Original Article

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Microneedle patch-enhanced palatal anesthesia with benzocaine: Efficacy and safety in a randomized double-blind crossover trial

Kensuke Kiriishi[1,*], Terumi Ayuse[1], Naomi Tanoue[2], Kaori Komeyama[1], Nobuaki Magata[1], Hanako Takahashi[2], Takashi Tominaga[3], Yuriko Hayashida[1], Hirotaka Imai[4], Takuro Sanuki[5], Takao Ayuse[3]

[1] Department of Special Care Dentistry, Nagasaki University Hospital, Nagasaki, Japan;
[2] Developmental and Nurturing Dentistry, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan;
[3] Clinical Research Center, Nagasaki University Hospital, Nagasaki, Japan;
[4] Imai Dental Clinic, Osaka, Japan;
[5] Department of Dental Anesthesiology, Nagasaki University Hospital, Nagasaki, Japan.

SUMMARY: Needle-insertion pain during dental local anesthesia remains one of the strongest triggers of dental anxiety. Conventional topical anesthetics show limited penetration through the thick palatal mucosa and often provide insufficient suppression of insertion pain. Microneedle (MN) patches have emerged as a minimally invasive drug-delivery platform capable of enhancing transmucosal permeability and topical anesthetic efficacy. This randomized, double-blind, crossover clinical trial evaluated the efficacy and safety of a benzocaine-loaded MN patch applied to the palatal mucosa prior to local anesthesia. Twenty adult patients requiring bilateral maxillary premolar scaling and root planing received MN or placebo patches in two study periods separated by a one-week washout. The primary outcome was the presence or absence of needle-insertion pain. Secondary outcomes included injection-phase pain assessed using a 100-mm visual analogue scale (VAS), numbness or discomfort at the application site, vital signs, and adverse events. Needle-insertion pain was reported in 2 of 20 cases (10%) under the MN patch condition, compared with 14 of 20 cases (70%) under the placebo patch condition, demonstrating a significantly lower incidence with the MN patch ($p = 0.00049$). In contrast, VAS scores for injection-phase pain did not differ significantly between conditions. No clinically relevant numbness, mucosal irritation, or MN-related adverse events were observed, and vital signs remained stable throughout both study periods. The benzocaine-loaded MN patch selectively attenuated superficial needle-insertion pain while maintaining an excellent safety profile. The absence of an effect on deeper injection-phase pain is likely attributable to the substantial thickness of the palatal mucosa. These findings support the clinical utility of MN-assisted transmucosal anesthesia as a novel drug-delivery modality in dentistry and provide a foundation for the development of minimally invasive analgesic systems.

Keywords: Microneedle patch, palatal anesthesia, randomized crossover trial, benzocaine, dental local anesthesia

1. Introduction

Dental treatment frequently evokes significant anxiety and fear among patients. Among the most consistently reported triggers are drilling noise and vibration and local anesthesia injections (*1-3*). Surveys of dental students and adult populations have demonstrated that local anesthesia injections represent one of the most anxiety-provoking dental procedures, regardless of sex. International studies similarly identify the drill and the injection needle as principal sources of dental fear, indicating that despite its clinical necessity, local anesthesia itself remains a psychological barrier for many patients (*1,2*).

Pain associated with dental local anesthesia is not a single entity but consists of at least two mechanistically distinct components: needle-insertion pain, arising from superficial mechanical stimulation at the moment of penetration, and injection-phase pain, primarily related to tissue distension, pressure, and chemical irritation during anesthetic deposition (*4,5*). However, most previous clinical studies have evaluated anesthetic pain as a single outcome, making it difficult to determine which component is affected by novel analgesic interventions.

The palatal mucosa represents one of the thickest and most pain-sensitive regions in the oral cavity, characterized by dense innervation, firm attachment to the periosteum, and limited tissue compliance (*6,7*).

For this reason, it has rarely been selected as a primary test site for minimally invasive anesthetic technologies. The present study intentionally targeted the palatal mucosa as a stringent and clinically relevant model and independently evaluated needle-insertion pain and injection-phase pain to allow a mechanistically precise assessment of microneedle (MN)-assisted transmucosal anesthesia.

