

Effectiveness of various formulations of local anesthetics and additives for topical anesthesia – a prospective, randomized, double-blind, placebo-controlled study

Christian Weilbach¹
Christian Hoppe²
Matthias Karst³
Michael Winterhalter⁴
Konstantinos Raymondos³
Arthur Schultz³
Niels Rahe-Meyer²

¹Department of Anesthesiology, Intensive Care, Emergency Medicine and Pain Therapy, St. Josefs-Hospital Cloppenburg, Cloppenburg, ²Clinic for Anesthesiology and Operational Intensive Care, Franziskus Hospital Bielefeld, Bielefeld, ³Clinic for Anesthesiology and Intensive Care, Medizinische Hochschule Hannover, Hannover, ⁴Clinic for Anesthesiology and Pain Therapy, Klinikum Bremen-Mitte, Bremen, Germany

Background: Topical anesthesia is used to control pain associated with many procedures in medicine. Today, the product most commonly applied for topical anesthesia in Germany is EMLA® (lidocaine/prilocaine). However, since prilocaine is a methemoglobin-inducing agent, there are limitations to its use, especially in neonates and infants. The aim of this study was to evaluate the effect of prilocaine and lidocaine as well as propylene glycol, a penetration enhancer, and trometamol, a buffer substance, in anesthetic creams.

Patients and methods: Twenty-nine healthy adults participated in this study. Standardized creams with eight different compositions were applied and left for 20, 40 or 60 min. After exposure to standardized painful stimuli (blunt/sharp with pressures of 0.2, 0.4 or 0.8 N), subjects rated the experimental pain using a visual analog scale.

Results: Significant results were only found with an exposure time of 60 min and a stamp pressure of 0.8 N. At a concentration of 20%, lidocaine was more effective compared to placebo and equally effective compared to lidocaine/prilocaine in controlling pain. The analgesic effect of the cream containing lidocaine 10% and additional trometamol was significantly superior to that of placebo and non-inferior to that of lidocaine/prilocaine. In this study, the penetration enhancer propylene glycol did not accelerate the onset of the analgesic effect. In contrast, the addition of trometamol (Tris/THAM) accelerated the onset of the effect compared to the native formulation (at 0.4 and 0.8 N). In all of the adult subjects of this study, the minimum exposure time was 60 min for any of the tested topical anesthetic creams.

Conclusion: The results of this study indicate that a cream containing 20% lidocaine, 38% trometamol and 10% propylene glycol may be used as an alternative to lidocaine/prilocaine with a comparable effect and without the need to extend exposure time.

Keywords: local anesthetics, topical anesthesia, EMLA®, topical anesthetic cream, lidocaine, prilocaine

Introduction

The topical effect of local anesthetics (LAs) has been known since 1884 when Koller first successfully used a cocaine solution for anesthesia in ophthalmic surgery.¹

With the surge in awareness of the importance of pain measurement and treatment in all fields of medicine,² LAs for topical anesthesia before punctures and other procedures have been widely adopted since the 1980s. The various products used differ in formulation and posology.³

Correspondence: Christian Weilbach
Department of Anesthesiology, Intensive Care, Emergency Medicine and Pain Therapy, St. Josefs-Hospital Cloppenburg, Krankenhausstraße 13, 49661 Cloppenburg, Germany
Email christian.weilbach@kk-om.de

Today, the product most commonly applied for topical anesthesia in Germany is EMLA® (lidocaine/prilocaine), which contains lidocaine and prilocaine in equal parts as active ingredients. However, since prilocaine is a methemoglobin-inducing agent, there are limitations to its use, especially in neonates and infants.^{4,5} This cream is also contraindicated in patients allergic to prilocaine.

The aminoamides lidocaine and prilocaine have similar physicochemical characteristics (e.g., both have a pKa value of 7.9)⁶ and are comparable in strength and duration of action.

The local availability of an LA is determined by the spread of the agent in the tissue and its diffusion along the concentration gradient.

Due to their low pKa values and lipophilic nature, both substances show a comparable fast onset of action. With increasing concentrations of the active ingredients, the strength of the effect increases as well.

When LAs are applied transdermally, the condition of the skin (extent of barriers to penetration), apart from skin perfusion and pH, has a significant impact on the onset and duration of the effect. Here, the lipophilic properties of an LA accelerate the passage through the stratum corneum, while the hydrophilic properties facilitate the passage through the remaining layers of the dermis.

