ARTICLE 2

ANALGESIC EFFICACY AND SAFETY OF AN INTRAORAL LIDOCAINE PATCH

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ABSTRACT

The effectiveness of intraoral lidocaine patches was tested by asking participants to rate the pain experienced after insertions of a 25-gauge needle. Needlesticks were performed at baseline and at various time points after patch placement. Each needlestick included contact with the periosteum. Lidocaine patches achieved significantly better analgesia than the placebo within 2.5 to five minutes after placement. Drug-related side effects were minimal and venous blood levels of lidocaine were low, averaging 10 to 14 times less than those achieved with a typical injection of lidocaine plus epinephrine. The authors conclude that the lidocaine patches used in this study are effective and safe in reducing needle insertion pain in adults.

To reduce the perception of pain associated with needle penetration, dentists often apply topical anesthetics to the oral mucosa before injecting local anesthetic solutions.[1] While a number of placebo-controlled clinical trials have studied the effectiveness of such topical agents, the results have been conflicting.[2-9] Only a few studies have demonstrated their efficacy[2-4]; most show no difference between the active topical preparations and the placebo.[5-9]

Common factors among investigations reporting efficacy include the use of needles no larger than 27 gauge, avoidance of the periosteum and the use of 5 percent lidocaine as one of the topical anesthetics.[2-4] By contrast, studies in which the topical agents were no more effective than the placebo involved the use of 25-gauge needles,[6,7,9] injection of local anesthetic solution after needle penetration,[5,7,8] contact with the periosteum,[7] short contact times (15 to 45 seconds) between the mucosa and the topical agent[5-7] and the use of phenol[5] or benzocaine[7,9] as the active topical agent.

These studies suggest that the likelihood of attaining acceptable topical anesthesia may be increased by using needles with a diameter of 27gauge or smaller, avoiding contact with the periosteum, keeping the topical anesthetic in contact with the mucosa for two minutes or longer and using lidocaine rather than benzocaine or phenol.

While the choice of topical anesthetic can be controlled easily by the clinician, the other variables are more difficult to control. For example, some regional anesthetic techniques—such as posterior superior alveolar blocks, infraorbital nerve blocks, buccal nerve blocks and mental nerve blocks[1]—and mandibular block injections often necessitate the use of 25-gauge needles.

Clinicians often have difficulty maintaining prolonged mucosal contact with an adequate concentration of the topical anesthetic. Most topical anesthetics come in gel form, which can be difficult to confine to one site. Furthermore, these gels can become diluted in the mouth, which leads to inadequate anesthesia.

Dentists also cannot always avoid contact with the periosteum when administering a local anesthetic. In fact, such contact is recommended with certain injections such as the buccal nerve, or the

long buccal, block.[1]

Thus, dentistry would benefit from the development of a topical anesthetic system that could adhere to the oral mucosa, maintain effective local anesthetic concentrations and demonstrate efficacy even when the local anesthetic was administered with 25-gauge needles and the periosteum was contacted. In addition, the topical agent should not appreciably add to systemic local anesthetic concentrations achieved by subsequent injections, an especially important consideration when treating children.[10-12]

Anesthetic patches containing lidocaine base that is dispensed through a bioadhesive matrix and applied directly to the oral mucosa recently have been approved by the U.S. Food and Drug Administration and are commercially available (DentiPatch lidocaine transoral delivery system, Noven Pharmaceuticals Inc.). These patches are available in 10 and 20 percent concentrations, each containing approximately 23 and 46 milligrams of lidocaine base per 2 square centimeters of patch, respectively. The lidocaine contained in the matrix diffuses directly through the mucosa while the patch is affixed.

This study evaluated the efficacy and safety of intraoral lidocaine patches at 10 and 20 percent concentrations. We compared the efficacy of these patches with that of placebo patches in reducing the pain associated with needle insertion in both the mandibular and maxillary arches. This study also documents the onset and duration of anesthesia and the pharmacokinetic profile of this system.

MATERIALS AND METHODS

This was a five-center, double-blind, randomized, placebo-controlled study. All study participants signed an informed consent form that had been approved by each center's respective institutional review board.

Participant selection. Participants had to be between 18 and 65 years of age, in good general health and have no contraindications to lidocaine or other local anesthetics. Women who were pregnant were not eligible for the study, and women who were accepted were asked to abstain from sexual intercourse or use an acceptable form of birth control during the study.

Dentistry would benefit from a topical anesthetic system that could adhere to the oral mucosa, maintain effective local anesthetic concentrations and demonstrate efficacy even when the local anesthetic was administered with 25-gauge needles and the periosteum was contacted.