2. Materials and Methods

2.1. Study design

This study was conducted as a randomized, double-blind, crossover clinical trial involving adult outpatients at Nagasaki University Hospital. Eligible participants were patients who required scaling and root planing (SRP) under local anesthesia in the bilateral maxillary premolar region. After obtaining written informed consent, participants were randomly assigned using a computer-generated allocation sequence (Research Electronic Data Capture [REDCap]) in a 1:1:1:1 ratio to one of four intervention sequences (MN→Placebo or Placebo→MN, with left-right variations). A crossover design was selected to minimize inter-individual variability in subjective pain outcomes. Allocation was concealed within REDCap and remained inaccessible to the operator until the start of each treatment session, thereby ensuring adequate allocation concealment.

2.2. Participants

Participants were eligible for inclusion if they met all of the following criteria: (1) Adults aged 18-85 years requiring bilateral maxillary premolar SRP under local anesthesia; (2) Presence of bilateral maxillary premolars; (3) Ability to provide written informed consent; (4) Regular outpatient attendance at Nagasaki University Hospital. Participants were excluded if any of the following applied: (1) Regular use of analgesic medications; (2) Known hypersensitivity to ester-type topical anesthetics; (3) History of or risk factors for methemoglobinemia; (4) Pregnancy or lactation; (5) Any condition deemed inappropriate for participation by the investigators. Written informed consent was obtained from all participants prior to enrollment.

2.3. Interventions

2.3.1. Washout and treatment schedule

Each participant attended two treatment sessions (Period I and Period II), separated by a washout interval of at least one week. This washout period was selected to minimize potential carryover effects related to microneedle-induced micro-perforation or residual benzocaine.

2.3.2. Randomized sequences

The four intervention sequences were as follows: (1) Period I: Left MN patch → Period II: Right placebo patch. (2) Period I: Right MN patch → Period II: Left placebo patch. (3) Period I: Left placebo patch → Period II: Right MN patch. (4) Period I: Right placebo patch → Period II: Left MN patch.

All procedures within each period-including patch application, local anesthesia, SRP, and outcome assessment-were performed by the same operator. To maintain double blinding, the anesthetist exited the treatment room during patch application, which was performed by the principal investigator. Only the investigator was aware of the allocation status.

2.3.3. MN patch

The MN patch used in this study was AnesPatch™ SS (CosMED Pharmaceutical), with the following specifications: (1) Needle length: 0.25-0.30 mm; (2) Number of microneedles: 350; (3) Patch size: 15.5 × 13 mm.

The microneedles generate micro-perforations approximately 150-200 μm in depth, confined to the epithelial layer and avoiding stimulation of deeper nociceptors. This structure enhances transmucosal permeability and may modulate superficial mechanical nociception.

A standardized amount of 0.1 g of 20% benzocaine gel was applied to the surface of the MN patch. The patch was placed on the palatal mucosa adjacent to the target premolar for 3 minutes.

Local anesthesia was administered using an Anesject II (NEI-201) syringe in Normal Mode (180 s/mL; approximately 1 MPa pressure). A fixed volume of 1.8 mL of 2% lidocaine containing 1:80,000 epinephrine was injected.

2.3.4. Placebo patch

The placebo patch was visually identical to the MN patch but lacked microneedles. The same amount of benzocaine gel (0.1 g) was applied to the patch surface. Application duration (3 minutes) and all subsequent anesthesia procedures were identical to those in the MN patch condition.

2.4. Outcome measures

The primary outcome is presence or absence of needle-insertion pain. Needle-insertion pain was assessed dichotomously (yes/no) at the moment of needle penetration. The secondary outcomes include: (1) Injection-phase pain, assessed using a 100-mm visual analogue scale (VAS) (0 mm = no pain; 100 mm = worst imaginable pain). Patients recorded VAS scores

while seated in the dental chair immediately after anesthetic delivery and before initiation of scaling or instrumentation. (2) Numbness or discomfort at the patch application site, assessed using VAS. (3) Vital signs, including heart rate, systolic and diastolic blood pressure, and oxygen saturation, monitored from baseline (T0) at 5-minute intervals. (4) Local reactions at the application site, including erythema, swelling, or ulceration. (5) Adverse events, recorded and classified according to severity.

