Arabian Journal of Pediatric Dentistry

Vol 2 (1)47 :-67

المجلة العربية لطب أسنان الاطفال

المجلد 2 العدد1 : الصفحات47-67

Investigating the impact of drug delivery systems on the efficacy of EMLA cream for palatine anesthesia in children aged 7 to 11 years.

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Abstract

Background & Aim: This research aims to find alternatives to the traditional painful palatine local injection used during the extraction of upper temporary teeth. The study seeks to enhance the effectiveness of EMLA cream over a suitable duration for child response (3 minutes) by utilizing drug delivery systems, including a permeability enhancer (DMSO), oral patches, and microneedle patches for palatine injections while using only lidocaine injections from the vestibular side.

Materials and Methods: The research sample consisted of 75 children, who were
randomly divided into five groups of 15 children each. The studied material or method was applied to each group as follows:

Group 1: (Conventional local palatine injection (control group)).

Group 2: (EMLA cream only).

Group 3: (Chemical permeability enhancer DMSO with EMLA cream).

Group 4: (Oral patches with EMLA Cream).

Group 5: (Microneedle patches dissolved with EMLA Cream).

Physiological scales were utilized to assess pain in the study. A pulse oximeter was employed to measure heart rate and oxygen saturation at different stages of the procedure (application, probing, and extraction) across the various groups being studied.

Results: The findings revealed that, at a 95% confidence level, there were no statistically significant differences in the average changes in oxygen saturation among the groups at any of the stages analyzed. Additionally, during the extraction phase, no significant differences were found in the average changes in heart rate between the research groups. However, for the other stages (application and probing), the significance level was found to be less than 0.05.

Conclusion: Both conventional palatal injections and extractions are generally painful procedures. By incorporating drug delivery systems, we can enhance the efficiency and comfort of the procedure for children.

Keywords: Permeability Enhancer, Oral Patches, Microneedle Patches.

Received: 9/1/2023

Accepted:5/2/2023

ISSN (Online):3078-4522

http://journal.damascusuniversity.edu.sy/index.php/index/index

دراسة دور بعض أنظمة توصيل الأدوية في تعزيز فعالية كريم EMLA في التخدير الحنكي عند الأطفال بأعمار تتراوح من 7-11 سنة

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الملخص:

خلفية البحث وهدفه: هدف هذا البحث لإيجاد بدائل للحقن الموضعي الحنكي التقليدي المؤلم عند قلع الأسنان المؤقتة العلوية وذلك عن طريق تعزيز فعالية كريم EMLA خلال زمن مناسب لتقبل الطفل (3 دقائق) باستخدام أنظمة توصيل الأدوية (معزز النفاذية(DMSO) – اللصاقات الفموية – لصاقات الإبر المجهرية) للتخدير الحنكي غير متبوع بحقنة تقليدية موضعية والاكتفاء بحقنة (ليدوكائين) من الجهة الدهليزية.

مواد البحث وطرائقه: تكونت عينة البحث من 75 طفلاً، تم تقسيم العينة بشكل عشوائي إلى 5 مجموعات لكل مجموعة 15 طفلاً، ليتم تطبيق المادة أو الطريقة المدروسة والخاصة بكل مجموعة كما يلي:

المجموعة الأولى: (حقن موضعي حنكي تقليدي (الشاهدة)).

المجموعة الثانية: (كريم EMLA لوحده).

المجموعة الثالثة: (معزّز نفاذية كيميائي DMSO مع كريم EMLA).

المجموعة الرابعة: (لصاقات فموية مع كريم EMLA).

المجموعة الخامسة: (لصاقات إبر مجهرية قابلة للذوبان مع كريم EMLA).

كما تم الاعتماد على المقياس الفيزيولوجي لتقييم الألم من خلال قياس معدل النبض ومعدل الأكسجة بجهاز(مقياس تأكسج النبضي) عند مراحل العمل التالية (التطبيق– السبر– القلع) لكل من المجموعات المدروسة.

النتائج: أظهرت نتائج الدراسة أنه عند مستوى الثقة 95% لا يوجد فروق دالة إحصائياً في متوسط مقدار التغير في معدل الأكسجة بين المجموعات المستخدمة مهما كانت المرحلة المدروسة. كما أنه عند القلع، لا توجد فروق دالة إحصائياً في متوسط مقدار التغير في النبض القلبي بين المجموعات المستخدمة في عينة البحث، أما بالنسبة لباقي المراحل المدروسة (تطبيق وسبر) فيُلاحظ وجود فروق دالة إحصائياً حيث أن قيمة مستوى الدلالة أصغر من القيمة (0.05).

