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Randomised Controlled Trial of a microneedle patch with a topical anaesthetic for relieving the pain of dental injections

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Short Title.

Dental injection pain relief with medicated microneedles

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Keywords.

Local Anaesthesia, facial pain, pain management

Conflict of Interest and Funding Statement

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The study was registered with ClinicalTrials.gov: NCT03629041

Randomised Controlled Trial of a microneedle patch with a topical anaesthetic for relieving the pain of dental injections

Abstract

Objectives

To determine whether a microneedle patch combined with 5% topical lidocaine reduces dental injection pain more than a patch without microneedles combined with 5% topical lidocaine.

Methods

This proof of principle randomised, two-treatment, double-blind, crossover split-unit design study in 16 healthy participants investigated levels of perceived pain from 3 increasing pain provoking challenges, when topical 5% lidocaine dental gel was applied to the oral mucosa with a microneedle patch and a patch with no microneedles, prior to infiltration with local anaesthesia on 2 visits. Pain was assessed by visual analogue scale (VAS) and 4-point verbal rating scale (VRS).

Results

15 participants completed the study. Mean pain scores, lower at buccal sites, increased in both groups across challenges 1-3: Test palatal 5.1, 11.9, 26.8; buccal 0.7, 2.8, 18.3; Control palatal 12.3, 18.7, 39.5; buccal 4.0, 6.9, 30.6. The microneedle patch plus lidocaine significantly lowered VAS pain scores at both sites for all challenges, the biggest mean difference seen palatally after challenge 3 (12.7, $p<0.001$). VRS pain scores were also significantly reduced for test compared to control for all 3 challenges ($p=0.014$). Buccal scores favoured the microneedle patch, significantly for pain challenge 3 ($p=0.025$). No adverse events occurred.

Conclusions

Prior oral application of a microneedle patch combined with 5% topical lidocaine gel reduced the pain experienced from dental infiltration. Microneedle patch use in the dental setting offers the prospect of improving degree and depth of anaesthesia from topically applied anaesthetic gel, without itself causing any pain.

Clinical Significance:

Dental injections are associated with fear and anxiety. Application of a microneedle patch, combined with topical anaesthetic, to the oral mucosa prior to delivery of the injection reduces the pain from this dental procedure. This novel technique may allay patients' apprehension of local anaesthesia and improve quality of life outcomes.

INTRODUCTION

Dental treatment is recognised to be associated with pain and anxiety [1-3] and according to the American Dental Association, fear of pain can prevent patients from visiting their dentists [4,5]. To minimise the discomfort derived from invasive dental procedures, patients routinely receive local infiltration anaesthesia so that treatment may be undertaken in a relatively painless manner. However, dental injections *per se* provoke pain [5,6], and indeed local anaesthetic injection has been demonstrated to be the most anxiety-provoking procedure for some patients [7,8]. Furthermore, because local anaesthetic is provided at a point of maximum apprehension, it can impart a powerful patient stimulus [9] which itself is a source of distress and may contribute to an overall state of dental anxiety. A number of procedural factors have been identified as drivers of pain derived from the delivery oral local infiltration anaesthesia, including the mechanical trauma of needle insertion, rapid distention of the soft tissues by the anaesthetic solution [10] and anatomical location of the injection site.

Topical anaesthetic agents may be applied to the oral mucosa to inure the patient to the discomfort of the subsequent infiltration. However, pain stimuli are blocked only in the superficial mucosal layer, due to poor drug penetration of soft tissues. Used alone, they do not provide sufficient depth of anaesthesia for operative dento-alveolar procedures. However, both direct chemical effects [11] and placebo effects [12,13] produce relief thereby contributing to positive responses from patients undergoing dental treatment. Lidocaine is widely used for its potent topical anaesthetic effect and low toxicity [11].