2.5. Statistical analysis

Normality of VAS distributions was assessed using the Shapiro-Wilk test. Normally distributed data were analyzed using paired *t*-tests, whereas non-normally distributed data were analyzed using the Wilcoxon signed-rank test. The presence or absence of needle-insertion pain was compared between conditions using McNemar's test. Period and carryover effects were evaluated using a linear model that included treatment, period, and sequence (MN→Placebo or Placebo→MN). A threshold of $p > 0.10$ was considered indicative of no clinically relevant period or carryover effects. All statistical analyses were performed using SPSS version 28.0 (IBM Japan), with statistical significance set at $p < 0.05$.

2.6. Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Nagasaki University Hospital Clinical Research Ethics Committee (Approval No. CRB7180001). All participants provided written informed consent prior to participation. The trial was registered in the Japan Registry of Clinical Trials (jRCTs072240080), and this report adheres to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.

3. Results

3.1. Participant characteristics

Twenty adult patients (10 males and 10 females) requiring bilateral maxillary premolar scaling and root planing were enrolled in this randomized, double-blind, crossover clinical trial. All participants completed both study periods without dropouts (Figure 1). Baseline demographic characteristics are summarized in Table 1. The mean age of the participants was 50.05 years (range: 26-74 years). The mean height was 163.21 cm (range: 147.00-180.00 cm), and the mean body weight was 60.28 kg (range: 42.35-82.00 kg). No statistically significant period effects or carryover effects were detected for any outcome measures (all $p > 0.10$). Detailed results of the period and carryover analyses are provided in Supplementary Table S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=286*).

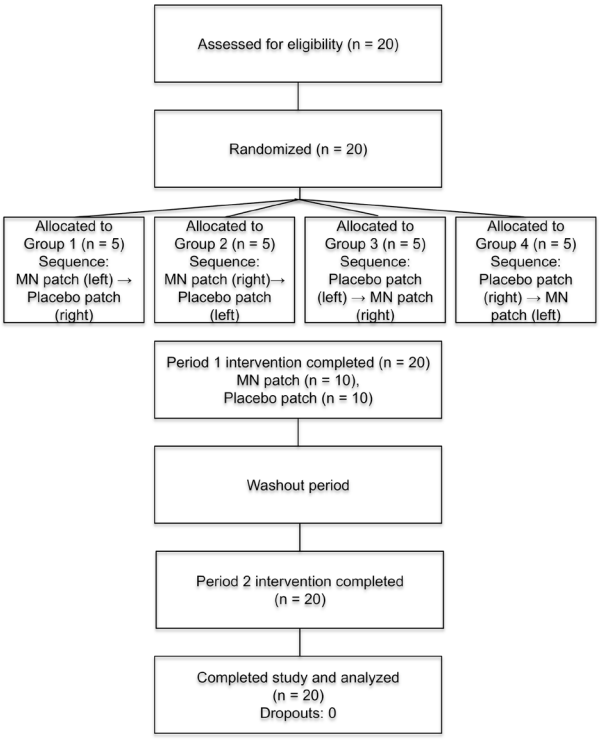

Figure 1. CONSORT flow diagram of the randomized crossover trial. Twenty participants were randomized into four groups ($n = 5$ per group) according to intervention sequence and application side (left or right). Each participant received both the microneedle (MN) patch and the placebo patch across two study periods separated by a washout interval. All participants completed both study periods and were included in the final analysis.

Table 1. Baseline characteristics of the study participants ($n = 20$: 10 males, 10 females; no dropouts)

Measures	Age (year)	Height (cm)	Body weight (kg)
Mean	50.05	163.21	60.28
Maximum	74.00	180.00	82.00
Minimum	26.00	147.00	42.35

Values are presented as mean (range). All participants completed both study periods of this randomized, double-blind, crossover trial without dropouts.

3.2. Needle-insertion pain

The proportion of participants reporting needle-insertion pain differed significantly between the two conditions. Needle-insertion pain was reported in 2 of 20 cases (10%) under the MN patch condition, whereas 14 of 20 cases (70%) reported pain under the placebo patch condition.