الاستنتاج: يعد كلاً من الحقن الحنكي التقليدي والقلع إجراءً راضاً بالمجمل، وباستخدام أنظمة توصيل الأدوية تم التمكن من إتمام الإجراء بطريقة فعالة وأكثر راحة.

الكلمات المفتاحية: معزّز نفاذية، لصاقات فموية، لصاقات إبر مجهرية قابلة للذوبان.

تاريخ الايداع:9 /2023/1
تاريخ القبول: 2022/5/18

Introduction:

Needle insertion and infusion of anesthetic solution into the palate can significantly impact children's comfort and acceptance of dental treatment, often leading to aversion from the very first step of the process (Tirupathi, Rajasekhar, et al. 2020). Several studies have explored various methods to alleviate the pain associated with palatal injections, including: - Computer-controlled delivery devices (de Camargo Smolarek, da Silva, et al. 2021).

- Local anesthetic alkalization (Gupta, Kumar et al. 2018).
- The use of 30-gauge insulin needles (Asokan, Rao et al. 2014).
- Pre-cooling of the palate (Chilakamuri, Nirmala, et al. 2020).
- Vibration devices (e.g., dental vibe) (de Camargo Smolarek, da Silva, et al. 2021).
- Heating local anesthetics (Gümüş and Aydinbelge 2020).
- Traditional surface anesthetics, such as benzocaine and lidocaine (Tirupathi, Rajasekhar et al. 2020).

While some studies have praised the effectiveness of these methods in reducing the pain of traditional palatal injections, others have found no significant differences (Primosch and Rolland-Asensi 2001; Nusstein, Lee, et al. 2004; Maia, Lemos et al. 2021). As the pain associated with palatal needles remains significant, some research has focused on alternatives to injections, such as:

- Utilizing local anesthetic articaine for infiltration from the vestibular side to the palate (Rathi, Khatri, et al. 2019; Gholami, Banihashemrad et al. 2021).
- Inserting a needle from the vestibular side of the interdental papilla over the alveolar bone to achieve anesthesia of the palatal papilla and surrounding gingiva (Janjua, Luqman et al. 2012).
– Applying EMLA cream as a surface anesthetic (Chugh, Singh, et al. 2021).
- Some researchers have even questioned the necessity of administering palatal anesthesia based on their beliefs (Badcock and McCullough 2007; Badenoch-Jones and Lincoln 2016; Cui, Zhang et al. 2018). The results of these alternative procedures have been varied. In our study, for the first time, we utilized drug delivery systems (DDS) to enhance the effectiveness of EMLA cream as an alternative to palatal injections.

DDS, or Drug Delivery System, is defined as an effective method that enhances the impact of surface drugs by reducing the properties of the mucosal barrier. This is achieved through various mechanisms, which are typically categorized into two main types: physical methods and chemical methods. Physical methods include techniques such as pre-cooling, vibration, ion transport, and microneedle arrays. Chemical methods involve the use of permeation enhancers and nanostructured carriers, which include liposomes, cyclodextrin, polymeric nanoparticle systems, solid lipid nanoparticles, and nanostructured lipid carriers. Additionally, polymer-based dosage forms such as hydrogels, bio-adhesive films, and patches also fall under this category. Combining different chemical and physical methods offers a promising approach to achieving effective anesthesia in the oral mucosa (San Chong, Miller, et al. 2014; Franz-Montan, Ribeiro, et al. 2017). Thus, this randomized controlled clinical study aims to eliminate the need for traditional palatal local injections during maxillary primary tooth extractions. The study seeks to enhance the effectiveness of EMLA cream within a child-friendly tolerance time of 3 minutes by utilizing one of the following drug delivery systems: DMSO, oral patches, or microneedle patches. This approach would provide palatal anesthesia without needing traditional local injections, relying instead on a lidocaine injection from the vestibular side.