With lidocaine/prilocaine cream, the strongest analgesic effect is achieved 45–60 min after application;⁷ among pre-term infants and newborns, the onset is faster as the barriers to penetration are lower.

While having the disadvantage of inducing methemoglobinemia, prilocaine has the advantage of lower cardio- and neurotoxicity compared to lidocaine.⁸

The aim of this study was to evaluate the effect of prilocaine and lidocaine as well as propylene glycol, a penetration enhancer, and trometamol, a buffer substance, in anesthetic creams containing various combinations and doses of these ingredients on the onset and duration of topical anesthesia.

Patients and methods

This trial was approved by the ethics committee of Hannover Medical School. Written informed consent was obtained from all the participants.

The study was conducted as a randomized, double-blind intervention study. For randomization, randomization tables provided by the Department of Biometry, Hannover Medical School, were used. Both the independent person who applied the cream and the subjects were blinded to the type of cream used.

The exclusion criteria were as follows: allergy and/or intolerance to the ingredients of the creams, congenital idiopathic methemoglobinemia (glucose-6-phosphate dehydrogenase deficiency) and general signs of relevant acute or chronic disease, such as infections, medication use or psychological distress at the day of testing or needle phobia.

Altogether, 29 healthy volunteers aged between 23 and 63 years (21 male) were included in the study.

Eight creams containing lidocaine (LA), prilocaine (LA), trometamol (Tris[hydroxymethyl]-aminomethan [Tris/THAM]) and propylene glycol (penetration enhancer) in various compositions (Table 1) were applied to the skin of the subjects in a standardized way using a 5-mm thick 200 × 200 mm template.

Standardized areas on the forearms of the subjects were exposed to the creams for 20, 40 and 60 min, respectively.

After wiping off the cream, a stimulation device was used to apply blunt (stamp) and sharp (single-use needles; Sterican; 0.55 mm diameter, 60° bevel) stimuli with a defined force (0.2/0.4/0.8 N).

The subjects rated the pain caused by the stimuli using a visual analog scale (VAS).⁹

The primary end points of this study were to show the superiority of the topical use of lidocaine over placebo and the non-inferiority of lidocaine to lidocaine/prilocaine. The values for the primary end points represented the degree of pain suppression as measured by the VAS after an exposure time of 60 min, using a pressure of 0.8 N.

Table 1 Study cream compositions

	Lidocaine (%)	Prilocaine (%)	pH (%)	Trometamol (Tris) (%)	Propylene glycol (%)	Base cream (g)	Lidocaine (%)
Placebo	0		Alkaline	1	10	0	98.92
3	10		Native	0	10	1.5	86.16
2	5		Alkaline	10	10	1.7	81.40
5	10		Alkaline	20	0	0	66.54
1	10		Alkaline	20	10	3.5	62.63
8	10		Alkaline	20	15	8.5	57.91
6	20		Alkaline	38	10	7.3	27.43
Lidocaine/prilocaine	2.5	2.5	Alkaline	?	?	?	?

Note: ? indicates the exact formula is not available.

Table 2 Descriptive statistics data on components of the study cream

Cream	Number of observations	VAS mean	VAS SD	VAS median	Lower quartile	Upper quartile
Lidocaine/prilocaine	29	0.583	1.099	0.200	0.100	0.400
Lidocaine 5%	29	1.014	1.178	0.400	0.300	1.200
Lidocaine 10% (mean)	87	0.947	1.034	0.600	0.200	1.400
Lidocaine 10% (propylene glycol 0%)	29	0.834	1.077	0.400	0.200	0.700
Lidocaine 10% (propylene glycol 10%)	29	0.883	0.788	0.700	0.200	1.300
Lidocaine 10% (propylene glycol 15%)	29	1.124	1.206	0.800	0.300	1.500
Lidocaine 20%	29	0.766	0.774	0.500	0.400	0.800
Lidocaine native	29	1.076	1.242	0.600	0.300	1.300
Placebo	29	1.255	1.423	0.600	0.400	1.900

Abbreviations: VAS, visual analog scale; SD, standard deviation.

Table 3 Differences between the VAS means of two study creams (pressure: 0.8 N; exposure time: 40 min)

Comparison	Number of observations	VAS mean	VAS SD	VAS median	Lower quartile	Upper quartile
Lidocaine 5% vs lidocaine/prilocaine	29	0.431	1.018	0.200	0.000	0.700
Lidocaine 10% vs lidocaine/prilocaine	29	0.300	1.241	0.200	0.000	0.900
Lidocaine 20% vs lidocaine/prilocaine	29	0.183	0.986	0.200	0.100	0.400
Placebo vs lidocaine 5%	29	0.241	1.013	0.200	-0.200	0.900
Placebo vs lidocaine 10%	29	0.372	1.230	0.400	-0.200	0.800
Placebo vs lidocaine 20%	29	0.490	0.977	0.200	-0.100	0.900

Abbreviations: VAS, visual analog scale; SD, standard deviation.