A 2 × 2 contingency table summarizing the presence or absence of needle-insertion pain is presented in Table 2. Figure 2 illustrates the marked reduction in the incidence of needle-insertion pain with the MN patch.

Paired comparison using McNemar's test demonstrated a statistically significant reduction in

	Placebo – Pain	Placebo – No pain
MN patch – Pain	2	0
MN patch – No pain	12	6

Figure 2. Comparison of needle-insertion pain between the microneedle (MN) patch and placebo patch conditions. Needle-insertion pain was reported in 2 of 20 cases (10%) under the MN patch condition and in 14 of 20 cases (70%) under the placebo patch condition. The 2 × 2 contingency table illustrates the presence or absence of needle-insertion pain, demonstrating a significantly lower incidence in the MN patch condition (McNemar test, $p = 0.00049$).

Table 2. 2×2 contingency table comparing the presence or absence of needle-insertion pain between the MN patch and placebo patch conditions

Patch Condition	Pain present	No pain	Total
MN patch	2	18	20
Placebo patch	14	6	20
Total	16	24	40

To assess potential carryover effects, VAS scores in the second period were compared between the two treatment sequences (MN→PL *vs*. PL→MN) using the Mann-Whitney *U* test. No significant differences were observed in any of the outcomes (all $p > 0.10$), indicating that no meaningful carryover effect was present.

needle-insertion pain under the MN patch condition compared with the placebo condition ($p = 0.00049$). These results indicate a clear and clinically meaningful attenuation of needle-insertion pain associated with MN patch application.

3.3. Injection-phase pain

Injection-phase pain was assessed immediately after anesthetic delivery using a 100-mm VAS and was evaluated independently by patients and by the operating dentist.

For patient-reported VAS scores, the mean ± standard deviation values were 28.8 ± 20.7 mm under the MN patch condition and 27.9 ± 27.7 mm under the placebo patch condition. Operator-rated VAS scores were 14.3 ± 18.5 mm for the MN patch condition and 19.0 ± 22.8 mm for the placebo condition.

Median values and interquartile ranges for both patient- and operator-rated VAS scores are summarized in Table 3. No statistically significant differences in injection-phase pain were observed between the MN patch and placebo patch conditions for either assessment, as illustrated in Figures 3A and 3B.

These findings indicate that the MN patch did not modify pain sensations associated with anesthetic deposition in deeper tissues, in contrast to its selective effect on superficial needle-insertion pain.

3.4. Numbness and local discomfort at the patch application site

VAS scores for numbness and discomfort at the patch application site were low in both conditions. Descriptive statistics for numbness induced by topical anesthesia and local discomfort are summarized in Table 4. No statistically significant differences were observed between the MN patch and placebo patch conditions, as illustrated in Figures 4A and 4B. No participants reported clinically meaningful numbness or discomfort attributable to patch application, indicating good local tolerability of the MN patch.

Table 3. Summary of dentist-rated and patient-reported VAS scores

Outcome	Patch Condition	Mean ± SD (mm)	Median (mm)	IQR(25-75%) (mm)
Dentist-rated VAS	MN	14.3 ± 18.5	7.5	0 - 28.0
	Placebo	19.0 ± 22.8	14.0	0 - 22.5
Patient-rated VAS	MN	28.8 ± 20.7	28.0	11.5 - 35.0
	Placebo	27.9 ± 27.7	18.0	7.0 - 42.0

Injection-phase pain was assessed immediately after anesthetic delivery using a 100-mm visual analogue scale (VAS; 0 = no pain, 100 = worst imaginable pain) and was evaluated independently by patients and by the operating dentist. Data are presented as mean ± standard deviation, median, and interquartile range (IQR).

Table 4. VAS scores for numbness induced by topical anesthesia and local discomfort at the patch application site

Outcome(VAS)	Patch Condition	Mean ± SD (mm)	Median (mm)	IQR(25-75%) (mm)
numbness induced by topical anesthesia	MN	20.0 ± 24.6	9.5	2 - 35.75
	Placebo	13.0 ± 18.7	9.5	0 - 12.25
Discomfort	MN	14.5 ± 23.5	6.0	0 - 13.5
	Placebo	7.9 ± 12.2	1.0	0 - 10.75

Values are presented as mean ± standard deviation, median, and interquartile range (IQR). VAS scores were assessed at the patch application site.