To reduce the number of participants who were susceptible to the placebo effect, we screened the volunteers. During the single-blind screening appointment (Visit 1), the investigators placed placebo, or nonactive, patches 2 millimeters apical to the mucogingival junction in both the maxillary and mandibular premolar region of all prospective participants (Figure 1). The investigators knew that the patches contained a placebo, but the volunteers did not know this. The order of patch placement (maxillary vs. mandibular) and the positioning of the patch on the left or the right side of the mouth were determined by a randomization code. In all cases, the second patch was placed on the opposing arch of the opposite side of the mouth.

Before patch placement, the mucosal site was dried with a sterile gauze pad. The placebo patch was then applied and left in place for 10 minutes. After 10 minutes, the investigators lifted the edge of the patch and inserted a sterile 25-gauge needle that was attached to a syringe through the mucosa at a 45-degree angle. They inserted the needle until the tip contacted bone and then immediately removed the needle. The patch was left in place for five minutes more before it was removed.

Immediately after the needlestick, participants assessed the intensity of pain they experienced on a five-point verbal scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. They also completed a 100-mm visual analog scale, or VAS, with "no pain" on the far left at 0 mm and "pain as bad as it can be" on the far right at 100 mm.

Investigators also assessed the occurrence and degree of local irritation at the application site, immediately before patch placement and 30 minutes after removal of the patch by visual inspection and intra-

oral photographs.

Participants who scored at least a 2 (moderate pain) on the five-point verbal rating scale had the same procedure repeated on the opposing arch and the opposite side of the mouth. Participants who scored less than a 2 following either needlestick were dismissed from the study.

For safety purposes, remaining participants underwent a series of medical and laboratory tests before entering the double-blind phase of the study. These included a complete physical examination, a 12-lead electrocardiogram, a serum chemistry evaluation, complete blood count with differential and platelet counts, complete urinalysis and screens to detect recent use of controlled dangerous substances. Women also were tested for pregnancy via a serum test. All test results had to be within normal limits, without significant abnormalities or, in the cases of controlled dangerous substances and pregnancy, negative.

Patch testing. Within 14 days of completing the screening visit and the medical evaluations, 101 participants were randomized into the double-blind phase of the study. This phase involved two treatment visits (Visits 2 and 3) during which placebo patches that contained no medication or active treatment patches that contained 10 percent lidocaine or 20 percent lidocaine were placed for 15 minutes on the buccal mucosa of the maxillary or mandibular premolar region, 2 mm apical to the mucogingival junction (Figure 1). Both the participants and the clinicians were blinded to the treatment assignment.

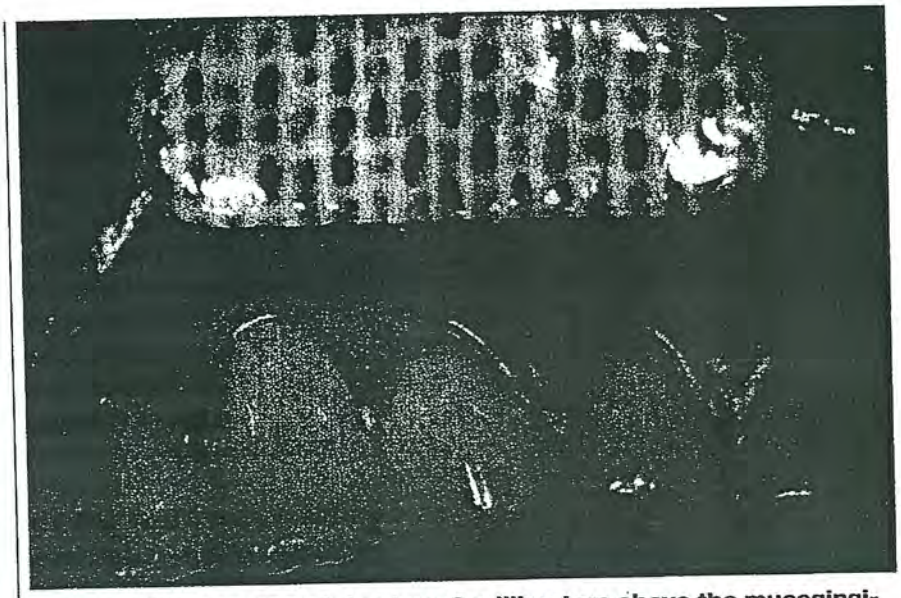

Figure 1. Transoral patch in place 2 millimeters above the mucogingival junction.

Baseline pain scores were established by having participants rate the pain they experienced from a 25-gauge needlestick on both the 100-mm visual analog scale and the five-point verbal scale, immediately before the patch was placed.