Research Materials and Methods:

The research sample consisted of 75 children who visited the pediatric dentistry clinics at Damascus University. The inclusion criteria for the study were as follows: A. Children aged 7 to 11 years. B. Presence of upper primary teeth indicating the need for extraction. C. Children who have never experienced dental trauma. D. Healthy children without neurological disorders or other general health issues. E. Cooperative children are classified as having positive or very positive behavior according to Frankel's behavioral scale. F. Children in the target sample had not received any sedatives or painkillers within three hours before the dental procedures. Exclusion criteria included: A. Allergy to local anesthetics. B. Congenital or idiopathic methemoglobinemia (Borle, 2014). C. Treatment with drugs that stimulate methemoglobin production. D. Presence of teeth with acute abscesses. Ethical approval was obtained from the Ethical Research Committee at Damascus University (Approval No. 1999) and permission was received to register the research in the clinical trials registry (Registration No. 05187494). Detailed explanations of the procedures were provided to the parents, outlining the potential benefits and risks, along with obtaining their written consent. The children included in the study were randomly assigned to five groups, with each group containing 15 children, as follows:

- Group A: Traditional local palatal injection (control)
- Group B: EMLA cream alone
– Group C: DMSO chemical permeability enhancer with EMLA cream
- Group D: Oral patches containing EMLA cream
- Group E: Dissolvable microneedle patches with EMLA cream

The following steps were followed in the exact order:

A. The child was seated in the dental chair and allowed to wait for 5 minutes to ensure a stable and comfortable position.

B. Initial measurements including heart rate and oxygenation levels were recorded using an Oxywatch fingertip pulse oximeter (Germany) at the beginning of the procedure.

C. The materials being studied were applied to the palatal side only, with each group receiving a different treatment:

- **Group A: Traditional Palatal Local Injection (Control)** A traditional palatal injection was administered using an anesthetic (Lidocaine HCL 2% with Epinephrine 1:80000, Korea) as shown in Figure 8.
- **Group B: EMLA Cream Alone** The palatal mucosa was dried with a 2x2 cotton ball, and then 0.2g of 5% EMLA cream (Aspen, Sweden) was applied 1 mm from the palatal gingival margin using cotton swabs for 3 minutes (Barcohana, Duperon et al., 2003). The area of application measured 14x14 mm, and the mouth remained open throughout the procedure, with saliva controlled using a salivary aspirator.
- **Group C: DMSO Chemical Permeability Enhancer with EMLA Cream** The palatal mucosa was dried with a 2x2 cotton ball, and then 0.2g of 5% EMLA cream (Aspen, Sweden) mixed with DMSO permeability enhancer was applied 1 mm from the palatal gingival margin. In a laboratory at the Faculty of Pharmacy, Damascus University, for every 10g of 5% EMLA cream, 1.026g of 100% DMSO was added using a Sartorius electronic balance, following the method outlined by Ray and Hodges (2015). The mixture was blended with a spatula to achieve a homogeneous consistency (refer to Figures 1-5). The application was performed with a cotton swab for 3 minutes, and the mouth remained open throughout the procedure, with saliva managed using a salivary pipette.
- **Group D: Oral Patches with EMLA Cream** The palatal mucosa was dried with a 2x2 cotton ball, after which 0.2g of 5% EMLA cream (Aspen, Sweden) was applied 1 mm from the palatal gingival margin using a 14x14 mm oral patch (Stomahesive, Convatec, USA) for 3 minutes, with the mouth closed during the procedure.
- **Group E: Dissolvable Microneedle Patches with EMLA Cream** The palatal mucosa was dried with a 2x2 cotton ball, then 0.2g of 5% EMLA cream (Aspen, Sweden) was applied 1 mm from the palatal gingival margin with a 14x14 mm, 0.25-micron dissolvable microneedle patch (Rael Microneedle Patches, California) for 3 minutes, also with the mouth closed throughout the application. The following parameters were recorded: heart rate and oxygenation rate using a pulse oximeter. At each stage of the procedure, the following were measured:

1. **Application:** This aimed to determine the reaction and extent of acceptance of the applied material (see Figures 31, 24, 18, 13, 8).
2. **Probing:** A dental probe was used in contact with the bone to assess the effectiveness of palatal anesthesia (Primosch and Rolland-Asensi 2001; Franz-Montan, De Paula et al., 2012) (see Figures 32, 25, 19, 14, 9).