Despite pre-treatment of the oral mucosa with anaesthetic gels, pain may still be experienced by the patient upon subsequent injection infiltration, impacting on the overall pain experience. Some areas of the oral cavity are difficult to pre-anaesthetise with topical anaesthesia to acceptable levels prior to infiltration injection. Two areas that are particularly difficult to pre-anaesthetise are the mucosa covering the hard palate and the upper anterior labial region. The palatal mucosa is tightly bound to the palatal shelf of the maxilla and drugs have been shown to be poorly absorbed through this highly keratinised tissue [14,15], while the upper anterior labial region has a high density of nerve endings [16]. The oral sites chosen for the study were the mucosa adjacent to the upper labial incisors and upper palatal premolars, representing these sites.

Recently, there has been significant growth in the area of microneedle assisted drug delivery. Advances in micro-fabrication technology have led to the development of several delivery devices, with industry, healthcare professionals and researchers closely following this pioneering field. Microneedles were developed in part to overcome patients' fear of needles. Microneedle patches create minute channels in the surface of the treated area through which topically applied drugs can pass more readily than by permeation alone. Human skin studies *in vitro* have shown that a microneedle patch increases permeation of lidocaine

and inulin through the skin [17]. The permeation of lidocaine also showed a large reduction in lag time which, in a clinical setting, hastens the onset of local anaesthesia [17].

The microneedles mucosal patch investigated in this study is designed to accelerate and improve the pain preventive outcome of pre-treatment anaesthetic gels by enhanced delivery and uptake, with minimum discomfort to the patient [18-20]. The authors consider that the use of microneedle patches combined with topical anaesthetic gel will result in increased effectiveness in reducing the discomfort associated with delivery of a local anaesthetic injection. Furthermore, the use of the microneedle device may result in an improved quality of life experience for the patient. The aim of this proof of concept study is to compare the level of perceived pain from a lidocaine local infiltration injection, after the oral mucosa was topically treated with lidocaine applied to a mucosal patch either with or without microneedles. The study hypothesis is that pain experience is reduced by topically treating the oral mucosa with lidocaine on a mucosal patch with microneedles, compared to lidocaine delivered on a mucosal patch without microneedles, prior to local infiltration of lidocaine.

METHODS

Study Design

The study was conceived as a proof of concept study to investigate a novel model of delivery of standard, accepted therapeutic agents used to produce topical anaesthesia. Participants were healthy volunteers attending for regular dental care who gave written informed consent. The study interventions were not in any way connected to their treatment plans as patients. The study was approved by the MHRA REF CI/2018/0027 and the NRES South West - Exeter NHS REC REF 18/SW/0122 and conducted in accordance with Good Clinical Practice. The study was registered with ClinicalTrials.gov.

This was a randomised, two-treatment, double-blind (with respect to the clinical assessor and participant), crossover split-unit design study undertaken in a UK private dental practice. Participants were randomised to receive an intra-oral mucosal application of a proprietary topical 5% lidocaine dental gel (Septodont®) applied to a microneedles patch or the same gel on a control patch without microneedles, prior to local anaesthesia delivered by infiltration injection through the oral mucosa at this predetermined site. The primary objective was to compare the level of perceived pain in healthy participants when administering an intra-oral infiltration local anaesthetic with prior application of a topical anaesthetic on a patch with and without microneedles. Any adverse events that occurred following application of the patches to the oral mucosa were to be recorded.

The microneedle patch

The microneedle patch (Innoture, UK) was a 2.4 x 2.4cm square appropriate for dental application, produced using a stencil printing technique. The patch consisted of a needle array 2 x 2cm comprising 625 needles with

approximate dimensions 300µm wide at the base, 90µm at the tip and height of 400µm (Figure 1). Prior to release for the study, all patches were defect tested to zero tolerance by microscopy.