Investigators then repeated the needlesticks at 2.5, five, 10 and 15 minutes after patch placement by lifting the edge of the patch. To test the duration of the topical anesthetic effect, investigators performed a final needlestick at 45 minutes after patch placement, which was 30 minutes after the patch had been removed. Each successive insertion was made slightly distal or mesial to the preceding one with a new needle.

Immediately after each needle insertion, participants rated the pain experienced using the visual analog scale and the verbal pain scale.

To measure plasma lidocaine concentrations, investigators drew 10-milliliter venous blood samples through an indwelling catheter in the antecubital fossa immediately before patch placement and at five, 10, 15 and 45 minutes after placement of the patch. These samples were spun at 3,000 revolutions per minute in a refrigerated centrifuge and stored for later gas-liquid chromatographic analysis.

To monitor mucosal irritation from the patch, the investigators took intraoral photographs and assessed the appearance of the mucosa at the patch application site before patch placement, and at 30 minutes and 24 hours after the removal of the patch. Local irritation was rated as follows: 0 = no irritation, 1 = minimal (blood vessels raised above normal levels), 2 = moderate (beet redness of mucosa, individual blood vessels not discernible) and 3 = severe (blister formation and necrosis evident).

One week later (Visit 3), all procedures (baseline pain assessments, double-blind patch placement, venous blood sampling, evaluations of local irritation and intraoral photographs) were repeated, with the needlesticks given and the patches applied on the opposing arch of

the opposite side of the mouth. The same treatment that had been administered during Visit 2 was administered during Visit 3. For example, a participant who had received the 10 percent lidocaine patch on the right maxillary buccal mucosa during Visit 2 received another 10 percent lidocaine patch on the mandibular left buccal mucosa on Visit 3. Again, the participants and investigators were blinded as to which patch was being used.

Data analysis. The primary efficacy variable evaluated in this study was the change from baseline in the visual analog scale pain score at 10 minutes after the application of the patches. Secondary efficacy variables included the change from baseline in visual analog scale pain scores at all other time points and the change in verbal pain scores at all time points.

We compared these changes on each arch between treatment groups using analysis of covariance, or ANCOVA. The ANCOVA model accounted for treatment, study center and treatment-by-study-center interactions, with baseline values included as the covariate. Significant differences ($P < .05$) were further contrasted using pairwise t-tests.

We determined the onset of anesthesia for both treatment groups in each arch. Anesthesia onset was defined as the first time point in which the difference in the visual analog scale pain score from baseline was significantly different between active treatment groups and the placebo group. We also determined the duration of action, which we defined as the last time point at which the treatment groups' visual analog scale pain score changes were significantly different from the placebo groups', minus the onset time of anesthesia.

Plasma levels of lidocaine were pooled and the mean concentrations at each sampling point were expressed graphically. Demographic data were compared between treatment groups using one-way analysis of variance, or ANOVA, and the χ^2 test.

TABLE

PARTICIPANT CHARACTERISTICS, INCLUDING MEAN BASELINE PAIN SCORES.

	PLACEBO PATCH	10% LIDOCAINE PATCH	20% LIDOCAINE PATCH
Sample Size	32	33	35
Male	16	18	21
Female	16	15	14
Age (Years)	28.4 (1.2)	28.9 (1.2)	28.5 (1.0)
Height (Inches)	67 (0.8)	68 (0.7)	67 (0.6)
Weight (Pounds)	164 (6.4)	157 (6.0)	161 (5.0)
Baseline VAS* Pain Score (mm)†			
Mandibular	53.0 (4.4)	48.9 (3.5)	56.2 (3.2)
Maxillary	59.0 (3.8)	49.3 (3.4)	58.8 (2.7)
Baseline Verbal Pain Score† (mm)†			
Mandibular	2.5 (0.2)	2.2 (0.1)	2.4 (0.1)
Maxillary	2.5 (0.1)	2.2 (0.1)	2.5 (0.1)

* VAS = visual analog scale.
† Data presented as mean values ± (standard error).

RESULTS

A total of 101 participants were enrolled in the double-blind phase of the study, of whom 100 were acceptable for the efficacy analysis (one participant violated the study protocol and had to be dropped from the study). The table lists the mean demographic and baseline pain data of each study group. The ratio of women to men, and the distribution across age, height and weight were similar between the three groups with no significant differences observed.

The mean baseline needlestick pain scores (before patch placement) were also fairly similar between the groups, with scores ranging from 49 to 59 mm on the 100-mm visual analog scale, and from 2.2 to 2.5 on the five-point verbal scale.