Note: If the child exhibited any intolerable negative reaction during probing, a traditional palatal injection would be performed. After completing the probing phase, a standardized waiting time of 1 minute was observed, after which the vestibular mucosa was anesthetized using an anesthetic (Lidocaine HCL 2% with Epinephrine 1:80000, Korea). The dosage was proportionate to the child's weight and administered slowly, followed by an additional wait time of 5 minutes to achieve deep anesthesia (Dasarraju and Nirmala 2020).

3. **Extraction:** This step aimed to assess the child's reaction during the extraction and the ability to complete the procedure (see Figures 33, 26, 20, 15, 10). It is important to note that neither the child nor the treating physician could be blinded due to the differences in the application materials used among the studied groups (Chugh, Singh et al., 2021). However, the statistical analyst was blinded, and the encoding was not deciphered until after the results were analyzed.

Figures Related to the Methods

Figure 1: Sensitive and Becher balance.

Figure 2: Calibration of 1 g of DMSO.

Figure 3: Calibration of 10 g of EMLA cream.

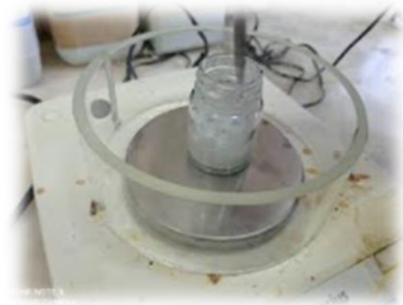

Figure 4: Mixing the resulting amount with a spatula.

Figure 5:Homogeneous consistency of the mixture (DMSO - EMLA).

Figure 6:A child from group A.

Figure 7: A second temporary maxillary left molar.

Figure 8: Application of conventional palatal injection.

Figure 9: Probing.

Figure 10: Extraction.

Figure 11; A child from group B.

Figure 12: A first temporary maxillary left molar.

Figure 13: Application of EMLA cream.

Figure 14: Probing.

Figure 15: Extraction.

Figure 16: A child from group C.

Figure 17: A second maxillary temporary molar on the right.

Figure 18:Application of DMSO-EMLA mixture.

Figure 19: Probing.

Figure 20: Extraction.

Figure 21: A child from group D.

Figure 22: A temporary maxillary left canine.

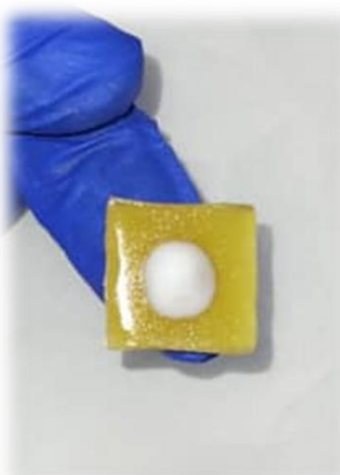

Figure 23: Oral patch combined with EMLA.

Figure 24: Application of the patch.

Figure 25: Probing.

Figure 26: Extraction.

Figure 27: A child from group E.

Figure 28: A first maxillary temporary molar on the left.

Figure 29: Microneedle patches.

Figure 30: Microneedle patch combined with EMLA.

Figure 31: Application of the patch.

Figure 32: Probing.

Figure 33: Extraction.

Statistical Study:

After the data were recorded on special forms, they were coded and entered into the computer for analysis. The statistical calculations for the research were conducted using SPSS version 13.0. The results were evaluated with a 95% confidence interval and a significance level of 0.05.

1. A descriptive analysis of the sample was performed.
2. A one-way analysis of variance (ANOVA) test was conducted to examine the significance of the differences in the average changes in heart rate and oxygenation levels among the groups in the research sample, based on the studied stages. If the ANOVA results indicated statistically significant differences between the groups, a pairwise comparison was performed using the Least Significant Difference (LSD) method. This was done to identify which groups differed fundamentally in each of the relevant stages.

Results:

First: Studying the differences between the five groups in terms of the amount of change in heart rate according to the school stage:

Table 1 displays the arithmetic mean, standard deviation, standard error, minimum, and maximum values of the changes in heart rate for the research sample, categorized by groups and study stages.

Stages studied:

When comparing the application of the material to the pre-work stage.

When comparing palatal probing to the stage of applying the material.

When extracting, compare it to the stage of probing.

