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Effectiveness of EMLA Cream in the Management of Arterio-Venous Fistula Needle Insertion Pain in Haemodialysis Patients

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Abstract

This systematic review is conducted to assess the effectiveness of EMLA-cream in the management of Arterio-Venous Fistula-AVF needle insertion pain in adult haemodialysis-HD patients compared with other alternative interventions. The main search was conducted in November 2020 and was updated on 5th December 2020. 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 allocate all studies relevant to the review, and to minimize location bias. The following databases were explored: Joanna Briggs Institute (JBI), the International Prospective Register of Systematic Reviews (PROSPERO), Cochrane Library, and the Campbell Collaboration Library of Systematic Reviews. The keywords "EMLA cream", "Arterio-Venous Fistula needle pain" and "hemodialysis patients" or "haemodialysis patient" were used for a scoping search in Google Scholar, whereas in the databases were (("EMLA") OR ("eutectic mixture of local anesthetic*) AND Arteriovenous*) OR "fistula needle* fistula cannula* and ("h#emodialysis patient OR * dialysis patient)). A total of 209 studies were found in this search and were filtered. Initially, any duplicated studies were removed, leaving 89 studies that were relevant to the inclusion and exclusion criteria. Two studies were included from

the hand search. There were no studies identified in the grey literature or backward and forward chaining search. Following this initial filtration, the titles and abstracts of the remaining studies were reviewed and 76 were excluded. The full text of 15 studies was read in full and nine were excluded for the following reasons: three studies were focused on mixed participants, six studies used other interventions and one study was a duplicate paper with the same author and different title. Five studies were taken forward for critical appraisal. EMLA-cream is an effective management strategy in reducing AVF needle insertion pain among adult HD-patients. However, despite the positive effect of EMLA cream in reducing HD needle insertion pain, with fewer side effects, the findings should be considered with caution, as there are some limitations, and further research is required.

Keywords: EMLA; Pain; Dialysis; Arterio-Venous Fistula

Introduction

Arteriovenous fistula-AVF is the main management for the delivery of good hemodialysis-HD sessions. Aghbolagh et al, showed 80% of HD patients experience moderate to severe pain during vein access needle insertion, but do not receive pain relief.[1] These patients receive AVF needles two to three times per week, which is often their greatest concern during HD treatment.[2] This struggle with pain may cause patients despair, frustration, and lack of adherence to the treatment.[3] However, some studies showed that without such pain relief intervention, HD patients' life quality may be disrupted, resulting in the desire to withdraw from HD treatment.[4,5] Therefore, managing the pain relief, could improve the quality of care and treatment of HD patients.

EMLA cream is a mixture of Lidocaine 25 mg/g and Prilocaine 25 mg/g. It is the preferred local anaesthetics and can be easily used by the patients themselves (Mirzaei et al. 2018). [6] The EMLA cream blocks the active and inactive sodium channels, blocking the conduction and absence of stimulation, reducing pain transmission. Accordingly, there are some interventions, such as 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 improve patients' satisfaction with the management strategies and hence to continue HD treatment.[4]

Haemodialysis is a painful process for patients suffering from renal failure. However, the capability to adapt to the pain psychologically varies among individuals A study by Jeon et al. (2020) found that females experience a greater pain dimension than male patients.[7] According to Brkovic et al. (2016), pain associated with HD needle venipuncture should be considered a health issue. 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.[8]

Despite the diversity of pain management and control methods in the past few decades, the rate of local anaesthetic application therapy is higher than others due to patient perceptions, ease of use, and several medical procedures used. Despite having chronic renal problems, HD patients also face some related health issues, of which the most common ones are insomnia, anxiety, and depression. From the study of Davison and Jhangri (2005), these three issues may increase the degree of pain sensation during the AVF needle penetration process.[9] Thus, the practical implication of a local anaesthetic is to improve compliance with the generated pain during the venipuncture process. [7,9]

EMLA cream is a mixture of two substances (Lidocaine and Prilocaine) and was commercialized in 1984 (as a non-invasive intervention). It is available as a cream, patch, or spray, and is widely used in medical procedures such as venipuncture, laser therapy, skin biopsy, lumbar puncture, vaccination, cryosurgery, and intradermal testing (Perez-Perez et al. 2006; Jeong 2016).[7,10]

No systematic reviews were found that specifically address the effect of EMLA cream in managing AVF needle puncture or insertion pain in adult HD patients. One study was conducted on EMLA compared with local infiltration anaesthesia in pain reduction during virginal delivery. It conducted by Abbas et al. (2020), reviewed four studies, with a total of 348 patients (the EMLA group of 173 patients compared with conventional local infiltration anesthesia in 175 patients) undergoing perineal repair after vaginal delivery. It found that EMLA cream can help to reduce pain during perineal repair after virginal delivery with a success rate of 95%.[11]

In terms of current interventions for managing pain in HD, there are a few strategies such as EMLA cream, Lidocaine spray or tape, Vapocoolant spray, and Promaxicam cream which may be used to

reduce and relieve patients' pain during needle insertion and persuade them to continue HD treatment (Ghods et al. 2015).[4] However, some studies showed that without such pain relief intervention, HD patients' life quality may be disrupted, resulting in the desire to withdraw from HD treatment (Bagheri-Nesami et al. 2014; Davison and Jhangri 2005). [5,9] Therefore, continuing assessment of the effectiveness of pain relief interventions is considered a highly important strategy to improve HD patients' quality of care and treatment adherence.