The mean changes from the baseline visual analog scale pain scores in the mandible and the maxilla after placement of the patches are shown in Figures 2 and 3.

In the mandibular arch, both active patch treatments significantly reduced needlestick pain compared with the matching placebo treatment (Figure 2). The onset of anesthesia, defined as the first time point when a treatment group's mean reduction in the visual analog scale

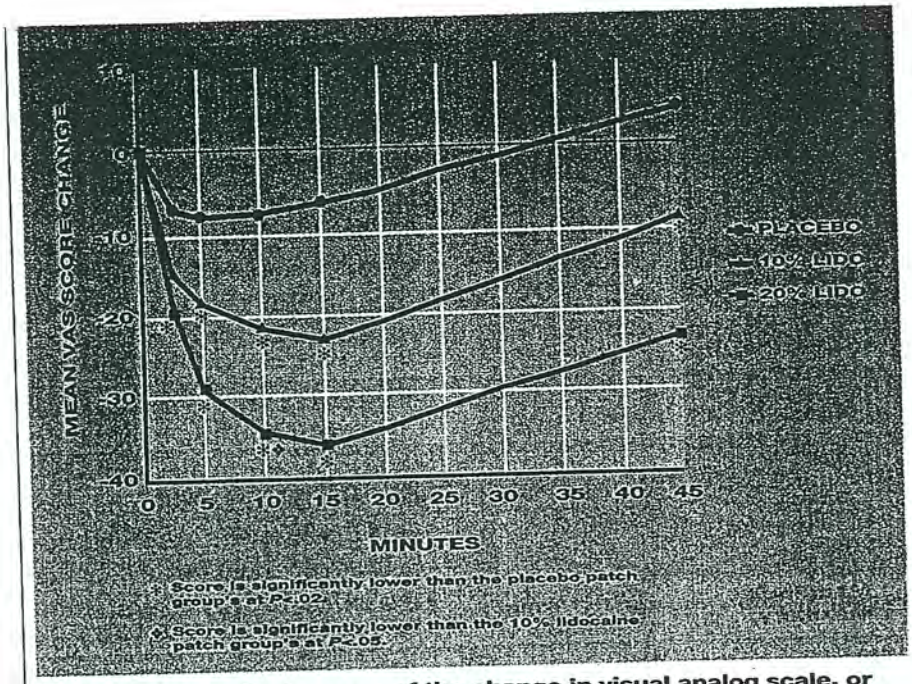

Figure 2. Time-effect curves of the change in visual analog scale, or VAS, pain scores from baseline for the placebo, 10 percent lidocaine (10% LIDO) and 20 percent lidocaine (20% LIDO) transoral patches placed on the mandible. Mean score changes are expressed in millimeters and are plotted against time in minutes.

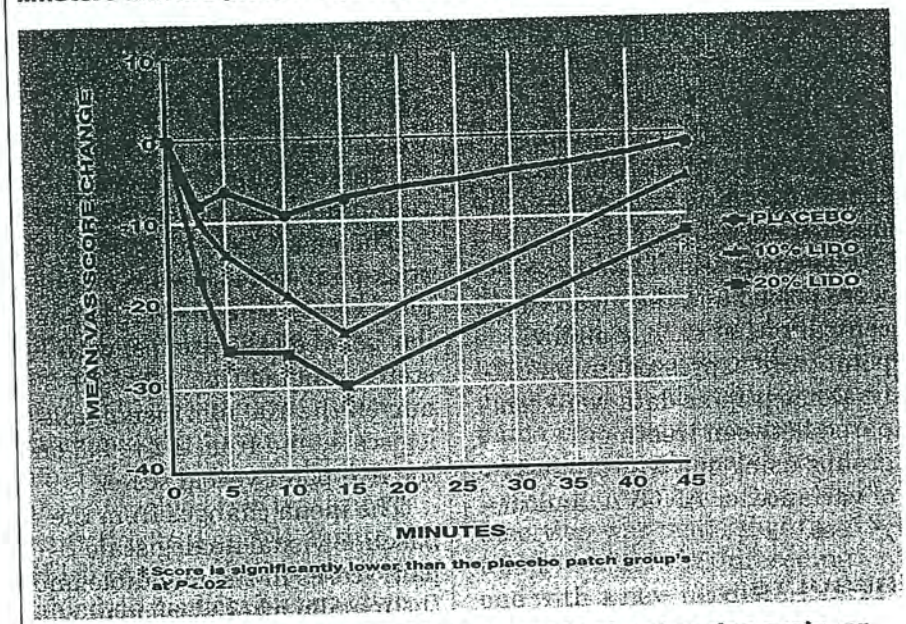

Figure 3. Time-effect curves of the change in visual analog scale, or VAS, pain scores from baseline for the placebo, 10 percent lidocaine (10% LIDO) and 20 percent lidocaine (20% LIDO) transoral patches placed on the maxilla. Mean score changes are expressed in millimeters and are plotted against time in minutes.

pain score from baseline differed significantly from the placebo group's ($P < .05$), was within 2.5 minutes for the 20 percent lidocaine patch and within five minutes for the 10 percent lidocaine patch. At all other time points (10, 15 and 45 minutes), both active patch concentrations significantly reduced needlestick pain compared with the placebo.