3.5. Physiological measures (vital signs)

Vital signs, including heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation, remained stable throughout all procedures. No clinically relevant changes were observed over time, and no significant differences were detected between the MN patch and placebo patch conditions at any measurement point. These results confirm that MN patch application did not induce systemic physiological alterations during dental treatment.

3.6. Local reactions and adverse events

No adverse local reactions, such as erythema, swelling, or ulceration, were observed following application of either the MN patch or the placebo patch. Mild aphthous-like lesions were observed in a small number of cases

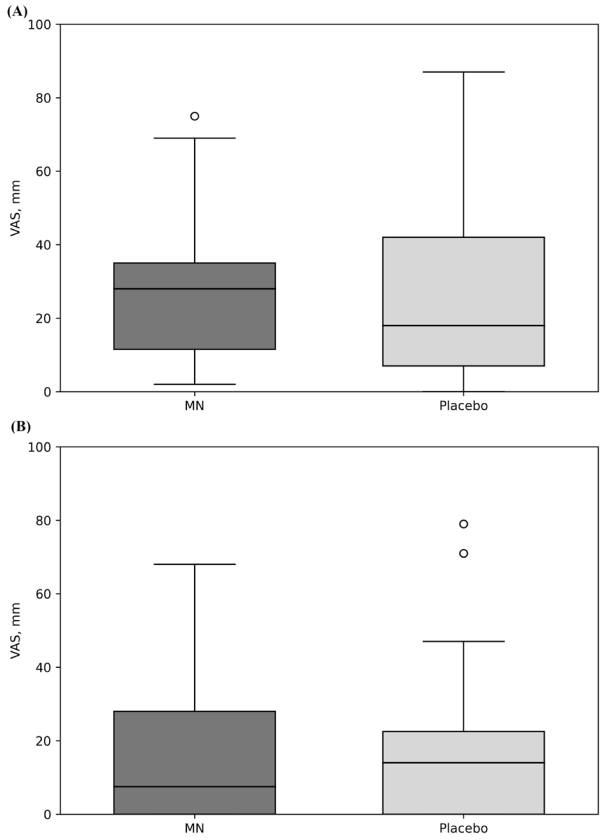

Figure 3. Injection-phase pain assessed using visual analogue scale (VAS) scores. (**A**) Patient-reported VAS scores during local anesthetic administration. (**B**) Dentist-rated VAS scores during local anesthetic administration. Box plots represent the median and interquartile range, with whiskers indicating the minimum and maximum values. Crosses indicate mean values. No statistically significant differences were observed between the MN patch and placebo patch conditions.

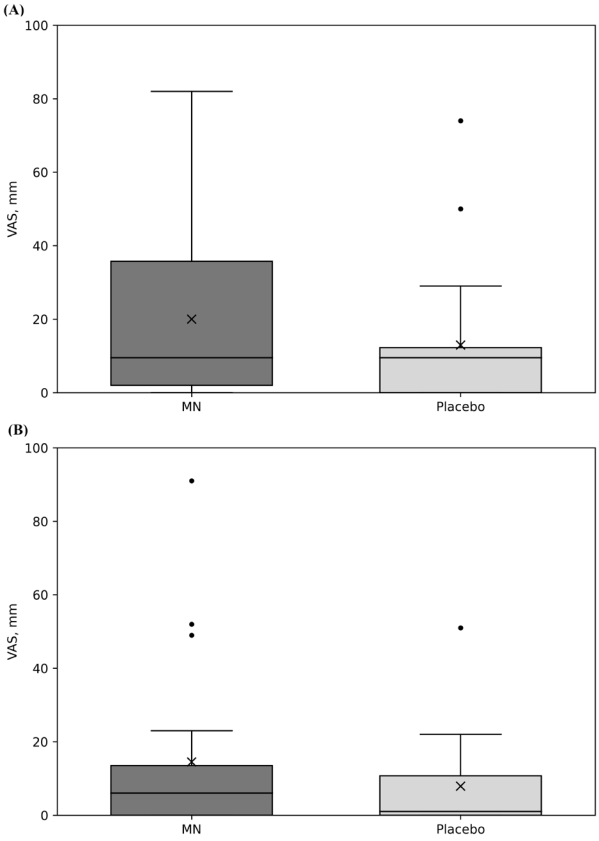

Figure 4. Patient-reported sensations associated with patch application. (**A**) VAS scores for surface numbness following patch application. (**B**) VAS scores for discomfort related to patch wearing. Box plots represent the median and interquartile range, with whiskers indicating the minimum and maximum values. Crosses indicate mean values.