This systematic review was conducted to evaluate the effectiveness in reducing AVF needle insertion pain, while the secondary aim was to assess if EMLA cream was safe to use for adult HD patients with no adverse implications or (side-effects) that might harm the patients.

Method

Search Approach

A systematic literature review was performed in December 2021 in multiple databases. The study design, search strategy, data abstraction, and excluded studies were determined using Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (www.prisma-statement.org). The items retrieved were restricted to publications in English.

This research aims to investigate the effectiveness of EMLA cream in clinical areas. Therefore, it was likely to find a few experimental papers addressing EMLA cream as an intervention for managing pain. Thus, the Population, Intervention, Comparison, and Outcome (PICO) framework was conducted to explain the research question and set up the inclusion criteria. This framework ensures that the key concept was addressed, and the focused papers were tailored to the aims and objectives of the research. The population was adult hemodialysis patients aged over 18 years, Intervention was ELMA cream (mixture of Lidocaine and Prilocaine), Comparison was an alternative intervention (e.g., Lidocaine, Vapocoolant, and Promaxicam), and the outcome was either primary (reduce and relieve of pain during AVF needle insertion) and secondary (no side effects upon patients' skin or safety). The inclusion and exclusion criteria are shown in table 1.

An initial scoping search was conducted to determine the keywords for the search strategy and ensure the availability of relevant papers. In addition, a scoping 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: Joanna Briggs Institute (JBI), International Prospective Register of Systematic Reviews (PROSPERO), Cochrane Library, and the Campbell Collaboration Library of Systematic Reviews.

The keywords "EMLA cream", "Arterio-Venous Fistula needle pain" and "hemodialysis patients" or "haemodialysis patient" were used for a scoping search in Google Scholar, whereas in the databases the following keywords were used (("EMLA") OR ("eutectic mixture of local anesthetic*) AND Arteriovenous*) OR "fistula needl* fistula cannula* and ("h#emodialysis patient OR * dialysis patient)).

The use of truncation was essential 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 also used to connect and define the search terms.

The main systematic search was conducted via 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 (back and forward chaining) were utilized to ensure that all relevant studies were found and considered in the review for the critical appraisal step. Also, grey literature was utilized in this review to limit publication bias.

The main search was conducted in November 2020 and was updated on 5th December 2020. 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 allocate all studies relevant to the review, and to minimize location bias. The search was limited to studies published in English only,

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. Also, truncation, quotation marks, parenthesis, and Boolean operators were utilized, and the number of references for each of them was identified,

Study selection

Original research articles reporting on the use of pain management for AVF needles for hemodialysis 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 by the Joanna Briggs Institute (JBI) critical appraisal tool.

There were two reviewers available to independently appraise the studies chosen, and the lists of essential questions of 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 if there was any disagreement. The third reviewer, a health-sector academic tutor, was asked to adjudicate. This ensured bias was minimized and hence enhanced the review's trustworthiness. Subsequently, the studies that met the essential questions were taken forward to the next stage, which was data extraction.

Data extraction and synthesis

After using the critical appraisal tool for the final filtering of the studies, the relevant data was extracted by using a valid extraction tool. This step was crucial to enhance the validity of the findings and allow the conclusion to be drawn clearly for extraction. The JBI data extraction tool was used for the data collection elements. Due to the heterogeneity of the included studies, meta-analysis was not applicable. Thus, the extracted data were synthesized by the authors as a narrative synthesis.

Results

Filtration

A total of 209 studies were found in this search and these were filtered. Initially, any duplicated studies were removed, leaving 89 studies that were relevant to the inclusion and exclusion criteria. Two studies were included from the hand search. There were no studies identified in the grey literature or backward and forward chaining search. Following this initial filtration, the titles and abstracts of the remaining studies were reviewed and 76 were excluded. The full text of 15 studies were read in full and 10 were excluded for the following reasons: three studies focused on mixed participants; and six studies used other interventions, for example cold massage, lavender aromatherapy, TENS therapy and one study was a duplicate paper with the same author and different title. Five studies were taken forward for critical appraisal, as shown in Figure 1.

