Archives of Anesthesiology and Critical Care (Autumn 2020); 6(4): 152-155.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison the Efficacy of EMLA Cream versus EMLA with High Frequency Sonophoresis in Decreasing Onset Time to Topical Anaesthesia in Adult Volunteers: A Pilot Study

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ARTICLE INFO

Article history:
Received 10 February 2020
Revised 01 March 2020
Accepted 15 March 2020

Keywords:
Sonophoresis;
EMLA cream

ABSTRACT

Background: Sonophoresis or phonophoresis is a well-known transdermal drug delivery mechanism. Usage of high frequency ultrasound for sonophoresis was initiated in late 1950s while the usage of low-frequency sonophoresis was investigated significantly during the past two decades. The objective was to analyze the efficacy of high frequency ultrasound probe in the penetration of EMLA cream in decreasing onset time for topical anaesthesia in adult healthy volunteers.

Methods: A prospective, open labelled, comparative study was conducted on patients reporting at the Pain Clinic our institute. Subjects received the intervention USG probe with EMLA either on the left or the right hand based on a random number chart, with the other hand of the same subject acting as a control. In group USG, the probe was applied directly on the cream without any added pressure. Sensory testing was done every 10 minutes by pin prick on both the hands of the patients NRS scores of both the hands were recorded at 10.20,30 and 40 minutes.

Results: Total 20 patients were selected for the study. Although a significant decrease in the pain scores in both the groups was observed after 40minutes, ($p<0.05$) both the groups are comparable at each point of time. We could not find any significant decrease in pain scores when groups are compared in intervals during the study period.

Conclusion: There is no significant difference in decreasing the intensity of pain scores upon application of ultrasound over EMLA in an adult population. Further studies have to be done to prove the efficacy in a larger population and pediatric ones.

Sonophoresis or phonophoresis is a well-known transdermal drug delivery mechanism. High frequency probe assisted delivery of drugs has been well studied in the past compared to low frequency probe delivery. Clinical studies have proved the efficacy of both the high and low frequency ultrasound probes in the transdermal delivery of drugs with different mechanisms. Usage of high frequency ultrasound for sonophoresis was initiated in late 1950s while the usage of low-frequency sonophoresis was investigated significantly during the past two decades [1-2]. The exact mechanism of sonophoresis was not understood till date. It was thought to be due of cavitation [3-4].

This principle was used for the clinical effects of many drugs topically. Eutectic mixture of local anesthetic (EMLA) is one of the most widely used topical analgesic in the perioperative period since the early 1980s [5]. One gram of EMLA cream contains 25 mg of lignocaine and 25 mg of prilocaine in equal proportions. Interesting factor is its formulation as an oil-in-water emulsion, which yields 80% concentration in the oil droplets, which facilitates its skin penetration in lesser time [6]. Despite its proven efficacy, its use has been limited by a few

The authors declare no conflicts of interest.

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factors such as availability and long onset time of 40minutes to 60 minutes [7-8].

In the perioperative areas and in the Emergency Department (ED), it is standard practice for children to receive topical anaesthesia before the procedures like cannulation to decrease the pain during procedure. Commonly used agents are EMLA® (eutectic mixture of local anaesthetics; 5% lidocaine and prilocaine in a 1:1 aqueous emulsion) and 4% amethocaine gel. Several studies have demonstrated that EMLA cream decreases the pain associated with venipuncture and venous cannulation after specified duration [9-10].

One of the alternatives for conventional drug administration in recent decades is the transdermal transport of drugs. It possesses various advantageous properties over conventional drug administration. The main barrier for this mode of delivery is the stratum corneum, which impedes percutaneous transport [11]. To overcome this barrier, ultrasound-based transdermal delivery of drugs is one of the techniques that is being investigated.

Our aim is to study the effect of sonophoresis on the transdermal penetration of EMLA cream. The objective was to analyze the efficacy of high frequency ultrasound probe in the penetration of EMLA cream in decreasing onset time for topical anaesthesia in volunteers.

Methods

A prospective, open labelled, comparative study was conducted on patients reporting at the Pain Clinic of our institute, after explaining the details of the study to the patients and obtaining their consent for participation in the same. This study was approved by AIIMS Rishikesh Institute ethics committee. As there are no previous studies done on this topic, a total of 20 patients were recruited for the study.

Inclusion criteria were all the healthy volunteers of age between 18 years to 60 years. Exclusion criteria was patients with coagulopathy or bleeding disorders and/or patients on anticoagulants, infection at the site of pin prick and hypersensitivity to local anesthetic agents used.

