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Quantification and analysis of pain in nonsurgical scaling and/or root planing

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Nonsurgical scaling and/or root planing, or SRP, is an effective treatment for periodontitis.¹⁻³ When performing SRP, clinicians may use hand instruments, sonic devices or a combination of the two. In either case, patients may have pain associated with the instrumentation that requires local anesthesia. Some patients, however, prefer to go without anesthesia owing to needle phobia, pain associated with injections, or the long and inconvenient duration of soft-tissue anesthesia.

Pain was reduced by 50 percent when subjects received the anesthetic gel as compared with the placebo gel.

A noninjectable anesthetic gel (lidocaine 25 milligrams per gram plus prilocaine 25 mg/g and thermosetting agents) (Oraqix, AstraZeneca, Södertälje, Sweden) has been developed to provide pain control in conjunction with SRP. It is a thermoreversible gelling system that is a low-viscosity fluid at room temperature that becomes

an elastic gel when introduced into periodontal pockets. Friskopp and colleagues⁴ showed that the anesthetic gel provided onset of anesthesia within approximately 30 seconds when placed into periodontal pockets and had a median duration of anesthesia, as assessed by probing of pocket depths, of approximately 20 minutes.

Although some investigators have evaluated patients'

DISCLOSURE

Dr. Henriksson and Ms. Otterbom own shares of AstraZeneca, Södertälje, Sweden.

Background. Three efficacy studies, comprising a database of 337 subjects, were conducted as part of the clinical evaluation of the noninjectable anesthetic gel Oraqix (AstraZeneca, Södertälje, Sweden). The authors discuss some of the challenges encountered when they interpreted the results of the clinical studies and present the results from an alternative analysis of the anesthetic efficacy.

Methods. The three multicenter studies were double-blind, randomized and placebo-controlled. Clinicians applied gel in the subjects' periodontal pockets before scaling and/or root planing, or SRP. Subjects recorded overall pain on a 100-millimeter visual analog scale, or VAS. In the studies, the evaluation of the anesthetic efficacy was based on absolute treatment difference (active-placebo). Investigators used an alternative post hoc approach to evaluate the effect expressed as a ratio (active:placebo).

Results. The studies demonstrated consistent and significant lower pain scores for the anesthetic gel versus the placebo gel, with point estimates of absolute treatment difference being 8, 4 and 10 mm. The alternative analysis verified that the estimated treatment effect in terms of a ratio was close to 50 percent in all three studies.

Conclusions. Treatment effects of the anesthetic gel relative to the placebo gel were described more appropriately by means of ratios instead of absolute differences. In this sample of 337 subjects, it was shown that pain was reduced by 50 percent when the anesthetic gel was used compared with when the placebo gel was used.

Clinical Implications. The authors found that the anesthetic periodontal gel is effective in reducing pain resulting from SRP.

experiences of pain and discomfort during nonsurgical SRP procedures,^{5,6} clinical data quantifying the pain associated with nonsurgical SRP in regular patients are limited. In a placebo-controlled, double-blind, crossover study evaluating the anesthetic effect of EMLA Anesthetic Cream (AstraZeneca), Svensson and

colleagues⁶ studied the pain intensity during non-surgical SRP in 20 patients who had mild chronic periodontitis. The median pain intensity, as recorded by the patients on a visual analog scale, or VAS (0-100 millimeters), was approximately 17 to 18 mm (interquartile range 7.0-45.5 mm) during placebo treatment. In comparison, approximately two-thirds of the patients experienced slightly moderate-to-strong pain on a five-point verbal rating scale, or VRS (none, mild, slightly moderate, moderate and strong).

As part of Oraqix's clinical evaluation as an anesthetic in nonsurgical SRP in patients with periodontitis, investigators performed three double-blind, randomized, multicenter, placebo-controlled studies,⁷⁻⁹ comprising a database of 337 subjects. Subjects recorded their instrumentation-related pain (that is, overall pain on completion of SRP) on a 100-mm VAS. Clinicians used hand instruments for all instrumentation.

Investigators' preplanned approach to evaluating the anesthetic efficacy of the anesthetic gel was to compare the absolute differences in overall VAS pain scores between subjects treated with the active drug and those treated with the placebo. For the purpose of sample size calculations, the investigators assumed a minimum clinically relevant difference in the overall VAS pain score comparing the anesthetic gel with the placebo gel to be 15 mm.