Type of studies

Four studies were RCT studies, and one was a quasi-experimental descriptive study [Table 2]. This heterogeneity confirmed the use of narrative synthesis rather than meta-analysis. The included studies had a good methodology, and the included participants were the same in all comparison, pre and post testing methodology and were blinded or double-blinded studies. Also, the expert and certified HD staff were the studies' assessors in all these studies.

Geographical location and clinical settings

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 explained the differences in clinical setting and their range of findings due to the diversity of the clinical environment and HD treatment methods in different countries. However, EMLA cream was used as a worldwide medication, and could be

applicable to all HD settings due to its easy use and application. The crucial point was the effect of EMLA cream in reducing AVF needle insertion pain in different HD facilities.

Regarding clinical setting, all studies originated from different clinical settings. However, four of them were conducted in single center HD facilities, except for the study by Fujimoto et al.'s (2020, which was conducted in six different HD centers. [12]

Participants

The number of participants in the included studies ranged between 40 to 75 [Table 2]. All included studies provided clear participant numbers. Malekshahi's study had the largest sample size (75) as it examined three different intervention groups. [13]

The participants in all studies were adult HD patients on regular treatment, and ranged between 18 to 82 years, except for George's study,[14] which included one patient aged 12 years old, for which no clear rationale was included. However, the important point was that all participants were on continuous treatment with AVF access which usually exposed them to anaesthesia medication for their AVF pain more often than others.

Regarding participants' gender, the included studies showed that the majority were male. Since this review was looking at HD patients with AVF only, and according to Weigert et al. (2020), [15] men are more likely to have AVF than women during HD treatment.

Patients' experiences in HD may affect the studies' results, in terms of fistula area (site), AVF cannulation techniques and diabetes mellitus status. Celik et al. (2011)[16] and George et al. (2014)[14] reported diabetes mellitus present in 54% and 30% of patients with radio-cephalic fistula, respectively. Whereas the other included studies did not provide any data on these essential points.

Intervention

EMLA cream was the main intervention in all included studies compared with other interventions (Lidocaine spray, Piroxicam cream, Ethyl chloride Vapocoolant spray, Placebo cream, Lignocaine infiltration) [Table 3]. However, the essential thing was the dose of each intervention, which was

provided in four studies apart from George's study.[14] The manufacturers of the interventions were reported in two studies only (Fujimoto et al. 2020; Celik et al. 2011).[12,16]

Factors affecting EMLA cream effectiveness

There were some factors which might affect the effectiveness of using EMLA cream as a local anesthesia for reducing and managing AVF needle insertion pain in adult HD patients. These were demonstrated in Table 3 and were a key component of the included studies. AVF needle size, cannulation technique, patients' experience in HD, and the dose and duration of EMLA applied was discussed in many studies.

Dose amount and time of EMLA applied.

The time of applying EMLA cream before AVF cannulation was 60 minutes in four studies, whereas the study of Mirzaei et al.[6] reported that it was only 20 minutes. This difference in the intervention dose (drug strength) and application time may impact upon the effectiveness of medicine used and hence may have led to insignificant findings. However, the strength of EMLA cream was almost the same in all the included studies (between 1 to 2gm), which could be explained by the manufacturing companies being different in the four geographical locations.

HD Needle Size

The size and diameter of AVF needles used in most studies was a 16-gauge needle, whereas the study of Celik et al.[16] used an 18-gauge needle. This was because certain facilities chose the needle gauge based on patient preference and the required machine blood pump. While there are no guidelines recommendation for a specific gauge, the pain relief effectiveness in HD patients may be affected by the size if a small gauge was used. However, these studies showed that using EMLA cream with 16 or 18-gauge HD needles had the same reduction in AVF needle insertion pain. Moreover, there were no significant differences reported for the complications, such as AVF site bleeding due to the use of different needle sizes.

Duration

The study duration was stated for all included studies. The longest period was four weeks (Mirzaei et al. 2018; Fujimoto et al. 2020),[6,12] followed by four days period (Celik et al. 2011; George et al.

2014),[14,16] and the shortest period was two days (Malekshahi et al. 2017).[13] However, Mirzaei's study repeated each intervention (three drugs) three times for everyone, whereas Malekshahi's study assessed EMLA cream for two days only.[13] Despite the differences in the studies duration, patients were satisfied with EMLA cream during AVF cannulation.

HD Access Area/Technique

Different fistula areas or sites and cannulation techniques were reported in some of the included studies. Mirzaei et al. (2018)[6] used forearm AVF sites for their participants, while George et al. (2014)[14] reported that all patients were treated with traditional AVF cannulation technique. The rest of the included studies did not provide any information about cannulation area and technique used. [12,13,16]

Wash-out

Two studies (Mirzaei et al. 2018; Fujimoto et al. 2020) [6,12] provided information about wash-out during their studies; whereas the rest of the studies did not report if they had conducted a wash-out.