after local anesthetic injection; however, all lesions were transient, clinically insignificant, and judged to be unrelated to MN patch use. No MN patch-related adverse events were identified.

4. Discussion

This randomized, double-blind, crossover clinical trial evaluated the clinical utility of a benzocaine-loaded MN patch applied to the palatal mucosa prior to dental local anesthesia. The principal finding of this study is that the MN patch significantly reduced needle-insertion pain, whereas injection-phase pain, assessed using VAS scores, did not differ between the MN and placebo conditions. Importantly, the MN patch demonstrated an excellent safety profile, with minimal local discomfort and no clinically relevant adverse events.

4.1. Selective attenuation of needle-insertion pain

The most clinically meaningful outcome of the present study was the marked reduction in needle-insertion pain observed with the MN patch. Needle-insertion pain represents the moment most strongly associated with dental anxiety and avoidance behavior. By significantly attenuating this superficial pain component, the MN patch directly targets the most fear-provoking phase of dental local anesthesia.

The selective nature of this effect is noteworthy. Needle-insertion pain arises primarily from mechanical stimulation of superficial nociceptors located within the epithelial and subepithelial layers of the oral mucosa. The MN patch generates controlled micro-perforations confined to these superficial layers, which may reduce mechanical resistance to needle penetration and modulate local nociceptive input. This mechanism is consistent with the observed reduction in insertion pain without concomitant changes in deeper pain sensations.

4.2. Lack of effect on injection-phase pain

In contrast to its effect on insertion pain, the MN patch did not significantly influence injection phase pain. Injection-phase pain is predominantly attributable to

tissue distension, pressure, and chemical irritation during anesthetic deposition and is mediated by deeper nociceptive structures, including the lamina propria and periosteal region.

The absence of an effect on injection-phase pain should not be interpreted as a limitation of the MN patch. Rather, it reflects a mechanistically expected outcome given the anatomical constraints of the palatal mucosa. The microneedles used in this study were designed to penetrate approximately 150-200 μm, remaining within the epithelial layer. In contrast, the palatal masticatory mucosa is substantially thicker, often exceeding 1.5 mm, particularly in posterior regions. As a result, MN-mediated micro-channels are unlikely to facilitate anesthetic diffusion to deeper nociceptive sites responsible for injection-phase pain.

4.3. Significance of palatal mucosa as a test site

A key strength of the present study lies in the intentional selection of the palatal mucosa as the application site. The palate represents one of the thickest and most pain-sensitive regions in the oral cavity, characterized by dense innervation, firm attachment to the periosteum, and limited tissue compliance. These anatomical features make effective pain control particularly challenging.

By demonstrating a significant reduction in needle-insertion pain even in this unfavorable environment, the present findings provide robust evidence for the superficial analgesic capability of the MN patch. This strengthens the external validity of the results and suggests that similar or greater benefits may be achievable in thinner and more compliant oral mucosal sites, such as the buccal attached gingiva.

4.4. Comparison with previous microneedle-based studies

Previous studies investigating MN-assisted oral anesthesia have reported heterogeneous results, largely due to differences in MN geometry, needle length, density, drug loading, and application site. For example, Daly *et al.* demonstrated reductions in injection-related pain using longer and denser MN arrays applied to thinner oral mucosa (*8*). Other experimental studies have reported enhanced transmucosal delivery of lidocaine using hydrogel-forming or high-density MN systems.

The present study differs from these investigations in several important respects (*9-15*). A relatively short MN length, limited needle density, and a small amount of benzocaine were employed, and the patch was applied to the palatal mucosa. Despite these conservative parameters, a significant reduction in needle-insertion pain was observed. This suggests that MN-induced modulation of superficial nociception may play a clinically relevant role independent of deep anesthetic diffusion.

