported that only one patient complained of skin rash.<sup>13</sup> In a study by Yin and Jiang,

which examined the effect of EMLA cream on two groups (applied for 30 and 60 minutes, respectively), EMLA cream was found to show no skin side-effects when used for only 30 minutes.<sup>21</sup> Therefore, it is clear that the duration of EMLA cream application plays a significant role in the incidence of adverse reactions. Furthermore, a study reported that HD patients had positive allergic reactions to prilocaine and negative reactions to lidocaine when used alone, but no reactions to the combination of the two in EMLA cream were reported.<sup>10</sup>

Regarding other vascular medications used by HD patients, some studies have mentioned that some skin reactions might have occurred with the use of EMLA cream because the patient was receiving cardiovascular medication, which was causing vascular constriction. This may produce a temporary skin reaction which patients recover from within a short period. None the less, this should be noted and acknowledged by patients and health providers.<sup>12</sup>

Overall, it was obvious from the findings of the included studies that EMLA cream is effective in reducing and inhibiting AVF needle insertion pain. This significant finding might be important in clinical practice for adult HD patients. Although some studies reported limitations and factors that might reduce the effectiveness of EMLA cream, the recommendation on the use of EMLA cream as a local anaesthetic for AVF pain reduction is conclusive.

## LIMITATIONS

This review has some limitations. Although a comprehensive search on several databases was conducted to find all relevant papers, no grey literature was found and unpublished studies were not included, which may have led to publication bias. The search was limited to studies written in English only due to time restrictions, and the reviewers utilised the English language; thus, some degree of language bias was inevitable.

Any study evaluating the degree of pain is subject to several limitations such as instruments used and patients' characteristics; therefore, the findings of the included studies, which examined the perception of pain, are limited. Furthermore, selection bias could have been maximised since most of the participants in the included studies were men. While four of the studies were RCTs, one was a quasi-experimental study, which could have introduced some bias to the review. Also, a low-ranking study on the hierarchy of evidence might contain some biases, such as performance, selection and measurement biases. Moreover, due to the heterogeneity of the primary studies, a meta-analysis was not conducted.

The data extraction and narrative synthesis processes were conducted by one reviewer due to time and academic restrictions. This could have increased the risk of conclusion and reporting biases. Furthermore, this review focused mainly on adult HD patients aged above 18 years. Moreover, the studies included in the review were from four countries and reported using different medication manufacturing companies; this might have affected the effectiveness of the EMLA cream used. However, the strength of the EMLA cream was almost the same in all the included studies (1–2 gm).

## RECOMMENDATIONS FOR FUTURE RESEARCH

This systematic review aimed to investigate the effectiveness of EMLA cream in reducing AVF needle insertion pain in adult HD patients and compared it with that of three other local anaesthesia methods used for the same purpose. The review found EMLA cream to be a highly effective, easy method of reducing or inhibiting AVF needle insertion pain in adult HD patients. Although the findings were based on four high-quality and one moderate-quality study with high heterogeneity, further research is needed on EMLA cream's effectiveness, bearing in mind this review's limitations.

The application of EMLA cream was shown to have a positive effect in reducing AVF needle insertion pain in all the included studies and was more convenient in clinical practice. However, it seems that applying EMLA cream for only 30 minutes was more convenient for HD patients and no side effects were observed in this time. However, EMLA cream might allow the staff nurse to use both AVF cannulation techniques (buttonhole and rope ladder) for their patients, according to their preference, which could encourage the patients to adhere to their HD treatment without fear.

Despite the findings from four RCTs, which are considered high-quality studies, there is need for future research on the use of EMLA cream in adult HD patients, in which significant and unbiased results would be maximised. In addition, inexact amounts of EMLA cream were applied for different durations, and there were more men than women across the studies, which did not allow for a strong conclusion. The authors of this review recommend that this be considered in future research.

Furthermore, there was limited data regarding AVF needle puncture techniques and fistula types (lower or upper arm area); this needs to be considered in future research. Moreover, HD patients' prior experience, diabetic status and psychological issues

could affect their sensation of needle pain. Therefore, further work highlighting these important data is needed in topical anaesthetics research. Finally, EMLA cream is a complex medication (comprising lidocaine and prilocaine) compared with the other three single medications (lidocaine, vapocoolant and piroxicam). Accordingly, the investigation of two complex anaesthetics is recommended and worthwhile.

The paucity of available literature on the use and effectiveness of EMLA cream in the chronic kidney disease population warrants more refined studies to determine its optimal utilisation and dosage and make it most efficacious while minimising its known toxicities. There is also a great need for prospective research on the quality of life of patients with end-stage kidney disease using the EMLA cream for pain management.

The authors recommend that the use of EMLA cream be considered in patients in which (1) cannulation has been attempted using intradermal lidocaine and the patient continues to complain of pain, (2) cannulation has not been attempted because the patient has a severe fear of needles and (3) children aged  $\leq 18$  years need to be cannulated.

EMLA cream is not recommended for patients who do not report experiencing discomfort with cannulation. Topical anaesthetics are expensive and there is no published evidence to support their widespread or universal use. EMLA cream is of paramount importance for the HD population, for whom significant pain is a concern and intradermal lidocaine has not been effective in patients with a fear of needles.

Finally, the authors recommend that continuous education on the correct application (how, how much and when to apply) and side effects of topical anaesthetics be provided to patients. The correct application of a topical anaesthetic maximises its effectiveness in reducing needling pain. Important points to cover in the teaching include the timing of application and onset of duration, correct application and side effects (redness/rashes or whitening at the site of application).

## Conclusion

This systematic review found EMLA cream to be a highly effective, easy method of reducing or inhibiting AVF needle insertion pain in adult HD patients. Although the findings were based on four high-quality and one moderate-quality study with high heterogeneity, more studies on EMLA cream's effectiveness are needed, keeping in mind this review's limitations.

## AUTHORS' CONTRIBUTION

HAS and IAS contributed to the conceptualization of this review; the methodology was done by HAS, HS and WAW. Software access was provided by IAS and HS; validation was completed by WAR and HS, and the formal analysis and review and editing of the manuscript were done by IAS, WAR and HS. Investigations, data curation and visualization and original draft preparation were done by HAS, WAR and HS, and resources were gathered by IAS, HS and WLR. This project was supervised by IAS, and project administration was done by WAR and HS. All authors approved the final version of the manuscript.

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