As Figure 2 shows, a positive dose-response relationship exists between the two active patches, with the 20 percent concentration producing a greater analgesic effect than the 10 percent concentration. From a statistical standpoint, the primary point of interest occurred 10 minutes after the application of the patches. At this time, the ANCOVA revealed that not only were the 10 percent ($P = .0004$) and the 20 percent ($P = .0001$) lidocaine patches significantly more efficacious than placebo, but the 20 percent patch was also more efficacious than the 10 percent patch ($P = .0464$), again indicative of a positive dose-response relationship between lidocaine patch concentrations. Analgesic duration in the mandibular arch was at least 40 minutes for the 10 percent lidocaine patch and at least 42.5 minutes for the 20 percent lidocaine patch.

In the maxillary arch (Figure 3), the analgesic onset of both active lidocaine patches occurred within five minutes, with both treatments being significantly more effective than placebo. Neither lidocaine concentration was significantly different than placebo at 2.5 minutes. At 10 and 15 minutes, the decrease in visual analog scale pain scores remained significantly greater for both lidocaine patches than for the placebo. However, only the 20 percent lidocaine group exhibited a significant decrease in pain compared with the placebo group at 45 minutes.

At the primary efficacy time point of 10 minutes, there was no difference between the active patches; the P-values for both the 10 percent ($P = .0035$) and 20 percent ($P = .001$) patches

were highly significant compared with the placebo. The analgesic duration in the maxillary arch was 10 minutes for the 10 percent lidocaine patch and at least 40 minutes for the 20 percent lidocaine patch.

The change from baseline in mean verbal pain scores (Figures 4 and 5) followed the same general pattern as the visual analog scale pain data with a positive dose-response relationship exhibited between the) and 20 percent lidocaine concentrations. In the mandibular arch (Figure 4), participants treated with the 10 percent patch exhibited significantly greater decreases in verbal pain scores than those treated with the placebo at 10 and 15 minutes, while the 20 percent lidocaine patch was significantly more efficacious than the placebo at all times except at 2.5 minutes after placement. In addition, the 20 percent lidocaine patch was significantly more efficacious than the 10 percent patch at five minutes.

In the maxilla (Figure 5), the '0 percent patch was signifi-antly better than placebo only at the 15-minute point, while the 20 percent patch was significantly more efficacious than the placebo at 2.5 through 15 minutes. At both 2.5 and five minutes, the 20 percent lidocaine patch also was significantly more efficacious than the 10 percent lidocaine patch.

Pooled plasma lidocaine concentrations achieved with the active patches are illustrated by the two lower curves in Figure 6. Lidocaine levels rose in a more or less linear fashion for the 15 minutes that the active patches were in contact with the oral mucosa, followed by a concentration plateau for the