Screening and enrolment

Potential participants attending their UK general dental practitioner for routine appointments were provided with a participant information sheet and invited to attend a screening visit. Following written informed consent, participants were allocated study numbers sequentially in ascending order based on screening visit attendance. Eligibility was assessed by the first study dentist who also undertook an oral soft tissue examination, recorded demographics, medical history and current/concomitant medications. Eligible participants were adults in good general and oral health, with at least one unrestored or minimally restored premolar and lateral incisor tooth in each quadrant, who were willing and able to comply with study procedures. Patients with soft tissue oral pathology, periodontal diseases, serious health conditions or known allergy to any study product were excluded. 16 participants who fulfilled all the inclusion criteria were recruited between 31 July to 8 August 2018 and proceeded to randomisation.

Two pairs of areas of the mouth were identified for assessment throughout the study for each eligible participant: the upper left and right palatal mucosa adjacent to the premolar area and the upper left and right buccal mucosa adjacent to the upper incisors. Only one palatal or buccal aspect was treated per treatment visit.

Participants were randomised by the study co-ordinator using the schedule provided by the study statistician based on their screening number to one of 4 treatment sequence groups (Figure 2). Participants were trained to use VAS scoring by study staff and their understanding verified by the clinician.

Treatment visits

Each participant made two treatment visits to the study site, 2 weeks +/- 3 days apart. At each visit participants received both treatments, one to the designated left-hand site and the other to its counterpart on the right. Those who were treated at palatal contralateral sites in visit 1 were treated at buccal contralateral sites in visit 2 and vice versa. The treatment allocated to the left side of the mouth was always delivered first.

For the test treatment, 0.5g of 5% lidocaine gel (Septodont, UK) was applied directly to the centre of the microneedle patch and applied by the clinician directly to the dried mucosa in the designated area. The pressure was released slightly, reapplied and held in place for 3 minutes so that the whole patch area received pressure and topical anaesthetic gel. For the control treatment 0.5g of 5% lidocaine gel was applied directly to the centre of a 2.4x2.4cm patch with no microneedles and was applied by the clinician directly to the dried mucosa using the same application methodology. The clinician delivering the injections was a dentist with many years of experience of delivering injections. For this study additional training was undertaken to ensure

that each injection was delivered slowly over a period of 30 seconds. The treatment patch applications were performed by a second study clinician to ensure blinding of the study to the first clinician.

For both treatments participants were asked to assess the pain related to the three separate needle insertion challenges immediately following patch removal: Challenge 1 - the needle penetrated the oral mucosa only; Challenge 2 - the needle was inserted through the oral mucosa to contact bone; Challenge 3 - the needle was inserted through the oral mucosa and an entire cartridge of 2% lidocaine hydrochloride (1 in 80,000 adrenaline) local anaesthetic was administered. Participants were asked to rate a pain response immediately after each challenge, using the VAS (100mm scale) and a four-point adjectival scale using a verbal grading of zero, mild, moderate or severe.

Statistical Methods

This study was designed to have 80% power to detect a difference in efficacy of analgesia between topical anaesthetic administration with and without microneedles at the conventional 5% two-sided alpha level provided this difference is at least 0.7 times the standard deviation (SD) representing the variation of this difference between different volunteers.

Two sites per participant were studied. Analyses for palatal tests were based on all 16 participants, whereas analyses for buccal tests were restricted to 15 participants as one participant withdrew after visit 1. Separate statistical analyses were performed for the results from palatal and buccal sites, for each of the three challenges. Summary statistics, based on all available participants, were calculated for each outcome measure for immediate post-treatment scores at sites with and without pre-application of microneedles. The paired differences in scores, microneedles minus no microneedles was assessed by paired t-test and Wilcoxon matched pairs signed-rank test. The Hills-Armitage approach [21] was used to adjust for the slight imbalance due to the withdrawal, using the Mann-Whitney test for the non-parametric analyses. Estimated differences between treatments are reported, with 95% confidence intervals, in addition to p-values.