Table: (1) displays the results of the one-sided ANOVA test, which examines the significance of differences in the average change in heart rate among the groups in the study, categorized by the studied stage.

Stage	GROUPS	Number of anesthesia cases	mean Standard	deviation Standard	10
The application of the material compared to the pre-work stage.	G3	15	0.40	7.35	1.90
	G4	15	-2.40	6.82	1.76
	G5	15	-4.33	5.78	1.49
	G2	15	1.87	4.82	1.25
	G1 (control group)	15	9.67	5.81	1.50
At the probe stage, compared to the application stage.	G3	15	-4.13	6.31	1.63
	G4	15	-0.67	4.20	1.09
	G5	15	-3.73	4.96	1.28
	G2	15	1.53	5.51	1.42
	G1 (control group)	15	-2.53	6.14	1.59
At the extraction stage, in comparison to the sounding stage.	G3	15	2.47	5.80	1.50
	G4	15	3.07	7.18	1.85
	G5	15	3.47	4.91	1.27
	G2	15	6.47	7.92	2.04
	G1 (control group)	15	3.60	5.74	1.48

Table: (2) displays the results of the one-sided ANOVA test, which examines the significance of differences in the average change in heart rate among the groups in the study, categorized by the studied stage.

stage	P VALUE
The application of the material compared to the pre-work stage	0.OOO
At the probe stage, compared to the application stage	0.035
At the extraction stage, in comparison to the sounding stage.	0.483

The table indicates that the significance level at the extraction stage is considerably greater than 0.05 compared to the six stages. This means that at the 95% confidence level, there are no statistically significant differences in the average change in heart rate between the extraction stage and the stage among the groups in the research sample.

Conversely, the significance level is less than 0.05 for the rest of the studied sample. This suggests that at the 95% confidence level, there are statistically significant differences in the average change in heart rate among at least two of the groups for the concerned patients in the research sample.

To identify which groups differ significantly in their ability to induce changes in heart rate, a pairwise comparison was conducted using the LSD method for binary pairing between Group C and the other four groups studied.

- Results of the Binary Comparison Using the LSD Method

Table: (3) presents the results of the binary comparison conducted with the LSD method. This table highlights the significance of the differences in the average change in heart rate observed when applying the material and during palatal probing across the research sample groups.

stage	I-J		P value
	I	J	
The application of the material compared to the pre-work stage.	G3	G4	0.219
		G5	0.040
		G2	0.518
		G1	0.00
	G4	G5	0.395
		G2	0.063
		G1	0.00
	G5	G2	0.008
		G1	0.00
	G2	G1	0.001
At the probe stage, compared to the application stage.	G3	G4	0.088
		G5	0.842
		G2	0.006
		G1	0.427
	G4	G5	0.130
		G2	0.275
		G1	0.354
	G5	G2	0.010
		G1	0.551
	G2	G1	0.046

The table above indicates that at the 95% confidence level, there are statistically significant two-way differences in the average change in heart rate when the substance is applied in conjunction with the contrasting phase in the work sample among the groups studied. The arithmetic mean values suggest that the ability to change (in absolute terms) heart rate in the traditional palatal injection group (control group) is significantly larger compared to the group exposed to the enhanced nephrotoxicity of the chemical DMSO.

When DMSO and EMLA were used together, heart rates increased in the traditional palatal injection group, whereas they decreased in each of the three experimental groups: those receiving oral patches with EMLA cream, soluble microneedles with EMLA cream, and EMLA cream alone. We observed that heart rate values decreased in the microneedle patch group when the substance was used alongside the contrasting phase of the work.

The solubility of EMLA cream was assessed in the group that received both the DMSO chemical booster and the EMLA cream, as well as in the group receiving only the EMLA cream. Our findings showed that heart rate values during the palatal application were higher than during the EMLA cream application phase. Additionally, heart rates decreased across all three groups studied: the combination of DMSO and EMLA cream, dissolvable microneedles with EMLA cream, and traditional palatal topical injections (control group).

Regarding the other binary comparisons analyzed, it is important to note that the significance level values were greater than 0.05. This means that at the 95% confidence level, there were no statistically significant differences in the average change in heart rate when applying the substance among the different groups in the research sample.