Statistics

Three studies (Fujimoto et al.; Malekshahi et al.; Celik et al.)[11,13,16] utilized descriptive analysis for their data. The study by Mirzaei et al.[6] utilized both descriptive analysis and inferential statistics for the study baseline and continuous data, whereas Fujimoto et al.[12] used inferential statistics.

Outcomes

Four studies measured their outcomes with the same tool, which was VAS, for measuring the effectiveness of interventions used before and after 1–2 minutes of AVF cannulation, whereas Fujimoto et al.[12] measured the patients' pain experience immediately after AVF cannulation and the QOL for each patient by using SF-36 form. However, all included studies measured outcome in three ways: 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 plays an essential role in the robustness of the synthesis process.[17] In this systematic review, only five primary studies were included because of the difficulty of finding more studies that met the inclusion criteria. Despite this low number, four RCT studies were in level two according to the hierarchy of evidence.[18] whereas Mirzaei et al.[6] paper was the only quasi-experimental study. Thus, the included studies were of high to moderate quality according to the Hierarchy of Evidence.

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

Most of the studies included in this review were high to moderate quality; thus, it would be appropriate to provide strong suggestions and recommendations for clinical practice about the effectiveness of EMLA cream in HD patients.

Discussion

This systematic review suggested that EMLA cream is an easy method that might have a strong effect in reducing and inhibiting AVF needle insertion pain in adult HD patients.

Effectiveness of EMLA and HD needle size used.

Four studies used the same AVF 16-gauge needle size [6,12,13,14], while one study utilized size 18-gauge for their patients.[16] The studies showed that EMLA cream compared favourably with other interventions in achieving patients' desired outcome about reducing AVF needle pain, despite the difference in AVF needle size. According to Van Loon et al.[19] there were no current guidelines recommending the use of HD needle size; therefore, each HD facility could use the standard size gauge of 14 to 18, based on patients' preferences, AVF vintage and expansion, and patients' tendency for bleeding. As all patients in the included studies were adults with mature AV fistulae (more than three months of HD AVF history), it did not appear to matter whether size 16 or 18 was used, as it did not affect the objective of each study. Moreover, all studies conducting both needle size gauges reported a statistically significant difference between the median pain reduction before and after the intervention used. Thus, it might be concluded that EMLA cream was effective despite the difference in needle size.

Time and dose of EMLA cream applied.

Although the findings showed that there was some variation in the level of EMLA dose applied and time of application before the AVF needle insertion, the results suggested that EMLA cream had a significant effect over other interventions in relieving the pain of AVF needle insertion. Moreover, the four RCT studies were considered as high-quality papers according to the hierarchy of evidence. Tadicherla and Berman (2006) 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 must be contained in oil droplets formulation to achieve their anesthetic effect.[20]

EMLA cream is a combination of lidocaine and prilocaine substances which exist as solids at room temperature, but once mixed, the melting point is lowered, and it becomes liquid and oil droplets.[21] Therefore, based on this formulation, it appears that EMLA cream has sufficient anaesthetic effect despite the amount of only 1 to 2gm applied in the studies. Furthermore, many studies have supported EMLA cream for its superior anaesthetic effect in clinical practice in the field of dermatology and paediatric care. [16,21,22]

Effectiveness of AVF area and cannulation technique

It was challenging to draw a conclusion regarding the effect of AVF cannulation techniques in reducing patents' pain during AVF needle insertion, as only one study (George et al. 2014)[14] reported significant information on the use of rope ladder AVF cannulation technique on their patients, whereas the rest of the studies did not report any information in this regard. However, there were two main AVF cannulation techniques: *Buttonhole* when inserting the AVF needle into exactly the same site and at the same angle every HD session (constant site), whereas *Rope Ladder* (named as traditional cannulation) is when the AVF needling sites are rotated every session (different site).[23]

Many primary studies have highlighted and tracked 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 between the two techniques, but there was increased risk of bacteremia and AVF needle site infection associated with use of buttonhole technique.[19,23-25] Therefore, this suggests

that there is no relation between the method of cannulation used and EMLA cream. Furthermore, researchers found that needle pain severity was affected by the staff who handled the procedure.[19,23,24] A cross-sectional survey by Parisotto et al.[25] conducted in nine countries, and a systematic review by Casey et al.[26] 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. This crucial point was clearly provided by Fujimoto et al.[12]; Mirzaei et al.[6], Malekshahi et al.[11], and George et al.[12] in their studies. In all these studies, AVF needles were inserted and assessed by skilled HD nurses.

HD patients' characteristics and experience

Worldwide, significant differences in clinical treatment for both genders (men and women) and elderly patients exist; thus, the results of several studies may be affected.[15] However, the findings of Fujimoto et al.[12], Mirzaei et al.[6], Malekshahi et al. [13], and George et al.[12] showed significant differences in the gender of participants, of which the majority were men and the percentage included in studies ranged between 62.5% to 70 %. Therefore, the findings might be affected negatively by the unequal proportions of gender. Researchers investigated the tolerance of pain in male and female subjects and concluded that men have a higher tolerance for pain than women.[27]

While most studies looked at adult patients aged between 18 and 82 years, the study of George et al.[14] reported that one patient was aged only 12 years. Therefore, the generalizability could be affected in this review because of the wide difference in participants' ages.