Subjects received the intervention USG probe with EMLA either on the left or the right hand based on a random number chart, with the other hand of the same subject acting as a control. For analysis total number of intervention hands and control hands were considered.

EMLA cream was applied on both groups for 40 minutes. In group USG, the probe was applied directly on the cream without any added pressure. Sensory testing was done every 10 minutes by pin prick on both the hands of the patients NRS scores of both the hands were recorded at 10.20,30 and 40 minutes.

The primary outcome, was detection of ≥50% or ≥4 point reduction in an 11-point numeric scale (NRS 11) to pin prick.

Results

Total 20 patients were selected for the study. Demographic data were presented in (Table 1). Comparison of NRS pain score was done at different time intervals (Table 2). Statistical analysis of intergroup variables at each specific time was done with Student T test using SPSS Statistics (IBM Corporation, Somers, NY) software, version 20.0 at intervals. And the intra group analysis was done by one way repeated ANOVA test. $P<0.05$ was taken as significant value.

Although there is a significant decrease in the pain scores in both the groups after 40minutes both the groups are comparable at each point of time. There is no significant decrease in pain scores when groups are compared in intervals.

Table 1- Demographic data of the patients.

S.No.	Parameter	Values (mean+SD)
1.	Number of Patients	20
2.	Gender (male: female)	8:12
3.	Age (years)	48+12
4.	Weight (kilograms)	64+11
5.	Height (cms)	165+9
6.	BMI	23+1.5

Table 2- Showing the NRS values (mean+SD).

	Control group	USG group	P value
0 Minutes	10	10	0.5
10 Minutes	10	10	0.5
20 Minutes	9.86+0.49	9.9+0.38	0.38
30 Minutes	7.6+0.78	7.53+1.09	0.39
40 Minutes	6.4+0.48	6.4+0.87	0.36
P value	0.001*	0.001*	

Discussion

Authors did not find a significant difference in the pain scores of the healthy volunteers till 40min of both the groups. After 40min a significant difference of pain scores was observed in both the groups (P value< 0.001*).

Conventional methods like the use of insulin needles for diabetes, can be painful. As a result, patients can be noncompliant with the prescribed medication resulting in severe medical complications. Several non-invasive methods were discovered for transdermal drug delivery in the recent past such as chemical medication using liposomes and chemical enhancers or physical mechanisms such as micro needles, iontophoresis, electroporation, and ultrasound. Ultrasound enhanced transdermal drug delivery offers advantages over other traditional drug delivery methods which are often invasive and painful.

Various studies were done to prove the efficacy of ultrasound based transdermal delivery of drugs. Because of the low skin permeability to these relatively large molecules its application in the practical point of view is limited till now.

Feiszthuber et al. [12] studied the effect of sonophoresis of insulin into skin agar models and porcine skin in vitro and found significant results. Yu et al. [13] studied the effect of sonophoresis on the transdermal delivery of rivastigmine versus transdermal patches and found the transdermal delivery of drug using ultrasound probe was significantly high. Other drugs like doxorubicin were also studied and found significant results [14]. This list of drugs is increasing day by day. Stratum corneum is the main barrier for the sonophoresis.

After extensive review of literature, we could not find out the effect of ultrasound on the transdermal delivery of commonly used EMLA cream in the preoperative and emergency department. The molecular weight of components of EMLA cream such as the Lignocaine is 234Da while the prilocaine is 220Da. From the past two decades the usage of Eutectic mixture of local anesthetic (EMLA) cream has grown in the perioperative area during cannulation [5]. The composition of one gram of EMLA is 25 mg of lignocaine and 25 mg of prilocaine in equal proportions. As it is oil in water emulsion and the proportion of oil formulation is high the penetration becomes easier [6].

In our study we did not find any significant difference between two groups of patients. This would be because of the skin permeability factor in the elder patients. The successful delivery of a drug across the skin depends on the physicochemical properties of the drug, such as molecular weight (<500 Da) shows better penetration of skin [15]. Another factor which affects is the gender of the patient in which males have more thickness of SC than the females [16]. When coming to the issue of age there are two school of thoughts like the stratum corneum is intact through-out the aging and the penetration of drugs decreases as the age increases [16] and the other factors are ethnicity, skin hydration, temperature etc.

Conclusion

There is no significant difference in decreasing the intensity of pain scores upon application of ultrasound over EMLA in an adult population. Further studies have to be done to prove the efficacy in a larger population and pediatric ones.

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