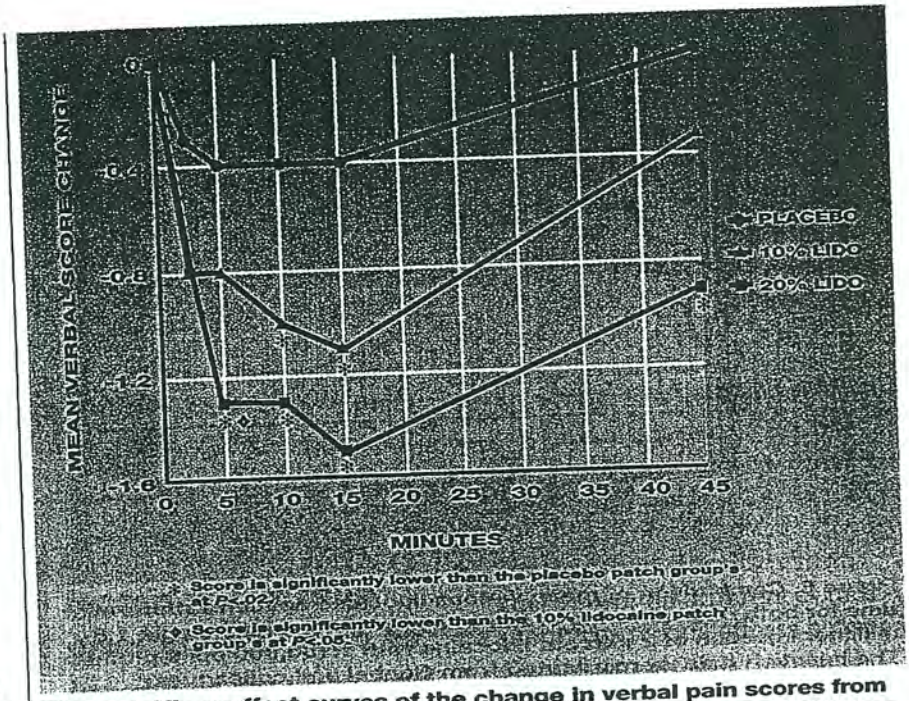

Figure 4. Time-effect curves of the change in verbal pain scores from baseline for the placebo, 10 percent lidocaine (10% LIDO) and 20 percent lidocaine (20% LIDO) transoral patches placed on the mandible. Mean score changes are plotted against time in minutes.

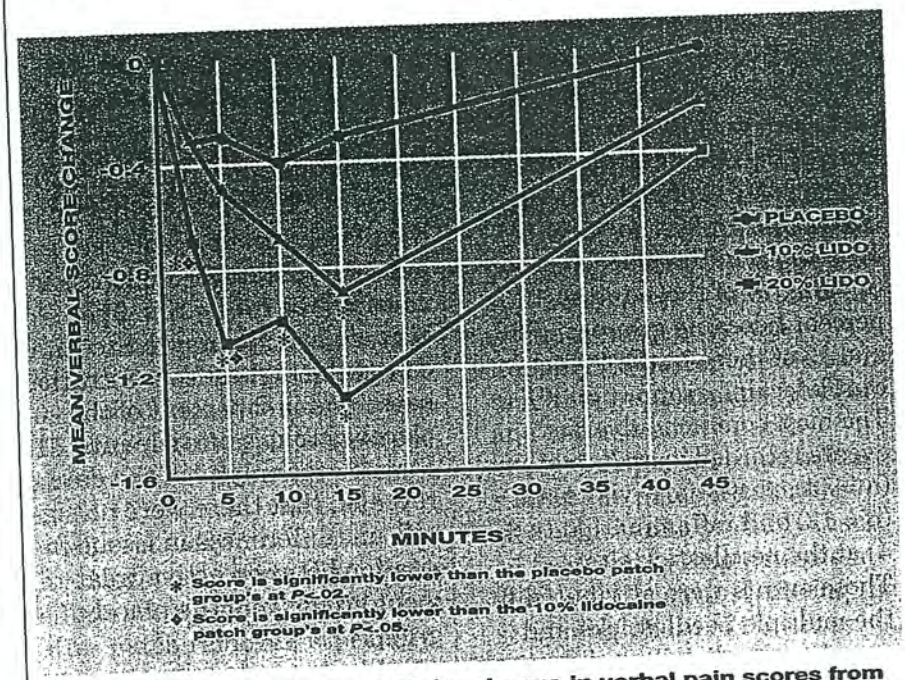

Figure 5. Time-effect curves of the change in verbal pain scores from baseline for the placebo, 10 percent lidocaine (10% LIDO) and 20 percent lidocaine (20% LIDO) transoral patches placed on the maxilla. Mean score changes are plotted against time in minutes.

next 30 minutes after the patches had been removed. On a relative scale, average peak blood levels were minimal, ranging from 15.84 nanograms/mL for the 10 percent lidocaine patch to 21.80 ng/mL for the 20 percent lidocaine patch.