These studies reported that many patients were on maintenance HD treatment for more than 10 years. Hence, patients' needle insertion frequency experience, history of HD treatment and mental status at the time of AVF cannulation might affect the sensation of pain severity.[28] Therefore, EMLA cream (or other local anaesthetics) may not give significant results for such patients. Thus, only those HD patients typically experiencing moderate to severe AVF needle pain should be considered for EMLA cream. A study by Heidari-Gorji et al.[29] found that anxiety can cause pain, while pain also causes anxiety. They found that anxiety among patients undergoing HD for a long duration was lower compared to those on dialysis for a short duration of time. And the sensation of pain was less among those patients on dialysis for long period of time.

Celik et al.[16] and George et al.[14] reported a significant effect of EMLA cream in their studies. However, Celik et al.[16] and George et al.[14] participants had diabetes of 24.4% and 38%, respectively. A RCT study conducted by Heidari-Gorji et al.[29] examined the perception of pain in 80 adult HD patients and found a relationship between pain sensation and diabetes status, but this argument needs further research to support it.

EMLA cream safety

Four studies reported information about the safety and tolerability of EMLA cream. The findings of Celik et al.[16] showed that skin bleaching was observed in 16% of EMLA group patients when EMLA was applied for between 45-60 minutes, whereas Malekshahi et al.[13] reported that only one patient complained of skin rash. However, in a study by Yin and Jiang,[21] examining the effect of EMLA cream on two groups, the first applied EMLA for 30 minutes, whereas the second group left it for 60 minutes. They concluded that EMLA cream when used for only 30 minutes was suitable and safe for HD patients without any skin side-effects observed. Therefore, it was clear that the duration of EMLA cream application might play a significant role in adverse reaction. Furthermore, studies suggested that HD patients had positive allergic reactions to prilocaine if used alone, and negative reactions to lidocaine, whereas no reactions were reported to the combination of the two in EMLA cream.[10]

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

Overall, it was obvious from the findings of the included studies that EMLA cream was effective in reducing and inhibiting AVF needle insertion pain. Therefore, this significant finding of the review might be important in clinical practice for adult HD patients. Although there were some limitations and factors that might reduce the effectiveness of EMLA cream in some studies, the

recommendation on the use of EMLA cream as a local anaesthetic for AVF pain reduction is conclusive.

Limitations

There are some limitations in this review. Although a comprehensive search was made to find all relevant papers in several databases, no hand-searching was carried out, no grey literature was found, and unpublished studies were not included, which can lead to publication bias. The search was limited to English studies only due to the time-frame restrictions, and the reviewers utilized 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 primary included studies, which examined the perception of pain, tend to be limited. Furthermore, selection bias could be maximized since most participants were men in all the included studies. While four studies were RCT, there was one quasi-experimental study, which could introduce some bias within the review. Aso, a low-ranked study on the hierarchy of evidence might contain some biases, such as performance, selection, and measurement biases. Moreover, due to the heterogeneity of primary studies, a meta-analysis was not conducted.

The data extraction and narrative synthesis were conducted and concluded by one reviewer, due to the time frame and academic restrictions. This can increase the risk of conclusions 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, which reported using different medication manufacturing companies, and this might affect the effectiveness of the EMLA cream used, having a different dose for each company.

Recommendations

This systematic review aimed to investigate the effectiveness of EMLA cream in reducing AVF needle insertion pain in adult HD patients compared with three other local anaesthesia methods used for the same purpose. The findings suggested that EMLA cream is an easy method that might have a strong effect in reducing and inhibiting AVF needle insertion pain in adult HD patients.

Although the findings were based on four high-quality studies, and one of moderate quality and high heterogeneity, further research is needed on EMLA cream with consideration of 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 seen to occur. However, EMLA cream might give the opportunity for the staff nurse to use both AVF cannulation techniques (Buttonhole and Rope Ladder) for their patients, according to preference, which could encourage the patients to adhere to their HD treatment without fear.

Despite the findings being built on four RCTs, considered high-quality studies, there are some recommendations on the need for future research on the use of EMLA cream in adult HD patients, in which significant and unbiased results would be maximized. In addition, inexact amounts of EMLA were applied, with different duration use, and there were more men than women across the studies, which may not give a strong conclusion. Accordingly, it is recommended to consider this in future research.