Results

Sixteen consenting participants aged 18 or over who fulfilled pre-specified eligibility criteria participated in the study. The mean age was 31.4 years (range 18.9 to 57.0), ten participants were male and six female, two self-identified as black, the remainder as Caucasian. Throughout the study, no adverse events were reported by the participants or by the study dentists. One subject withdrew after visit 1 without providing any reason. No deficiencies attributed to the study devices were reported. Patient flow through the study is shown in Figure 2.

Table 1 presents summary statistics and Table 2 the corresponding analyses for VAS scores following palatal and buccal administration and challenges 1 to 3. Pain scores increased steadily from challenge 1 to challenge

3 and were slightly lower on the buccal compared to the palatal sites. In particular, those for VAS scores for buccal administration of challenge 1 were remarkably low. Analyses following all three challenges showed a statistically significant advantage for pain control in favour of patches with microneedles compared to those without.

Table 1. VAS scores for challenges 1-3

Challenge	Location	Treatment	Mean	SD	Minimum	Maximum
1	Palatal	Test	5.1	5.8	0.0	23.0
		Control	12.3	11.6	0.0	35.0
	Buccal	Test	0.7	1.0	0.0	3.0
		Control	4.0	5.8	0.0	20.5
2	Palatal	Test	11.9	11.3	0.0	43.5
		Control	18.7	12.4	0.5	36.0
	Buccal	Test	2.8	4.0	0.0	16.0
		Control	6.9	6.6	0.0	20.0
3	Palatal	Test	26.8	20.1	1.0	71.0
		Control	39.5	25.1	2.5	83.0
	Buccal	Test	18.3	17.5	0.0	51.5
		Control	30.6	20.7	3.0	73.5

Abbreviation: SD=Standard Deviation

Table 2. Paired treatment differences control-test for challenges 1-3

Challenge	Location	Adjusted/ Unadjusted	Mean difference	95% confidence limits		p-value	
				Lower	Upper	Parametric	Non-parametric
1	Palatal	Unadjusted ^a	7.2	2.6	11.8	0.004	0.002
		Adjusted ^b	7.2	2.4	12.0	0.007	0.002
	Buccal	Unadjusted ^a	3.3	0.3	6.3	0.034	0.005
		Adjusted ^b	3.3	0.1	6.6	0.046	0.009
2	Palatal	Unadjusted ^a	6.8	2.8	10.8	0.003	0.006
		Adjusted ^b	6.8	3.4	10.1	0.001	0.005
	Buccal	Unadjusted ^a	4.0	1.1	7.0	0.011	0.002
		Adjusted ^b	4.1	1.0	7.2	0.014	0.002
3	Palatal	Unadjusted ^a	12.7	6.9	18.4	<0.001	0.001
		Adjusted ^b	12.7	7.2	18.1	<0.001	0.001
	Buccal	Unadjusted ^a	12.2	4.4	20.1	0.005	0.002
		Adjusted ^b	12.2	3.9	20.5	0.008	0.003

a: unadjusted analysis: parametric, paired t test; non-parametric, Wilcoxon matched pairs signed-rank test

b: adjusted analysis: parametric, Hills-Armitage method [21]; non-parametric, Mann Whitney

Table 3 shows the results for verbal responses to the three challenges at buccal and palatal sites. In the palatal region the use of a microneedle patch plus 5% topical lidocaine gel statistically and significantly lowered the

pain associated with all 3 challenges compared to using the patch with no microneedles with the same gel. In the buccal area this benefit was seen for challenge 3 but did not reach conventional statistical significance with challenges 1 and 2.