The conventional approach used by the investigators to analyze the anesthetic efficacy of the anesthetic gel in the individual studies demonstrated consistent and statistically significant lower pain scores for the anesthetic gel versus the placebo gel, with point estimates of absolute treatment effects (placebo-anesthetic gel) being 8, 4 and 10 mm in the three studies.

In this article, we explore some of the challenges encountered when we analyzed the clinical study data, and we present the results from an alternative analysis of the anesthetic efficacy of Oraqix. This approach may provide clinicians with a more practical translation of the data.

MATERIALS AND METHODS

Subjects enrolled in the three clinical studies required periodontal SRP in at least one quadrant of their jaws that had not undergone SRP in the previous 12 months (six months in the study by Magnusson and colleagues⁹). The studies were double-blind, randomized, placebo-controlled, parallel-group multicenter studies;

the number of centers in the studies ranged from four to eight.

Clinicians treated one quadrant in each subject. They assessed the severity of periodontitis in each subject's treated quadrant by recording pocket depths (six sites per tooth), bleeding on probing and the number of hypersensitive teeth (teeth sensitive to an air blast). They based the evaluation of the anesthetic efficacy (anesthetic gel versus placebo) on a comparison of the subject's pain measurements during SRP. Clinicians applied the study drugs toothwise before SRP. The main outcome variable was the subject's experience of overall pain at the completion of SRP in the study quadrant. The subjects recorded their overall pain on a 100-mm VAS with the left endpoint marked "no pain" and the right endpoint marked "worst pain imaginable." Subjects also recorded their pain experiences on a five-point VRS (no pain, mild pain, moderate pain, severe pain and very severe pain). The investigators always had subjects complete the VAS assessment before the VRS assessment. In Magnusson and colleagues,⁹ they recorded a VAS pain score per tooth in addition to the overall VAS pain score.

The clinicians applied the anesthetic gel or the placebo gel according to randomization using a standard dental cartridge system with a blunt applicator, starting at the most posterior tooth of the selected quadrant. They left the gel in the periodontal pocket of each tooth for 30 seconds to two minutes and then began SRP. If there was an interruption due to pain, they reapplied the gel directly in the pocket of the same tooth and resumed the SRP after waiting 30 seconds to two minutes. If the clinician did not interrupt the SRP after reapplication owing to pain, the procedure continued in a sequential fashion. However, if the subject still found the SRP to be painful after reapplication, the clinician applied more gel and classified the subject as needing rescue anesthetics, which was an efficacy variable in the studies.

Statistical methods. The investigators analyzed the overall VAS pain scores and mean tooth VAS pain score per subject in the individual studies using a stratified Wilcoxon rank sum test, stratified by center. They then calculated the 95 percent confidence interval and Hodges-Lehmann point estimate, or HL estimate, of the difference between treatments. They regarded the two-sided test as statistically significant if $P \leq .05$. In an

TABLE 1

| DEMOGRAPHICS, BY STUDY. | | | | |
|--|------------|-----------------|----------------------------|-------------------|
| STUDY AND COUNTRY | STUDY DRUG | NO. OF SUBJECTS | MEDIAN AGE (YEARS) (RANGE) | SEX (MALE/FEMALE) |
| Jeffcoat and colleagues, ⁷ United States | Active | 63 | 43 (20-71) | 25/38 |
| | Placebo | 59 | 46 (21-86) | 31/28 |
| Donaldson and colleagues, ⁸ Canada | Active | 63 | 47 (23-75) | 26/37 |
| | Placebo | 67 | 45 (23-80) | 30/37 |
| Magnusson and colleagues, ⁹ United States | Active | 43 | 46 (21-71) | 15/28 |
| | Placebo | 42 | 48 (21-77) | 19/23 |