4.5. Placebo patch effects and patient perception

The placebo patch used in this study was structurally identical to the MN patch except for the absence of microneedles. Both patches demonstrated good mucosal adhesion and prolonged benzocaine retention, which may have contributed to partial anesthetic effects in the placebo condition. In addition, psychological factors, including expectancy and procedural rituals associated with patch application, may have influenced pain perception.

These factors likely contributed to the lack of difference in injection-phase pain between conditions and highlight the importance of considering both pharmacological and contextual influences when evaluating pain outcomes in dental settings.

4.6. Clinical implications

From a clinical perspective, the MN patch offers a targeted and pragmatic approach to improving patient comfort during dental local anesthesia. By selectively reducing needle-insertion pain without introducing systemic effects or clinically relevant adverse events, the MN patch addresses a critical barrier to dental treatment acceptance.

This approach may be particularly beneficial for patients with dental anxiety or phobia, pediatric patients, individuals with special healthcare needs, and patients with heightened pain sensitivity. Importantly, the MN patch requires minimal additional chair time and does not interfere with standard anesthetic techniques.

4.7. Limitations and future directions

Several limitations should be acknowledged. This was a single-center study with a modest sample size, and the absence of a no-patch control group limits the ability to fully disentangle placebo and contextual effects associated with patch application. In addition, only palatal application was evaluated, and all procedures were performed by a single operator to minimize procedural variability, which may limit the generalizability of the findings.

First, the study population consisted exclusively of adult patients undergoing periodontal treatment that required palatal local anesthesia. Accordingly, caution is warranted when extrapolating these results to broader dental populations, such as pediatric patients, individuals with extreme dental anxiety or phobia, or patients with special healthcare needs. Although these populations may potentially benefit most from attenuation of needle-insertion pain, their pain perception, behavioral responses, and oral mucosal characteristics may differ from those of the present study cohort. Future investigations specifically designed for these populations are required to clarify the clinical applicability and

external validity of microneedle-assisted anesthesia across diverse dental settings.

Second, although no local or systemic infections were observed during the study period, the short-term impact of microneedle-induced micro-perforations on oral mucosal barrier function was not directly evaluated. The creation of transient micro-channels theoretically raises concerns regarding microbial translocation or increased susceptibility to local infection. This concern persists despite the fact that the microneedles were designed to remain within the epithelial layer and that all applications were conducted under routine clinical conditions. Future studies incorporating microbiological assessments, inflammatory markers, or biomarkers of mucosal barrier integrity would be valuable to more comprehensively address this theoretical safety consideration.

Finally, future research should explore further optimization of microneedle geometry, needle length, and drug loading, as well as evaluation at alternative oral mucosal sites with different anatomical and mechanical properties. The incorporation of objective pain-related or physiological measures, such as heart rate variability or pupillometry, may also strengthen mechanistic understanding and support broader clinical translation of this minimally invasive anesthetic approach.

5. Conclusion

This randomized, double-blind, crossover clinical trial demonstrated that a benzocaine-loaded MN patch significantly reduced needle-insertion pain during dental local anesthesia, while having no measurable effect on injection-phase pain. The MN patch was well tolerated, caused minimal local discomfort, and was not associated with clinically relevant adverse events or systemic physiological changes.

The selective attenuation of needle-insertion pain is likely attributable to the superficial action of MN-induced micro-perforations within the epithelial layer of the palatal mucosa, whereas deeper pain associated with anesthetic deposition remained unaffected due to anatomical constraints. These findings highlight the mechanistic specificity of MN-assisted transmucosal anesthesia.

While further studies in broader patient populations and with focused safety assessments are warranted, the MN patch represents a safe, simple, and clinically feasible adjunct for targeting the most anxiety-provoking component of dental local anesthesia. This approach may improve patient comfort and acceptance of dental treatment, particularly in patients with dental anxiety, heightened pain sensitivity, or special healthcare needs.

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**Address correspondence to:*
Kensuke Kiriishi, Department of Special Care Dentistry, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail: kiriishi@nagasaki-u.ac.jp

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