Table 3 Verbal response scores for challenges 1-3

Challenge	Descriptor	Palatal		Buccal	
		Test	Control	Test	Control
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
1	Zero	8 (50)	5 (31)	15 (100)	13 (87)
	Mild	8 (50)	8 (50)	0 (0)	2 (13)
	Moderate	0 (0)	3 (19)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
		^a Wilcoxon test: $p = 0.014$		^a Wilcoxon test: $p = 0.157$	
2	Zero	8 (50)	3 (19)	14 (93)	11 (73)
	Mild	5 (31)	9 (56)	1 (7)	4 (27)
	Moderate	3 (19)	4 (25)	0 (0)	0 (0)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
		^a Wilcoxon test: $p = 0.014$		^a Wilcoxon test: $p = 0.083$	
3	Zero	1 (6)	1 (6)	3 (20)	1 (7)
	Mild	7 (44)	3 (19)	8 (53)	7 (47)
	Moderate	8 (50)	10 (63)	4 (27)	7 (47)
	Severe	0 (0)	2 (13)	0 (0)	0 (0)
		^a Wilcoxon test: $p = 0.014$		^a Wilcoxon test: $p = 0.025$	

a: compares the verbally reported pain scores for test and control treatments

Discussion

This proof of principle study evaluated whether topical anaesthetic delivery using a microneedle patch can reduce pain caused by the subsequent insertion of a dental needle into the palatal or buccal mucosa and injection of a standard local anaesthetic preparation.

The study hypothesis was confirmed, there was a significant difference in volunteer perceived pain relief after topically treating the oral mucosa with lidocaine on a mucosal patch with microneedles as opposed to without microneedles prior to giving a lidocaine local infiltration. Pain was assessed by two pain scales, a visual analogue scale and 4-point verbal adjectival scale. Both VAS and verbal data analyses supported our anticipation that administration of topical lidocaine anaesthetic with microneedles would be associated with pain levels lower than those experienced without microneedle use. Further, there were no reports of any adverse events following application of the patches to the oral mucosa, demonstrating excellent tolerance of

this procedure in dental treatment. This novel proof of principle study validates the concept that microneedles surjected with topical lidocaine gel improved the pain reduction effects of this topical anaesthetic.

Microneedle patches as vehicles of drug delivery are available in various dimensions and designs according to the target tissue and pharmacological requirements [22]. In particular, the length of the microneedle should enable epithelial puncture whilst avoiding triggering pain pathways in the deeper tissues [23]. The anticipation of pain caused by the method of drug administration is an important consideration related to patient acceptance and compliance [24]. The microneedles in each mucosal patch used in this study were conical with 90-300µm diameter circular base and 400µm height. Each microneedle was designed to puncture the outer surface of the epithelium, approximately 150-250µm penetration under pressure. Microneedle dimensions and penetration elicit no mucosal pain response as nerve cells and capillaries are located deeper than the depth of penetration in the designated intra-oral areas of study. No adverse events were reported from the co-investigator performing a visual oral soft tissue examination and no device deficiencies with the mucosal patch were reported. One subject withdrew for reasons not connected to the study. These findings indicate that the microneedle patches are safe to use and had good subject acceptance.

Topical anaesthetics alter pain thresholds by controlling pain sensations through a blockade of signals transmitted from the peripheral sensory nerve fibres [11]. However, they are only effective in blocking the pain stimuli in the superficial layer of the mucosa. Local anaesthetics used for topical anaesthesia must therefore have superior mucosal permeability to easily reach free nerve terminals [25].

Lidocaine hydrochloride is absorbed effectively from mucous membranes and is a useful surface anaesthetic. It can be used in concentrations up to 10% and may be applied to reduce pain preceding administration of a local anaesthetic injection in preparation for invasive dental treatment. It is effective on alveolar, but not palatal mucous membrane [11]. The duration of action of the topical anaesthetic is approximately 10 minutes, with the subsequent procedure ideally being performed two minutes after administration [11]. Lidocaine was chosen as the topical anaesthetic gel in this study for its effective absorption and widely accepted use. A 5% preparation was chosen as it is readily commercially available in the UK. The efficacy of topical local anaesthetic agents is enhanced when the mucosal surface is dry [11]. This was achieved in this study for both the surface mucosa and also the microneedle patch with good effect. Topical anaesthetic agents are concentrated to facilitate infiltration and should be applied as a thin layer over a small area to avoid toxicity. This made lidocaine an ideal choice for a proof of principle study with microneedles as demonstrated in this study. Following the successful outcome of this study, other topical local anaesthetics such as articaine, may be investigated, as it demonstrates good action within the connective tissue, but poor transit through the oral mucosa.