TABLE 2

| DENTAL ASSESSMENT AT BASELINE, BY STUDY. | | | | | | |
|--|------------|-----------------|---|---|---|---|
| STUDY AND COUNTRY | STUDY DRUG | NO. OF SUBJECTS | MEDIAN NO. OF TEETH TREATED PER PATIENT (RANGE) | MEDIAN MEAN POCKET DEPTH (mm*) [†] (RANGE) | MEDIAN % OF BLEEDING POCKETS [†] (RANGE) | MEDIAN % OF HYPERSENSITIVE TEETH [†] (RANGE) |
| Jeffcoat and colleagues, ⁷ United States | Active | 63 | 7 (1-8) | 3.5 (2.3-5.3) | 33 (0-100) | 0 (0-100) |
| | Placebo | 59 | 7 (1-8) | 3.6 (2.7-4.8) | 42 (0-100) | 0 (0-100) |
| Donaldson and colleagues, ⁸ Canada | Active | 63 | 7 (1-8) | 3.5 (2.6-5.8) | 43 (5-100) | 0 (0-75) |
| | Placebo | 67 | 7 (1-8) | 3.5 (2.8-5.3) | 45 (0-100) | 0 (0-100) |
| Magnusson and colleagues, ⁹ United States | Active | 43 | 7 (3-8) | 3.9 (2.6-5.7) | 52 (0-100) | 20 (0-86) |
| | Placebo | 42 | 7 (1-8) | 3.9 (2.4-6.5) | 56 (0-100) | 14 (0-86) |

* mm: Millimeters.
 † Investigators calculated the mean pocket depths (using all six probing sites per tooth), percentage of bleeding pockets and percentage of hypersensitive teeth for each patient.

alternative analysis investigating relative differences, they used the same statistical method, based on logarithm-transformed VAS values, with VAS values equal to 0 set at 0.5 before transformation. Investigators calculated HL estimates and confidence interval limits in a log scale and then back-transformed through antilogarithms. This process provided a VAS treatment difference in anesthetic efficacy expressed as ratio between the anesthetic gel and the placebo.

In addition, the investigators examined the relationship between median placebo VAS pain scores and HL estimate treatment difference at each center, using linear regression. They used Spearman rank correlation coefficients to compare the relationship between overall VAS pain score and overall VRS rating, and between overall VAS pain score and mean tooth VAS pain score per subject.

RESULTS

Demographics. The three studies included 337 subjects at 18 study centers. Clinicians treated 169 subjects with the anesthetic gel and 168 subjects with the placebo gel. We present demographic characteristics and baseline assessments

in Tables 1 and 2. The sex, age distribution and severity of periodontitis are representative of subjects with moderate periodontitis. The demographic characteristics were well-matched between the treatment groups.

Main outcome variable: HL estimates of treatment effect. To detect a treatment difference of 15 mm, the average pain score for the placebo group must be greater than 15 mm. In Jeffcoat and colleagues⁷ and Donaldson and colleagues,⁸ the variation across centers in median VAS pain scores was large among subjects treated with the placebo gel. Some had very low VAS pain scores with placebo (Figure 1). We found that the treatment effect in these two studies was most pronounced at study centers that had high VAS pain scores in the placebo group. The third study’s investigators, Magnusson and colleagues,⁹ amended the study protocol to recruit “pain-sensitive” subjects, defined as having a VAS pain score greater than or equal to 30 mm on probing of pocket depths. Otherwise the protocol remained essentially the same.

The estimated treatment effects in overall VAS pain scores were consistently and statistically significantly lower for the anesthetic gel compared

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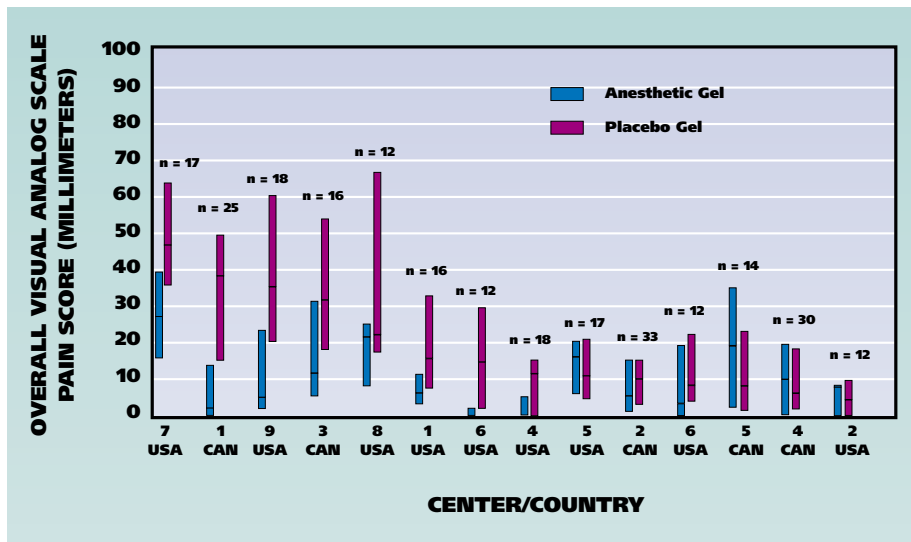