Only measurements obtained at a stamp pressure of 0.8 N and an exposure time of 60 min were included in the primary analysis because no significant advantages over placebo were found for shorter exposure times and lower stamp pressures.

Results

The subjective VAS pain data showed the lowest mean for lidocaine/prilocaine with 0.583 (Table 2); the mean for the effect of lidocaine 20% was 0.766 which was in the same order of magnitude. The VAS values obtained with creams containing lidocaine in lower concentrations or placebo were higher.

In the primary and secondary analyses, paired comparisons of two study creams were carried out, from which the difference between the means was calculated (Table 3). The highest VAS value differences were found for the pairs placebo vs lidocaine 20% (0.490) and lidocaine 5% vs lidocaine/prilocaine (0.431).

Student's *t*-test for paired samples was used to determine the superiority/non-superiority of the active ingredient over placebo.

For non-inferiority comparisons, a shifted *t*-test with a non-inferiority margin of 1 was used. For each comparison, the estimator (mean of differences) and the corresponding two-sided 95% confidence interval were also reported (Table 4).

For each lidocaine concentration, the superiority over placebo was accepted if the lower limit of the 95% confidence interval for the difference in means (placebo vs lidocaine) was >0 (Table 5). For each lidocaine concentration, the non-inferiority to lidocaine/prilocaine was accepted if the upper margin of the 95% confidence interval for the difference in means (lidocaine vs lidocaine/prilocaine) was >1 (Table 6).

For lidocaine 20% vs placebo, the *p* value was significant with 0.0117 for a difference in means of 0.490 (95% confidence interval, 0.118–0.861). Since the *p* value is smaller than the predefined type I error (0.05), the superiority of lidocaine 20% over placebo is proven. The same applies to the non-inferiority of lidocaine to lidocaine/prilocaine with a difference in means of 0.183 for a 95% confidence interval of 0.192–0.558 and a *p* value of 0.0001. While for lidocaine 10%, no superiority over placebo was demonstrated

Table 4 Superiority of lidocaine 20% to placebo and non-inferiority of lidocaine to lidocaine/prilocaine

Pairwise comparison	Difference in means	95% Confidence interval	<i>p</i> value
Superiority of lidocaine 20% to placebo	0.490	0.118/0.861	0.0117
Non-inferiority of lidocaine 20% to lidocaine/prilocaine	0.183	-0.192/0.558	0.0001

Table 5 Superiority of lidocaine over placebo – effect of exposure time and stamp pressure

Exposure time (min)	Stimulus (N)	Comparison	Difference in means	95% Confidence interval		p value
40	0.2	Placebo vs lidocaine 20%	0.248	–0.078	0.574	0.1302
		Placebo vs lidocaine 10%	0.148	–0.208	0.505	0.4016
		Placebo vs lidocaine 5%	0.083	–0.173	0.339	0.5136
	0.4	Placebo vs lidocaine 20%	0.307	–0.225	0.838	0.2469
		Placebo vs lidocaine 10%	0.366	0.032	0.699	0.0331
		Placebo vs lidocaine 5%	0.224	–0.208	0.656	0.2968
60	0.8	Placebo vs lidocaine 20%	1.072	0.528	1.617	0.0004
		Placebo vs lidocaine 10%	0.821	0.328	1.314	0.0020
		Placebo vs lidocaine 5%	0.745	0.297	1.193	0.0020

Table 6 Non-inferiority of lidocaine vs lidocaine/prilocaine – effect of exposure time and stamp pressure

Exposure time (min)	Stimulus (N)	Comparison	Difference in means	95% Confidence interval		p value
40	0.2	Lidocaine 20% vs lidocaine/prilocaine	0.117	–0.052	0.286	<0.0001
		Lidocaine 10% vs lidocaine/prilocaine	0.217	–0.046	0.480	<0.0001
		Lidocaine 5% vs lidocaine/prilocaine	0.283	0.093	0.473	<0.0001
	0.4	Lidocaine 20% vs lidocaine/prilocaine	0.217	–0.107	0.541	<0.0001
		Lidocaine 10% vs lidocaine/prilocaine	0.159	–0.136	0.453	<0.0001
		Lidocaine 5% vs lidocaine/prilocaine	0.300	0.032	0.568	<0.0001
60	0.8	Lidocaine 20% vs lidocaine/prilocaine	–0.079	–0.349	0.190	<0.0001
		Lidocaine 10% vs lidocaine/prilocaine	0.172	–0.055	0.400	<0.0001
		Lidocaine 5% vs lidocaine/prilocaine	0.248	0.000	0.497	<0.0001