Discussion:

Research Protocol Analysis

In this study, we started with the palatal side and used lidocaine as the local anesthetic for the vestibular side to prevent the possibility of the anesthetic seeping from the vestibular side to the palatal area, which could affect the results. Existing literature presents conflicting evidence regarding the ability of anesthetic substances to penetrate palatal tissues. Some studies have praised the effectiveness of 4% articaine over 2% lidocaine in children when used for vestibular injections, suggesting that it may eliminate the need for palatal injections (Rathi, Khatri, et al. 2019; Gholami, Banihashemrad, et al. 2021). However, other research indicates that articaine fails to infiltrate the palatal tissues effectively (Mittal, Sharma, et al. 2015; Kolli, Nirmala, et al. 2017).

Our protocol aligned with the findings of Chugh, Singh, et al. (2021).

The focus of our research was limited to the palatal side. This is because palatal injections are considered the most painful injections in the oral cavity. The palatal mucosa has a strong attachment to the periosteum, which necessitates applying positive pressure during administration. Additionally, the thick keratinized layer of the palatal tissue resists the effects of surface anesthesia (Franz-Montan, Baroni, et al. 2015; Kolli, Nirmala, et al. 2017; Janani and Kumar 2018; Sundar, Shetty, et al. 2020). Complications such as burning, ulceration, tissue swelling, and the reactivation of latent viruses like herpes simplex virus can also occur in these tissues (Sharma 2017).

Consequently, there has been a shift in contemporary dentistry toward finding alternatives to palatal injection (Gunasekaran, Babu, et al. 2020).

Moreover, the depth of penetration of EMLA cream is comparable to the depth of insertion of the palatine needle (5 mm) required to reach the superficial palatine nerve (Reed, Malamed, et al. 2012; Kageyama, Maeda, et al. 2021). This suggests that it may be possible to avoid the painful palatal injection altogether.

There is a notable difference in the study conducted by Munshi, Hegde et al. (2001), where EMLA cream was applied on both the vestibular and palatal sides during maxillary tooth extractions in children aged 4 to 13 years, thus eliminating the need for a needle. This approach was successful for extracting loose teeth, but its effectiveness was limited for other cases.

To ensure broader applicability, our study focused solely on the palatal side due to the anatomical location of the superior alveolar nerve, which requires a needle penetration depth of 15 mm (Reed, Malamed et al. 2012; Kageyama, Maeda et al. 2021). This restricts the use of EMLA cream on the vestibular side, where the penetration depth is only 5 mm. Chugh, Singh et al. (2021) conducted a study that involved applying 5% EMLA cream solely on the palatal side, along with an injection of 2% lidocaine with 80,000:1 adrenaline on the vestibular side, achieving satisfactory anesthesia in the palatal dome during maxillary tooth extraction in adults.

In our current study, the time required to apply the research materials was 3 minutes, which differs from the 10 minutes taken in both the Munshi et al. (2001) and Chugh et al. (2021) studies.

It is important to consider that the duration of treatment is closely linked to children's behavior, rather than solely the area of local anesthesia or the complexity of the procedure (Davidovich, Wated et al. 2013). Therefore, Jamali, Najafpour et al. (2018) recommended that no stage of treatment should exceed 5 minutes to encourage cooperation from the child.

Furthermore, Barcohana, Duperon et al. (2003) indicated that the effectiveness of EMLA cream remains similar when applied for different time intervals (10, 5, or 3 minutes). Thus, in this study, we opted for a 3-minute application time as an alternative to palatal injection.

Discussion of the Selection of Research Materials:

The combined surface anesthetic (EMLA) distinguishes itself from its conventional counterparts by effectively infiltrating the keratinized tissues in the palatal vault (Al-Melh and Andersson, 2007). A study conducted by Vickers, Marzbani et al. (1997) confirmed that no local harmful effects occurred from applying a large amount (8 mg) of EMLA cream for 30 minutes. After 40 minutes, the maximum concentrations of lidocaine (418 ng/ml) and prilocaine (223 ng/ml) were observed, both of which were significantly lower than the known toxic levels of these drugs (4.4 μg/ml and 6.0 μg/ml, respectively). The inclusion criteria for this research focused on healthy children aged 7-11 years, thus preventing the risk of methemoglobinemia.