Figure 1. Box plot of overall visual analog scale, or VAS, pain scores, by center and treatment group, ordered according to decreasing center medians for placebo. The bottom and the top edges of each box are the 25th and 75th percentiles, and the center horizontal line is the 50th percentile (median). USA: United States of America. CAN: Canada. Sources: Jeffcoat and colleagues⁷ and Donaldson and colleagues.⁸

with the placebo gel in all three studies (Table 3). In Magnusson and colleagues⁹ study with pain-sensitive subjects, the HL estimate of treatment difference was 10 mm, with median overall VAS pain scores of 11 mm and 27 mm for anesthetic gel and placebo, respectively. In contrast, the VAS pain scores on probing in the screening phase for subjects subsequently treated with the anesthetic gel and the placebo gel were 61 mm and 64 mm, respectively.

Linear regression median center VAS pain score versus center HL estimate. Figure 2 shows the relationship between the HL estimated treatment effect of the placebo gel versus

anesthetic gel (mm VAS score) and median VAS pain scores of subjects who received the placebo gel at each of the 18 study centers. With increasing center median pain scores in the placebo groups, the HL estimate (mm VAS score) increases, and the slope of a regression line through the intersection of the x- and y-axes (point estimate of the slope = 0.51) suggests not only that the anesthetic gel reduces the VAS pain score by 51 percent compared with the placebo gel, but also that the treatment effect could be described better as a constant ratio

than as a numerical difference.

Alternative post hoc analysis of the main outcome variable. We log-transformed the individual subject data on overall VAS pain score to provide a treatment difference expressed as ratio between the anesthetic gel and the placebo gel. Table 4 shows the results of the alternative analysis. The HL estimated treatment effect in terms of a ratio is close to 50 percent in all three studies, which would mean that pain, as assessed by overall VAS pain scores, was reduced by approximately 50 percent when the anesthetic gel was used instead of the placebo gel.

Overall VAS pain score versus VAS pain

TABLE 3

| ESTIMATED ABSOLUTE TREATMENT DIFFERENCE (PLACEBO-ACTIVE) WITH RESPECT TO OVERALL VAS* PAIN SCORES BETWEEN ANESTHETIC GEL AND PLACEBO GEL, BY STUDY. | | | | |
|---|---------------------------------------|------------------------------|--------------------------------------|------------------------|
| STUDY AND COUNTRY | LOWER CONFIDENCE INTERVAL LIMIT (mm†) | HODGES-LEHMANN ESTIMATE (mm) | UPPER CONFIDENCE INTERVAL LIMIT (mm) | P VALUE TWO-SIDED TEST |
| Jeffcoat and colleagues, ⁷ United States | 2 | 8 | 13 | < .005 |
| Donaldson and colleagues, ⁸ Canada | 0 | 4 | 10 | .01 |
| Magnusson and colleagues, ⁹ United States | 4 | 10 | 19 | < .005 |
| All | 4 | 7 | 11 | < .005 |

* VAS: Visual analog scale.
† mm: Millimeters.

score per tooth. In Magnusson and colleagues' study (n = 85),⁹ the investigators also recorded the VAS pain score per tooth during SRP in addition to the overall VAS pain score, which they recorded on completion of SRP of the entire study quadrant. Using the Spearman rank correlation coefficient, they found a statistically significant correlation between overall VAS and median VAS pain score based on VAS pain score per tooth ($r = .86$, $P = .0001$) (Figure 3).