Furthermore, there was limited data regarding AVF needle puncture techniques and type of fistula (lower arm or upper arm area); hence, this needs to be considered more in future research. Moreover, HD patients' experience, diabetic status, and psychological issues could affect the sensation of needle pain. Therefore, further research is needed to highlight these important data in any topical anaesthetics research. Finally, EMLA cream is a complex medication (Lidocaine and Prilocaine) compared with the other three single medications (Lidocaine, Vapocoolant, Piroxicam). Accordingly, the investigation of two complex anaesthetics would be recommended and worth studying.

The paucity of available literature on the use of ELMA cream in the CKD population and its effectiveness warrants the need for more refined studies to determine the optimal utilization of its usage and dosage to make them most efficacious while minimizing known toxicities. Also, there

is a great need for prospectives research about the quality-of-life for improving pain management in end-stage kidney disease using EMLA cream.

It is recommended to consider using EMLA in patients in which (1) cannulation has been attempted using intradermal lidocaine and the patient continues to complain of pain, or (2) cannulation has not been attempted because the patient has a severe fear of needles, and in (3) children aged 18 years and under.

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

It is recommended to provide continuous education to patients about the correct application (how, how much, and when to apply) and the side effects of topical anaesthetics. Correct application of a topical anaesthetic maximizes the effectiveness of the medication in reducing needling pain. Important points to include in teaching include timing of application and onset of duration, Correct application, and Side effects: redness /rashes or whitening at the site of the application.

Conclusion

This systematic review aimed to investigate the effectiveness of EMLA cream in reducing AVF needle insertion pain in adult HD patients compared with three other local anesthesia methods used for the same purpose. The findings suggested that EMLA cream is an easy method that might have a strong effect in reducing and inhibiting AVF needle insertion pain in adult HD patients. Although the findings were based on four high-quality studies, and one of moderate quality and high heterogeneity, further research is needed on EMLA cream with consideration of this review's limitations.

Authors' Contribution

HAS. and IAS contributed to the conceptualization, the methodology was done by HAS, HS and WAW. Software by IAS and HS, validation was completed by WAR and HS, 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, 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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599 **Table 1 shows the various inclusion and exclusion criteria.**

	Inclusion Criteria	Exclusion Criteria
Population	Fully conscious adult hemodialysis patients (age > 18) years old Male or female with arterio-venous fistula (AVF) > 2 months	Hemodialysis patients, < 18 years old Patients with less than 2 months of AV fistula surgery Patients with unconscious state or (mental disorder) Patients with known history of neuropathy disease and skin allergies or eczema
Intervention	EMLA cream (mixture of Lidocaine and Prilocaine)	Pain relief and medicine Pharmaceutical intervention
Comparison	Alternative interventions (e.g. Lidocaine, Vapocoolant, Promaxicam)	-
Outcome	The effectiveness of EMLA cream in pain management during AVF needle insertion	Outcome not reported
Study design	Quantitative research including RCT and quasi-experimental studies Grey literature	Qualitative studies Case report Expert opinion
Setting	In-centre haemodialysis Unit (hospital)	Home dialysis Not in hospital
Time-span	No time limit	
Language	Studies published in the English language	Studies with only title and abstract in English, but the remainder in a different language Other languages

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Table 2: Shows the setting, country, sample size, gender, age range and hemodialysis experience of participants of the five studies.

Study ID.	Setting	Design	Sample size	Gender	Age Range	HD Experience
1. Mirzaei et al. (2018)	S. R Hospital,; Iran	Quasi-experimental study	40 Patients Pre/Post test similar	Male:25 62.5% Female:15 37.5%	Above 18 years (Mean age SD: 55.25 years).	More than 3 months on hemodialysis treatment, (Mean HD time 4.98 years) With easy AVF access
2. Fujimoto et al. (2020)	Six Japanese HD facilities; Japan	Multi-center randomized crossover study. RCT	66 Patients Group EL: 32 patients Group LE: 34 patients	Group EL: Male 20 (62.5%), Female 12 (37.5%). Group LE: Male 18 (52.9%) Female 16 (47.1%).	Above 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)
3. Malekshahi et al. (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	Above 18 years 3 patients (4%: younger than 30) 18 patients (24% between 30 to 49) 54 patients (72% older than 50 years)	More than 3 months on HD treatment Less than 1 year: 7 patients (9.3%) Between 1-3 years: 27 patients (34.7%) More than 3 years: 42 patients (56%) With HD vascular access

4. Celik et al. (2011)	S. University Hospital; Turkey	Randomized, placebo-controlled, crossover study RCT	41 Patients All patients randomly received three different interventions during three consecutive HD treatments	Male: 21 patients 51.2% Female:20 patients 48.8% No specific data reported for the groups	Between 32 to 82 years (57.5 ± 13.3)	10 Persons with diabetes (24.4%) 7 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%
5. George et al. (2014)	C. M. C. Hospital; India	Single-centre, crossover study RCT	50 Patients -EMLA group -Lidocaine -Infiltration group	Male patients: 35 (70%) Female patients: 15 (30%)	Between 12 to 82 years (Mean SD: 57.5) *One patient was only 12 years old*	22 Hypertensive patients (44%) 19 persons with diabetes (38%) 27 Patients with radio-cephalic fistula (54%) 23 Patients with brachiocephalic fistula (46%)