All 101 participants who entered the double-blind phase of

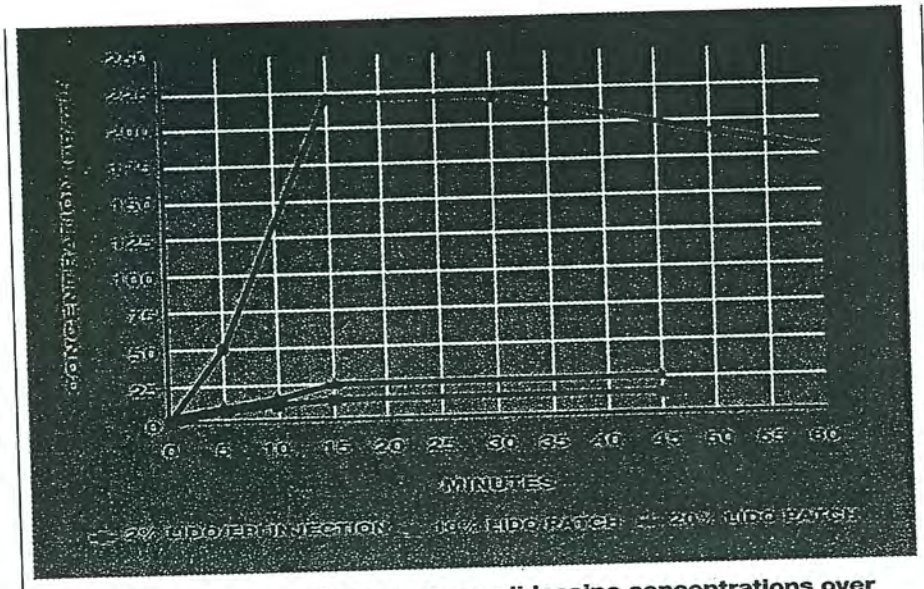

Figure 6. Comparison of mean venous lidocaine concentrations over time for both dosage forms of the transoral patch and a single 1.8-milliliter injection of 2 percent lidocaine with 1:100,000 epinephrine. The injection data were adapted from Goebel and colleagues.[17]

the study were evaluated for side effects. Investigators recorded all side effects regardless of whether they seemed to be directly related to the patch. Thirty-seven participants reported a total of 43 adverse events. Participants who exhibited adverse events came equally from all three study groups: 10 of those in the placebo group (n = 32), 14 of those in the 10 percent lidocaine group (n = 33) and 13 of those in the 20 percent lidocaine group (n = 36). The most common adverse events recorded were hematoma (n = 14), post-study–visit pain (n = 12) and inflammation (n = 4) at the needlestick sites. These events were attributed to the multiple needlesticks and were equally distributed among treatment groups.

Investigators assessed local tissue irritation 30 minutes and 24 hours after the patches were removed. At 30 minutes after removal, 15 percent of both active treatment groups displayed minimal irritation compared with 13 percent of the placebo group. In addition, 3 percent of the placebo participants displayed moderate tissue irritation. At 24 hours, 11 percent of the participants in the 10 percent lidocaine group, 15 percent of the participants in the 20 percent lidocaine group and 10 percent of the participants in the placebo group displayed minimal irritation. Moderate irritation was evident in 4 percent of participants who received the highest concentration patch and in 2 percent of the placebo group's participants. Statistical analysis of the data revealed that there were no significant differences in tissue irritation between active treatment groups and the placebo group.

DISCUSSION

The piercing of mucosa by dental injection needles is a routine part of local anesthetic delivery. However, this event is accompanied by significant trepidation in many patients. In one study, patients rated the feel of the injection needle penetrating the mucosa as the most fear-provoking stimuli in dentistry; while just the sight of the needle itself was ranked as the second most fear-provoking event.[13] Other investigations have supported these negative connotations associated with dental needles and injections among patients.[14,15] Fear of painful stimuli, such as needle penetration, appears to be learned and is thought to be a major contributor to the avoidance of routine dental care.[9,13-15] Therefore, any procedure that significantly reduces the unpleasantness of dental injections could serve as a positive reinforcer toward obtaining dental care.

While dentists often apply topical anesthetics to reduce the discomfort associated with local anesthetic injections, only a few clinical trials have demonstrated their efficacy beyond that of matching placebo treatments.[2-4] One widely quoted investigation by Yaacob and colleagues, which reported that the topical application of 5 percent lidocaine was highly effective in reducing needle insertion pain,[2] may have suffered from a methodological flaw. In this investigation the active lidocaine preparation was always tested before the matching placebo ointment. A later study by Martin and colleagues found that participants experience significantly more pain on the second injection than the first injection, regardless of whether the injection was preceded by the active or placebo topical agent.[9] Thus, Martin and colleagues suggested that the order in which the injections were given in Yaacob and colleagues' study may have contributed to the topical anesthetic effectiveness that was reported.[9]

From a clinician's perspective, there were other potential shortcomings of the studies supporting topical anesthetic efficacy. All three investigations used needles no larger than 27 gauge and all avoided needle contact with the periosteum.[2-4] In studies where the needle size was 25 gauge[6,7,9] or periosteum was contacted,[7] the effectiveness of the topical anesthetic agents was no better than the placebo. Since 25-gauge needles are routinely used in dentistry and contact with the periosteum is often unavoidable, it would be of great benefit to the clinician to have in his or her armamentarium a topical anesthetic preparation that would be efficacious in these instances.