Valid, reliable and reproducible assessment of pain is essential for effective study of pain in clinical trials. Acute pain can be reliably assessed with tools such as the visual analogue scale (VAS) [26-28] a commonly used scale, considered the gold standard for pain studies [29]. The VAS represents an immediate, subjective evaluation of the prevailing intensity of pain [30] by the volunteer. The measured numerical score can be used to track pain progression and compare the pain between volunteers undergoing the same procedures in the study [31]. It is also easy and straightforward to administer [29] and has the advantage of producing a definitive measurement which can be assessed by blinded study personnel. In the present study the VAS was confirmed and validated, by also capturing the pain experienced with a categorical verbal scoring (VRS) system. This methodology uses words to describe the magnitude of pain (none, mild, moderate, severe), is a quick and simple tool with a high validity as an indicator of pain intensity. However, it has been reported to be less precise and sensitive than VAS [32].

As in all crossover designs, this study was planned to detect a realistic difference between treatments using highly efficient paired analyses requiring only a small sample size. The assumed treatment difference of 0.7 times the SD of within-subject differences was achieved in all analyses. As anticipated, the p-values for the 4-point verbal assessment of pain were less strongly statistically significant than those for the VAS: indeed, two of the verbal response analyses failed to yield p-values below 0.05. Conversely, a few respondents gave a slightly worse VAS score for the test treatment than the control. This did not occur with the 4-point verbal scale, indicating that no participant regarded the microneedle challenge, as worse than the corresponding challenge without microneedles. This suggests that the occasional VAS difference that slightly disfavours the application with microneedles may be disregarded. A 100 point scale may be considered as spurious precision here, notwithstanding clear, validated instruction in its use - it is too much to expect participants, especially when recumbent, to make exactly the same mark on a linear scale on different occasions to correspond to what they regard as a similar level of pain. On balance, taking together the results from the two distinct scoring methods to record pain, the findings clearly demonstrate the benefit of topical anaesthetic delivery using a microneedle patch to reduce pain caused by the subsequent insertion of a dental needle into the palatal or buccal mucosa and injection of a standard local anaesthetic preparation. Dental injections are common and of a short duration which allows the assessment of individual experiences immediately after administration, ensures that data are recorded contemporaneously and minimizes the potential for bias from the effect of memory.

This study was designed to achieve the highest feasible degree of blinding, particularly with respect to the participant, to eliminate bias. This was achieved by concealing the test or control patch and clinician blinding was also achieved by using different clinicians to administer the treatment and assess the pain response. This ensured that the results are robust and demonstrated the effectiveness of topical lidocaine action when

administered with microneedle patches. A wide range of ages of participants were chosen with relatively similar gender ratios. Females mostly report higher anxiety in regard to tooth extraction than males and young patients usually feel more anxious than older ones [9], although there were no significant differences demonstrated in this study.

Conclusion

Both the VAS and verbal data analyses support the premise that administration of topical lidocaine with microneedles prior to receiving local infiltration anaesthesia is associated with pain levels that are either lower than or equal to those experienced when administered without microneedles. Microneedle patches used within the dental setting therefore offer the possibility of improving the degree and depth of anaesthesia from topically applied anaesthetic gel, without themselves causing any pain. The results provide evidence that this application would be advantageous especially to patients with high pain anticipation anxiety. If this method of pain control could be self-applied under clinician direction in future dental treatment, it may further reduce pain and anxiety by patient empowerment.

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Figures

Figure 1. The Microneedle patch. The picture on the left shows a top down view of the microneedle patch against a ruler to show total patch area. The image on the right is of a single microneedle (taken from the side) on the polyurethane base.

Figure 2. CONSORT diagram, patient flow through the study