Table 3: Shows the Intervention, its manufacture, period, hemodialysis access/technique, needle size and the washout period

Study ID.	Intervention	Medicine (Drug) Manufacture	Period	HD Access Area / Technique	HD Needle Size/Diameter	Wash-Out	Follow-Up
1. Mirzaei et al. (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 5 pieces, applied on fistula site 2 mins before cannulation	Not reported	Total of 4 weeks Each intervention repeated 3 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 (researchers) Last week considered as wash-out to assess any interferences of medicines used
2. Fujimoto et al. (2020)	EMLA cream 1g, applied 1 hour before AVF puncture Lidocaine tape 18mg, applied 30 mins before AVF puncture	Reported	Total of 4 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 patients	Regular follow-up provided. Interventions drugs safety (side-effects) monitored

3. Malekshahi et al. (2017)	EMLA cream 2g Piroxicam cream 2g Placebo (Vitamin A+D) cream 2g Distributed to patients (25+25+25), instructed to apply 2g of each on fistula area and covered with transparent tape for 1 hour before HD session	Not reported	Two stages on 2 days Before and After HD session One session no intervention + one session with intervention	Not reported	16 gauge for all patients	Not reported	Follow-up measurement during intervention process provided Short-term side-effect checklist provided for assess intervention medications used
4. Celik et al. (2011)	Ethyl chloride Vapocoolant spray: 10cm distance for 2 seconds EMLA cream 5%: 2ml applied 45-60 mins before fistula needle insertion Placebo cream: 2 ml applied 45-60 mins before fistula needle insertion	Reported	4 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
5. George et al. (2014)	EMLA cream: applied a thick layer for 1 hour before cannulation	Not reported	4 HD sessions (4 days)	Traditional area technique	16 gauge for all patients	Not reported	Regular follow-up provided

	Subcutaneous infiltration of lidocaine performed by 26 gauge needle		50 patients randomized in 2 groups, each started with either EMLA or injectable Lidocaine infiltrated				

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

Study ID.	**Clinical Outcomes/ Findings**	**Measure/ Scale**	**Results/Findings**			
1. Mirzaei et al. (2018)	EMLA cream is most effective, easy and safe method.	During the first 3 HD sessions, there was no intervention (control group); therefore, patients were asked to report their pain experienced by using visual analogue scale (VAS). Then numeric pain assessment scale (ranging between 0 - 10) was used for intervention stage 2 minutes after fistula needles insertion (three methods).	***Control Group***	***Mean***	***SD***	***P. value***
			No intervention	7.45	0.88	P<0.001
			Experimental Group	***Mean***	***SD***	***P. value***
			EMLA cream (20 min)	2.8	0.7	P<0.001
			Lidocaine spray (5 s)	4.22	1.13	P<0.001
			Ice pack (2 min)	5.38	0.83	P<0.001
			• *Patients were satisfied with the EMLA cream as an easy and effective method in reducing pain during fistula needles insertion compared to Lidocaine spray and Ice pack.* • *Findings indicated that there were differences in mean pain intensity in the three methods, as the EMLA cream was significantly more effective than Lidocaine spray and Ice pack.*			

2. Fujimoto et al. (2020)	This paper examined three hypothesis: 1. EMLA cream inhibited pain during AVF puncture	A 100mm straight line VAS used to measure the AVF puncture pain by asking the patients to draw a slash on the line based on their received pain -Left end indicating minimal pain (no pain at all) -Right end indicating maximum pain (worst pain I have experienced)	**EMLA Followed by Lidocaine**	**Carry over effect**	**Period effect**	**Treatment effect**
			(n:32) 18.9± 18.2 * 7.3± 16.4	P= 0.64	P= 0.46	P= 0.00001
			Lidocaine Followed by EMLA	Carry over effect	Period effect	Treatment effect
			(n:34) 10.4± 11.7 19.0 ± 17.4	P= 0.64	P= 0.46	P= 0.00001
	2. Quality of Life (QOL) in HD patients (Carryover/period and treatment effect)	Patients asked to fill out evaluation form (Six subscales in the SF-36) Rating (Worst) 0 – 100 (Best)	*No statistically significant difference was observed in the treatment effect between EMLA and Lidocaine tape*			
		Role physical	P= 0.97			
		bodily pain	P= 0.99			
		Vitality	P= 0.96			
		Social functioning	P= 0.37			
		Role emotional	P= 0.11			
		Mental health	P= 0.95			
	3. No drug-related adverse events reported	The side effect of each intervention (drug) was evaluated after the examination	*No Adverse events reported*			

