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EMLA (Eutectic Lidocaine/Prilocaine) Cream to Reduce Pain during Arteriovenous Fistula Puncture in Adult Patients Undergoing Hemodialysis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objectives : Patients with end-stage renal disease requiring hemodialysis undergo life-sustaining renal replacement therapy to maintain physiological homeostasis. Intradialytic discomfort represents the predominant physical and psychological source of pain associated with hemodialysis procedures, with intensity noted particularly during cannulation of the arteriovenous fistula, which remains the gold standard modality for vascular access. These individuals perpetually endure procedural pain, substantially compromising the quality-of-life metrics and, in the extreme, refraining from adhering to this life-preserving therapy. Thus, pain management is of paramount importance. The eutectic mixture of local anesthetics (EMLA) cream is a topical formulation comprising 2.5% lidocaine and 2.5% prilocaine, designed for enhanced dermal penetration to provide effective local analgesia during percutaneous procedures. This study aims to systematically analyze the safety and efficacy of EMLA cream as pain control in patients undergoing hemodialysis.
Methods : This review was conducted in adherence to the PRISMA guidelines. The literature search was performed across electronic databases, including PubMed, ScienceDirect, and Scopus. Forest plots were generated to illustrate the pooled effect estimates for each outcome of interest using R software and Review Manager 5.4.
Results : Seven randomized controlled trials were deemed appropriate for review and meta-analysis, amounting to 1,375 patients. In comparison to placebo and alternative local anesthetics, pain intensity was lower in the EMLA group (mean difference [95% CI] of -2.58 [-3.22,-1.94], $p<0.00001$ and -0.99 [-1.57,-0.42], $p=0.0007$, respectively). EMLA provided similar pain reduction as nonpharmacological approaches did, although this comparison did not reach a statistical significance (mean difference [95% CI] of -0.26 [-1.98, 1.45], $p=0.76$). Concerning safety considerations, EMLA showed an acceptable adverse event profile with a low incidence of local cutaneous reactions (pooled proportion of 7% [95% CI 0.00–0.15], $I^2=75.1\%$, $p=0.0012$).
Conclusions : EMLA cream provides effective pain management during arteriovenous fistula cannulation in adult hemodialysis patients while demonstrating favorable patient tolerability and simple application in clinical practice.

Graphical Abstract of EMLA (Lidocaine:Prilocaine) in Reducing Pain in HD Patients.png

Graphical Abstract

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7 RCTs

1,375 patients on hemodialysis

EMLA vs control

Study or Subgroup	EMLA Mean	EMLA SD	EMLA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aihara 2019	4.7	2.11	15	6.86	2.07	15	11.5%	−2.16 [−3.66, −0.66]
Al-Jubouri 2024	4.5	1.84	270	6.97	1.56	273	29.3%	−2.47 [−2.76, −2.18]
Babamohamadi 2022	2.06	2.19	30	6.2	1.49	30	18.5%	−4.14 [−5.09, −3.19]
Çelik 2011	1.07	1.06	41	3.34	1.95	41	23.1%	−2.27 [−2.95, −1.59]
Malekshahi 2017	1.36	1.22	25	3.16	2.25	25	17.6%	−1.80 [−2.80, −0.80]
Total (95% CI)			**381**			**384**	**100.0%**	**−2.58 [−3.22, −1.94]**

Heterogeneity: Tau² = 0.34; Chi² = 14.05, df = 4 (P = 0.007); I² = 72%
Test for overall effect: Z = 7.92 (P < 0.00001)

Mean Difference IV, Random, 95% CI
Favours EMLA | Favours control

EMLA vs other local anesthetics

Study or Subgroup	EMLA Mean	EMLA SD	EMLA Total	other local anesthetics Mean	other local anesthetics SD	other local anesthetics Total	Weight	Mean Difference IV, Random, 95% CI
Al-Jubouri 2024	4.5	1.84	270	5.29	1.51	236	34.2%	−0.79 [−1.08, −0.50]
Çelik 2011	1.07	1.06	41	1.4	1.24	41	29.2%	−0.33 [−0.83, 0.17]
Malekshahi 2017	1.36	1.22	25	2.88	2.39	24	16.3%	−1.52 [−2.59, −0.45]
Shaheen 2022	2.94	1.27	32	4.81	2.13	32	20.3%	−1.87 [−2.73, −1.01]
Total (95% CI)			**368**			**333**	**100.0%**	**−0.99 [−1.57, −0.42]**