In our current study, for the first time, we preferred using DMSO as a permeation enhancer mixed with EMLA cream, based on evidence that it can penetrate both hydrophobic and hydrophilic molecules (Notman, den Otter et al., 2007; Marren, 2011). Additionally, the patches utilized in this study are designed to confine the surface anesthetic at the application site, preventing dilution by saliva. This feature is crucial as unwanted anesthesia in other areas and an unpleasant taste can occur from dilution (Al-Melh and Andersson, 2007; Bågesund and Tabrizi, 2008; Madadian and Renton, 2019).

In 1990, Noven Pharmaceuticals developed an oral patch containing both lidocaine and benzocaine (Shehab, Basheer et al., 2015), but a commercial product for EMLA cream patches is yet to be released. Therefore, we used paste patches with manually added EMLA cream, similar to the methodology in the studies by Svensson and Petersen (1992) and Primosch and Rolland-Asensi (2001), where patches were applied to relieve pain prior to palatal injections. In our current study, these patches served as an alternative to injections.

Furthermore, fully soluble microneedles, made from water-soluble or bioreceptive polymers, dissolve the drug within the needle matrix, functioning in a single step (Kang, 2017). A specialized reservoir was initially manufactured to hold the anesthetic; however, difficulties in its production and slow release led to the development of soluble microneedles using centrifugation technology (Lee, Lee et al., 2020). Challenges in manufacturing these microneedles and the absence of a commercial product for oral use (SERPE) prompted our study to utilize a commercial product of soluble microneedle adhesives for application on the palatal dome. This approach offers a viable alternative to traditional palatal injections, typically used for treating skin conditions, by stimulating collagen and elastin through the micropores created (Cohen and Elbuluk, 2016).

Considering the structural similarities between oral mucosa and skin (Shaikh, Singh et al., 2011), the permeability of the oral mucosa is significantly higher—approximately 4000 times more than that of skin (Shaikh, Singh et al., 2011). This characteristic allows skin patches to effectively penetrate the stratum corneum palatineum and dissolve in the interstitial fluid, creating micropores (Lee, Lee et al., 2020). Additionally, the tight adhesion framework surrounding the microneedle patch was enhanced by incorporating EMLA cream, addressing the disadvantages of EMLA such as low viscosity and a bitter taste (Primosch and Rolland-Asensi, 2001; Al-Melh and Andersson, 2007), thereby facilitating a streamlined, single-step procedure.

Discussion of the Study Results:

This study examined the differences in heart rate changes among five groups during various stages of the procedure. The results indicated that there were statistically significant differences between the groups when comparing the data from the pre-work stage to after the application of the material. Analyzing the arithmetic averages revealed the following order of heart rate changes:

1. Traditional local palatal injection: 9.67
2. EMLA cream only: 1.87
3. Chemical permeability enhancer (DMSO with EMLA cream): 0.40
4. Oral patches with EMLA cream: -2.40
5. Soluble microneedle patches with EMLA cream: -4.33

From these findings, we can conclude that the heart rate change was most significant in the traditional palatal injection group, where heart rates increased significantly. In contrast, all three other groups (oral patches with EMLA cream, soluble microneedle patches with EMLA cream, and EMLA cream only) experienced a decrease in heart rate. Specifically, the group using soluble microneedle patches with EMLA cream had the most pronounced decrease, while both the DMSO chemical permeability enhancer group with EMLA cream and the EMLA cream-only group experienced an increase.

These results may be attributed to the higher pain level associated with the traditional palatal injection, which was the primary motivation for conducting the study. Both the EMLA cream-only group and the DMSO with EMLA cream group encountered some disadvantages during application, such as unpleasant taste, low viscosity, and the requirement to keep the mouth open throughout the procedure. On the other hand, the soluble microneedle patch group successfully avoided the discomforts associated with EMLA cream, such as taste and viscosity issues. Additionally, the ability to close their mouths during application contributed to a higher acceptance rate among children, as they were less bothered by the microneedles.

In contrast, the oral patches group, despite having similar advantages to the microneedle patches, was less well-received by the children. This may be attributed to the oral patches' thickness and the discomfort they caused when the child closed their mouth.

Furthermore, our findings align with the study by Primosch and Rolland-Asensi (2001), which compared benzocaine patches to oral patches containing EMLA cream and found no evidence indicating that paste patches were superior in terms of comfort and acceptance among children. However, our results diverged from those in the study conducted by Svensson and Petersen (1992), which demonstrated the effectiveness of paste patches (when combined with EMLA cream) in reducing pain before a palatal injection in adult patients. In that study, three out of twenty patients reported dissatisfaction, primarily due to the unpleasant taste, which led to mild vomiting reactions, likely attributed to the larger 3×3 cm patches used.