One major problem with conventional topical anesthetic gels is their lack of bioadhesiveness to the oral mucosa.[4,16] This leads to a movement of the topical anesthetic away from the application site, with the effect being a reduction in tissue analgesia. A relatively prolonged contact time of the topical anesthetic with the oral mucosa appears to increase the likelihood of efficacy.[3,4,16]

The transoral system used in this study employs lidocaine base contained in a bioadhesive patch, a delivery method that improves the duration of contact with the oral soft tissues as compared with conventional gels.

The overall effectiveness of both concentrations of the lidocaine patch was notable considering the relative magnitude of the painful stimuli delivered during the study. (Not only were 25-gauge needles used to make multiple penetrations over a 45-minute period, but the periosteum intentionally was contacted with each needlestick.) Onset of analgesia was rapid, evident within 2.5 to five minutes after placement in the mandibular arch and within five minutes after placement in the maxillary arch.

A positive dose-response relationship was observed, with the 20 percent patch producing analgesia that was more profound and of longer duration than that of the 10 percent patch. An inspection of the time-action curves for both the reduction in visual analog scale and verbal pain scores reveals that the maximum analgesic effects occurred between five and 15 minutes after placement of the transoral lidocaine patches.

It is possible that selected soft-tissue procedures, such as localized scaling and curettage, gingivectomies and biopsies, could be performed using this delivery system without conventional local anesthetic injections.

At 15 minutes, the patches were removed from the oral cavity. However, residual analgesic effects were evident 30 minutes after patch removal, especially in participants treated with the 20 percent concentration.

These results suggest that duration of analgesia will be directly proportional to the time the patch remains in contact with the oral soft tissues. It is possible that selected soft-tissue procedures, such as localized scaling and curettage, gingivectomies and biopsies, could be performed using this delivery system without conventional local anesthetic injections. At the very least, the profundity of soft-tissue anesthesia produced by this system may lead to a better acceptance of dental injections as a whole. This is especially important in the pediatric dental population, where traumatic dental experiences can produce adult dental phobics.[15]

The other major issue explored in this investigation was the safety of the lidocaine transoral system. In this regard, there were no differences in the instances of side effects between the treatment and the placebo transoral systems. Most reported or observed side effects (n = 43) were related to the study procedure, resulting from six 25-gauge needlesticks contacting periosteum at the patch application site. These included hematoma formation (n = 14), pain (n = 12) and inflammation (n = 4) at the application site. The amount of mucosal irritation observed at the application site was also very similar between treatment groups. Roughly 15 percent of the participants in all groups (placebo and the two active patch groups) displayed some irritation at the patch application site, which also probably resulted from the multiple needle insertions. In contrast, during the screening phase of the study, where only one needlestick was performed on participants wearing placebo patches, only about 3 percent of the volunteers displayed local irritation.

In addition to efficacy and a lack of significant observable side effects, an extremely desirable property of any new topical anesthetic delivery system

would be minimal systemic absorption of the local anesthetic. The total amounts of lidocaine contained in these patches—23 mg for the 10 percent formulation and 46 mg for the 20 percent formulation—are significant, considering that one cartridge (1.8 mL) of 2 percent lidocaine contains 36 mg of local anesthetic. However, the pharmacokinetic analyses revealed that systemic lidocaine absorption with both active patch formulations was extremely small, with peak plasma lidocaine concentrations averaging in the 16- to 22-ng/mL range. To put these blood levels in perspective, Figure 6 compares the blood levels of lidocaine achieved in this study with those reported by Goebel and colleagues,[17] following the infiltration injection of a single cartridge of 2 percent lidocaine with 1:100,000 epinephrine. Peak blood levels after injection were achieved within 15 minutes and averaged 220 ng/mL, roughly 10 times higher than that achieved with the 20 percent patch and 14 times higher than that achieved with the 10 percent patch. Thus, plasma concentrations of lidocaine attained from the 15-minute placement of a single transoral patch will not appreciably add to local anesthetic blood levels achieved by subsequent injections. While only adults were evaluated in this study, low systemic lidocaine absorption is of particular importance in the pediatric dental population, where excessive local anesthetic blood levels have led to disastrous effects.[10,11,18]

CONCLUSION

In summary, the 10 percent and 20 percent lidocaine patches tested in this study appear to be both highly efficacious and safe in reducing needle insertion pain in the maxillary and mandibular premolar mucosa of adults. This is the first study in which any topical anesthetic formulation was superior to a placebo when 25-gauge needles were used to pierce the mucosa and the periosteum was contacted intentionally. Systemic blood levels achieved with this system were extremely low, and no significant drug-related adverse events were reported. ■

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