Heterogeneity: Tau² = 0.23; Chi² = 11.11, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 3.40 (P = 0.0007)

Mean Difference IV, Random, 95% CI
Lidocaine spray | Ethyl chloride spray | Proxicam gel | Proxicam gel
Favours EMLA | Favours other anesthetics

EMLA vs nonpharmacological management

Study or Subgroup	EMLA Mean	EMLA SD	EMLA Total	nonpharmacological Mean	nonpharmacological SD	nonpharmacological Total	Weight	Mean Difference IV, Random, 95% CI
Al-Jubouri 2024	4.5	1.84	270	3.98	1.32	262	55.4%	0.52 [0.25, 0.79]
Babamohamadi 2022	2.06	2.19	30	3.3	2.42	30	44.6%	−1.24 [−2.41, −0.07]
Total (95% CI)			**300**			**292**	**100.0%**	**−0.26 [−1.98, 1.45]**

Heterogeneity: Tau² = 1.36; Chi² = 8.28, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.30 (P = 0.76)

Mean Difference IV, Random, 95% CI
Cryotherapy | Valsalva Maneuver
Favours EMLA | Favours nonpharmacologic

Pain Reduction of EMLA vs other local anesthetics

Study or Subgroup	EMLA Mean	EMLA SD	EMLA Total	other local anesthetics Mean	other local anesthetics SD	other local anesthetics Total	Weight	Mean Difference IV, Fixed, 95% CI
Fujimoto 2020	1.9	1.74	34	0.73	1.64	32	36.9%	1.17 [0.35, 1.99]
Malekshahi 2017	2.48	1.58	25	1.4	2.18	25	22.1%	1.08 [0.02, 2.14]
Shaheen 2022	3.56	1.35	32	2.14	1.78	32	41.0%	1.42 [0.65, 2.19]
Total (95% CI)			**91**			**89**	**100.0%**	**1.25 [0.76, 1.75]**

Heterogeneity: Chi² = 0.32, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 4.95 (P < 0.00001)

Mean Difference IV, Fixed, 95% CI
Lidocaine tape | Proxicam gel | Proxicam gel
Favours other anesthetics | Favours EMLA

Local Side Effects of EMLA

Study	Events	Total	Proportion	Proportion	95%-CI	Weight
Aihara, 2019	0	15		0.00	[0.00; 0.22]	17.1%
Babamohamadi, 2022	10	30		0.33	[0.17; 0.53]	11.2%
Celik, 2011	1	41		0.02	[0.00; 0.13]	19.5%
Fujimoto, 2020	0	66		0.00	[0.00; 0.05]	20.6%
Shaheen, 2024	1	32		0.03	[0.00; 0.16]	18.8%
Malekshahi, 2017	4	25		0.16	[0.05; 0.36]	12.8%
Random effects model	**16**	**209**		**0.07**	**[0.00; 0.15]**	**100.0%**

Heterogeneity: I^2 = 75.1%, τ^2 = 0.0085, p = 0.0012

0 0.1 0.2 0.3 0.4 0.5

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Table 1. Characteristics of the included studies and the patients.