When comparing the changes in heart rate during palatal probing across different application methods, we found statistically significant differences between the group applying only EMLA cream and each of the three other groups studied: those using the chemical permeability enhancer DMSO with EMLA cream, soluble microneedle patches with EMLA cream, and traditional palatal local injections.

Analyzing the arithmetic averages of the heart rate changes, we observed the following order among the groups:

- **EMLA cream only**: 1.53
- **Oral patches with EMLA cream**: -0.67
- **Traditional palatal local injection**: -2.53
- **Dissolvable microneedle patches with EMLA cream**: -3.73
- **Chemical permeability enhancer DMSO with EMLA cream**: -4.13

From this data, we conclude that heart rates during palatal probing increased in the group that received EMLA cream alone, while they decreased in each of the three other groups (DMSO with EMLA cream, soluble microneedle patches with EMLA cream, and traditional palatal local injection).

This difference can be attributed to the application time of EMLA cream (3 minutes), which was likely insufficient when not combined with one of the delivery systems.

Furthermore, we found that the physical (microneedles) and chemical (permeability enhancer) delivery systems were more effective in achieving anesthesia within a 3-minute timeframe, which is suitable for children's acceptance. Their efficacy was comparable to that of the palatal injection (the control group), in contrast to the pharmaceutical delivery form from the oral patches.

It is worth noting that there are no previous clinical studies that have measured changes in heart rate during probing.

The current study aligns with the findings of Daly, Claydon et al. (2021), which demonstrated that applying a solid microneedle patch containing 5% lidocaine gel significantly reduces pain from local anesthetic injections in adult patients. This study compared the microneedle patch with a 5% lidocaine gel patch that did not include microneedles, and the results were assessed using a self-report visual analog scale (VAS).

No adverse events were reported by the examiner who conducted a visual examination of the soft tissues in the mouth, and no defects in the microneedle patches were identified. Additionally, our results are consistent with the study by Chugh, Singh et al. (2021), which involved 102 participants divided into two groups. The experimental group received EMLA cream applied alone on the palatal side for 10 minutes, followed by a conventional injection on the vestibular side. The control group received conventional injections on both the palatal and vestibular sides. According to the VAS results, the control group reported no pain during probing after the palatal injection. In contrast, the experimental group had a mean pain score of 1.50 (± 0.92) at probing. Notably, one patient in the experimental group experienced severe pain during palatal probing and was subsequently given conventional anesthesia, as in the control group. However, the children in the current research sample did not exhibit intolerable pain that required a conventional palatal injection.

The results also indicated that the significance level was greater than 0.05 during the extraction stage compared to the probing stage. This suggests that at a 95% confidence level, there are no statistically significant differences in the average change in heart rate between the groups in the research sample.

Second A comparison of the five groups regarding the change in oxygenation rates at different stages was conducted. The findings of this study revealed that there were no statistically significant differences in the average change in oxygenation rates among the groups, regardless of the stage examined within the research sample.

Conclusions

1. Both traditional palatal injections and extractions are generally effective procedures. By utilizing drug delivery systems, we were able to complete the procedures in a more efficient and comfortable manner for the child.

Both the EMLA-only group and the DMSO with EMLA cream group experienced drawbacks during the application, such as an unpleasant taste and low viscosity, requiring the children to keep their mouths open throughout the process. In contrast, the dissolvable microneedle patches eliminated the issues associated with EMLA cream, making the application more acceptable for the children by allowing them to close their mouths. The children were not bothered by the microneedles, whereas those in the oral patches group showed less acceptance, despite having similar advantages, likely due to the thickness of the patches and the discomfort they felt while keeping their mouths closed.

In terms of anesthesia effectiveness, the application time for the EMLA group (only 3 minutes) was insufficient without the use of a delivery system. However, both the physical (microneedles) and chemical (permeability enhancer) delivery systems performed better, achieving effective anesthesia within a time frame that was acceptable to the children—3 minutes. These methods demonstrated similar effectiveness to traditional palatal injections (the control group), in contrast to the oral patch delivery system.

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