($p=0.1143$), a trend toward non-inferiority to lidocaine/prilocaine ($p=0.0051$) was revealed. Since the superiority of lidocaine 10% over placebo could not be demonstrated, the confirmatory analysis ended there.

In this study, the penetration enhancer propylene glycol did not accelerate the onset of the analgesic effect ($p>0.05$). In contrast, the addition of trometamol (Tris/THAM) accelerated the onset of the effect compared with the native formulation (at 0.4 N, $p=0.0331$; at 0.8 N, lidocaine, $p=0.002$).

Discussion

In our study, we formulated creams for topical anesthesia of the skin with various ingredients and compared their effects on onset time and strength of the analgesic effect.

These formulations, containing the LA agent lidocaine in various concentrations, trometamol (Tris/THAM) to create an alkaline environment and propylene glycol as a penetration enhancer, were compared to lidocaine/prilocaine cream.

Since lidocaine/prilocaine contains prilocaine, a methemoglobin-inducing agent, this product has only limited use in pediatric patients, especially among neonates.^{4,5}

The question to be answered was whether cream formulations containing lidocaine in various concentrations in facultative conjunction with additives for enhanced penetration

and tissue alkalization can achieve topical anesthesia equal to that achieved with lidocaine/prilocaine.

One primary end point of this study was the superiority of lidocaine over placebo. For an exposure time of 20 min, none of the tested lidocaine concentrations (5%, 10%, 20%) showed an advantage over placebo with regard to their analgesic effects. Only when the exposure time was increased to 40 min, the analgesic effect of the lidocaine cream was significantly stronger than that of placebo, but only for lidocaine 10% cream. After an exposure time of 60 min, all creams (lidocaine 5%, 10%, 20%) had a significant effect (Table 4).⁸ There is no pharmaceutical preparation for topical anesthesia available that achieves a shorter time to onset of a satisfactory anesthetic effect in adults.⁸

The second primary end point of this study was the non-inferiority of lidocaine 20% to lidocaine/prilocaine. This was shown for each of the three concentrations of lidocaine and each of the evaluated exposure times (20, 40 and 60 min) (Table 4).

Adding trometamol to the cream enhanced the effect of lidocaine. This is understandable because with the use of a buffer in an alkaline tissue environment, the lipophilic LA agent can penetrate better through neuronal membranes into the cytoplasm of the nerve cells.¹⁰ In contrast, adding propylene glycol did not result in an acceleration or augmentation of the

analgesic effect of the lidocaine cream within the set-up of this study. Rather, there was a (nonsignificant) trend toward a reduction in the strength of the effect (negative differences of means); this study does not have the scope to explain this finding.

Any discrepancies between the results of our study and those of other studies may be due to the lack of a quantitatively standardized application of the cream and strength of the painful stimulus.¹⁰

Neither with lidocaine/prilocaine nor with our lidocaine cream, it was possible to reduce the exposure time of 45–60 min until the onset of a satisfactory effect (in adults). This is in line with earlier studies.^{11,12} Shorter application times (20–30 min) were only achieved with a heated topical lidocaine/prilocaine patch (Synera®/Rapydan®).¹³

Especially in neonates and infants, the induction of methemoglobin by prilocaine is of importance, as for this reason topical analgesia with lidocaine/prilocaine is restricted to only a limited number of skin areas.^{5,6,14} Therefore, it is reasonable to contemplate whether a cream for topical anesthesia without prilocaine (e.g., based on the formulation evaluated in this study) should be made available to pediatricians and pediatric anesthetists as a finished medicinal product.

Conclusion

The results of this experimental study indicate that a cream containing 20% lidocaine, 38% trometamol and 10% propylene glycol may be used as an alternative to lidocaine/prilocaine with a comparable effect and without the need to extend exposure time. However, further studies in a clinical setting are needed to establish the safety and effectiveness of this cream in clinical practice, especially in neonates and infants.

Disclosure

The authors report no conflicts of interest in this work.

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