Author (year of publication)	Study design	Setting	Sample Size	Intervention	Pain Measurement	Age, in mean and SD (years)	Duration of hemodialysis, in mean and SD (months)	Concomitant Kidney Diseases	Diabetes
Alhara et al. (2019)	Randomized, placebo-controlled, double-blind, crossover trial	A dialysis unit in a hospital in Japan	30 patients EMLA: 15 patients, Placebo: 15 patients	**EMLA cream** (1 gram) was applied to a 10 cm^2 area above the stenotic lesion of the skin 60-120 minutes before the AVF puncture. **Placebo** (heparinoid cream) was applied to a 10 cm^2 area above the stenotic lesion of the skin 60 to 120 minutes before the AVF puncture.	**VAS** (non-graded 0-100 mm horizontal line) was assessed **immediately** after AVF puncture	68±11	53±50	Diabetic nephropathy (67%) Hypertensive nephrosclerosis (23%) Chronic glomerulonephritis (13%) Polycystic kidney disease (3%)	63%
Ali-Jaboori et al. (2024)	Randomized, controlled, open-label, trial	9 dialysis centers in Iraq	1041 patients EMLA: 270 patients, Cryotherapy: 262 patients, Lidocaine spray: 236 patients, Control: 273 patients	**EMLA cream** (1.5 gram) was applied to a 6 cm^2 area on the AVF for 28 minutes before the AVF puncture **Cryotherapy** was applied by placing five cubes of ice (4x2x2 cm) in a plastic bag and covering with a layer of cotton cloth for 5 minutes on the site of the AVF before the AVF puncture. **Lidocaine spray** was applied thrice on the AVF 5 minutes before the AVF puncture.	**VAS** (non-graded 0-100 mm horizontal line) was assessed **immediately** after AVF puncture	47.7±13.5	Not reported	Not reported	15.30%
Babamohamadi et al. (2022)	Randomized, controlled, open-label, trial	A dialysis unit in a hospital in Iran	90 patients EMLA: 30 patients, Valsalva maneuver: 30 patients, Control: 30 patients	**EMLA cream** (5 gram) was applied on the skin and covered with a transparent dressing by the patients 1 hour before the dialysis session. **Valsalva Maneuver** was performed through the instruction of blowing in a plastic tube connected to a mercury barometer after taking a deep breath, raising the mercury column to 20–25 mmHg for 16–20 seconds before the AVF puncture	**NRS** (0-10) was assessed **2 minutes** after AVF puncture	54.11±13.49	58.03±45.80	Not reported	55.50%
Celik et al. (2011)	Randomized, placebo-controlled, open-label crossover trial	A dialysis unit in a university hospital in Turkey	41 patients were randomly assigned to different interventions: EMLA, ethyl-chloride spray, and control, in consecutive dialysis treatments	**EMLA cream** (2 ml) was applied to the two puncture sites under an occlusion dressing 45-60 minutes before the AVF puncture. **Ethyl-chloride (sapocoolant) spray** was sprayed at the distance of approximately 10 cm for 2 seconds. The liquid sprayed on the skin was allowed to evaporate for 10 seconds and the AVF puncture was performed 20 seconds later. **Placebo** cream was applied to the two puncture sites under an occlusion dressing 45-60 minutes before the AVF puncture.	**VAS** (non-graded 0-100 mm horizontal line) was assessed **immediately** after AVF puncture	57.0±13.3	70.5±57.4	Unknown etiology (41.5%) Diabetic nephropathy (24.4%) Hypertension (14.6%) Glomerulonephritis (9.8%) Amyloidosis (2.3%) Lupus nephritis (2.4%)	24.40%
Fujimoto et al. (2020)	Randomized, open-label, crossover trial	6 dialysis centers in Japan	66 patients EMLA followed by lidocaine tape: 32 patients, Lidocaine tape followed by EMLA: 34 patients	**EMLA cream** (1 gram) was applied using a fixation tape at each puncture site 1 hour before the AVF puncture. **Lidocaine tape** was applied at each site to be punctured 30 minutes before the AVF puncture.	**VAS** (non-graded 0-100 mm horizontal line) was assessed **immediately** after AVF puncture	65.84±10.57	73.17±52.08	Not reported	65.15%
Malekshahi et al. (2017)	Randomized double-blind trial	A dialysis unit in a hospital in Iran	75 patients EMLA: 25 patients, Piroxicam: 25 patients, Placebo: 25 patients	**EMLA cream** (2 grams) was applied on the skin and covered with a transparent dressing by the patients 1 hour before the dialysis session. **Piroxicam gel** (2 grams) was applied on the skin and covered with a transparent dressing by the patients 1 hour before the dialysis session. **Placebo** cream (2 grams of vitamin A and D cream) was applied on the skin and covered with a transparent dressing by the patients 1 hour before the dialysis session.	**Visual scale** (a 10 cm ruler) was assessed **immediately** after AVF puncture	≥ 50 (72%) 30-49 (24%) <30 (4%)	Not reported	Not reported	Not reported
Shaheen et al. (2022)	Randomized double-blind crossover trial	A dialysis unit in a military hospital in Pakistan	32 patients EMLA followed by piroxicam gel: 16 patients, Piroxicam gel followed by EMLA: 16 patients	**EMLA cream** 5% was applied as a thick film without rubbing into the skin and covered with an adhesive tape 1 hour before the AVF puncture. **Piroxicam gel** 0.5% was applied as a thick film without rubbing into the skin and covered with an adhesive tape 1 hour before the AVF puncture.	**NRS** (0-10) was assessed **immediately** after AVF puncture	46.44±11.58	38±28.89	Not reported	25%

AFV=arteriovenous fistula, EMLA=eutectic mixture of local anesthetics, NRS=numerical rating scale, SD=standard deviation, VAS=visual analogue scale