<table>
<tr><td></td><td></td><td></td><td colspan="6">Overall Result:
• EMLA cream is better than Lidocaine tape in reducing AVF puncture pain
• No significant differences between EMLA and Lidocaine in terms of patients' QOL
• No side-effects reported in both methods.</td></tr>
<tr><td rowspan="13">3. Malekshahi et al . (2017)</td><td rowspan="12">1. EMLA cream relieved pain caused by AVF cannulation</td><td rowspan="12">All patients asked to indicate the amount of pain after Cannulation by using visual scale (no pain 0-10 most pain)</td><td>Criteria</td><td>Mean</td><td>Median</td><td>SD</td><td>IR*</td><td>P value</td></tr>
<tr><td colspan="5">EMLA</td><td rowspan="9">0.001</td></tr>
<tr><td>Before</td><td>3.84</td><td>4</td><td>1.65</td><td>2.5</td></tr>
<tr><td>After</td><td>1.36</td><td>1</td><td>1.22</td><td>1.5</td></tr>
<tr><td>Reduction</td><td>2.48</td><td>3</td><td>1.58</td><td>2</td></tr>
<tr><td colspan="5">Piroxicam</td></tr>
<tr><td>Before</td><td>4.28</td><td>5</td><td>1.93</td><td>2.5</td></tr>
<tr><td>After</td><td>2.88</td><td>2</td><td>2.39</td><td>4</td></tr>
<tr><td>Reduction</td><td>1.40</td><td>1</td><td>2.18</td><td>2</td></tr>
<tr><td colspan="5">Placebo</td></tr>
<tr><td>Before</td><td>3.92</td><td>4</td><td>2.14</td><td>2.5</td></tr>
<tr><td>After</td><td>3.16</td><td>3</td><td>2.25</td><td>3.5</td></tr>
<tr><td>Reduction</td><td>0.76</td><td>0</td><td>1.71</td><td>1</td></tr>
<tr><td colspan="6">• Median pain reduction in EMLA group was much higher in the Piroxicam and Placebo groups
• EMLA cream is a more effective and easy method than Piroxicam gel in reducing the pain during AVF cannulation</td></tr>
<tr><td>2. Some skin bleaching in the EMLA group</td><td>Short –term side-effect checklist used for all three groups during and after medication used</td><td colspan="6">One hour after the application of medications:
• Skin bleaching observed in 16% of EMLA group
• No side-effect observed in the remaining groups (Piroxicam and vitamin A+D)</td></tr>
<tr><td></td><td></td><td>Control Group</td><td colspan="6">Control</td></tr>
</table>

<table>
<tr><td rowspan="4">4. Celik et al. (2011)</td><td rowspan="3">1. EMLA Cream is effective than ethyl chloride Vapocoolant in preventing AVF needle pain</td><td>Patients' pain assessed by VAS before and after the first intervention
VAS (0-100) score</td><td colspan="3">VAS Score: 0-75

Sever pain : 5 (12.25)</td></tr>
<tr><td>Intervention Group</td><td>EMLA cream</td><td>Ethyl chloride Vapocoolant spray</td><td>Placebo cream</td></tr>
<tr><td>Every patient received one of three interventions (EMLA, ethyl chloride Vapocoolant and placebo cream) and pain was measured by VAS</td><td>- 0-44

0 (0%)</td><td>- 0-53

0 (0%)</td><td>- 0-75

8 (19.5%)</td></tr>
<tr><td colspan="3">• EMLA cream resulted in significantly lower pain scores compared to ethyl chloride Vapocoolant spray and control groups.</td></tr>
<tr><td>2. Safety and tolerability of EMLA cream</td><td>All patients' AVF sites were inspected and reported 2 hours before and after cannulation for redness, swelling and local skin reactions</td><td colspan="3">• One patient who used EMLA cream had a transient skin rash</td></tr>
<tr><td rowspan="3">5. George et al. (2014)</td><td rowspan="3">1. EMLA cream is suitable for managing AVF cannulation pain</td><td rowspan="3">An hour before the HD treatment, patients asked to apply the medication.
Then used VAS (1-10) to assess the pain and data was recorded</td><td>Variables</td><td colspan="2">Mean ± SD</td><td>P value</td></tr>
<tr><td>Pain with anaesthetic</td><td>0</td><td>4.7 ± 1.05</td><td>0.00</td></tr>
<tr><td>Pain on cannulation</td><td>2.91 ± 1.31</td><td>2.02± 0.71</td><td>0.00</td></tr>
</table>

			• Pain score was significantly higher in infiltration group and the pain on cannulation was slightly higher in EMLA group. • Patients felt more stressed during Lidocaine infiltration than AVF cannulation which makes them prefer EMLA cream.
	2. Side-effects of EMLA reported	Any patients reporting itching, irritation and erythema during and after application of medication.	• No patients had side-effects.