Overall VAS pain score versus VRS rating. In the pooled data (n = 337), the correlation coefficient (Kendall τ rank correlation) between overall VAS pain score and the five-point VRS rating of pain in association with SRP was 0.68, suggesting that a VAS pain score of approximately 35 mm would correspond to "moderate pain" (Figure 4).

Tolerance and treatment outcome. In these placebo-controlled studies, we found that the anesthetic gel was well-tolerated, and we observed no signs of systemic toxicity in the subjects. Local reactions in the oral cavity, which occurred in 15 percent and 13 percent of anesthetic gel- and placebo-treated subjects, respectively, were the most common adverse events. All of these events were transient and had mild-to-moderate intensity, reflecting a pat-

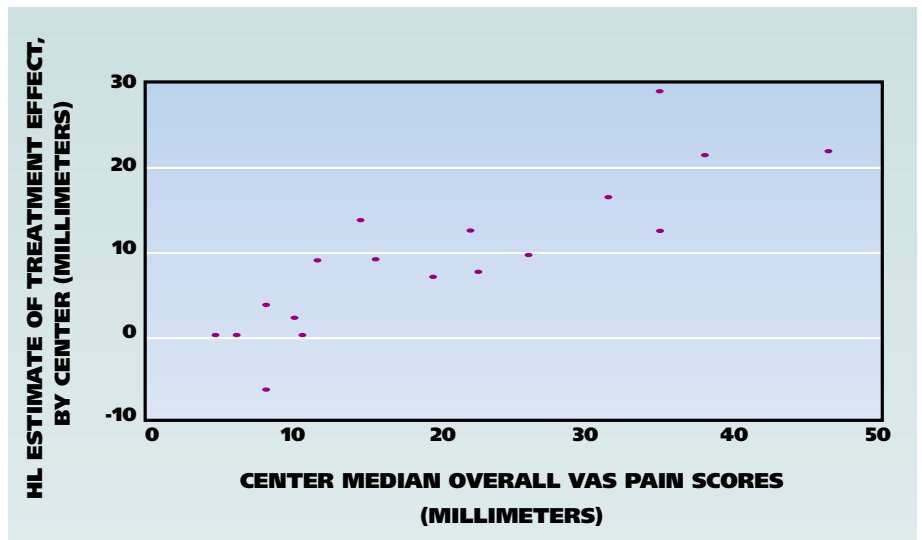


Figure 2. Overall visual analog scale, or VAS, Hodges-Lehmann point estimate, or HL estimate, of treatment effect by center versus center median overall visual analog scale, or VAS, pain scores in the placebo groups. Sources: Jeffcoat and colleagues,⁷ Donaldson and colleagues⁸ and Magnusson and colleagues.⁹

tern of reactions we anticipated with nonsurgical SRP. Sixty-eight percent of the 169 subjects who were treated with the anesthetic gel had adequate anesthesia for completing SRP without any interruption due to pain. After a second application of the anesthetic gel due to pain during instrumentation, the clinicians completed SRP in another 24 percent of subjects. The corresponding figures among subjects who received the placebo gel were 63 percent and 23 percent, respectively. Thirteen subjects (8 percent) who received the anesthetic gel and 24 subjects (14 percent) who received the placebo gel discontinued the study treatment owing to pain, in

TABLE 4

| ESTIMATED TREATMENT RATIO (ACTIVE:PLACEBO) WITH RESPECT TO OVERALL VAS* PAIN SCORES BETWEEN ANESTHETIC GEL AND PLACEBO GEL, BY STUDY. | | | | |
|---|--------------------------------------|------------------------------|--------------------------------------|------------------------|
| STUDY AND COUNTRY | LOWER CONFIDENCE INTERVAL LIMIT (mm) | HODGES-LEHMANN ESTIMATE (mm) | UPPER CONFIDENCE INTERVAL LIMIT (mm) | P VALUE TWO-SIDED TEST |
| Jeffcoat and colleagues, ⁷ United States | 0.35 | 0.55 | 0.82 | < .005 |
| Donaldson and colleagues, ⁸ Canada | 0.25 | 0.50 | 1.00 | .01 |
| Magnusson and colleagues, ⁹ United States | 0.24 | 0.47 | 0.74 | < .005 |
| All | 0.35 | 0.50 | 0.63 | < .005 |

* VAS: Visual analog scale.
 † mm: Millimeters.

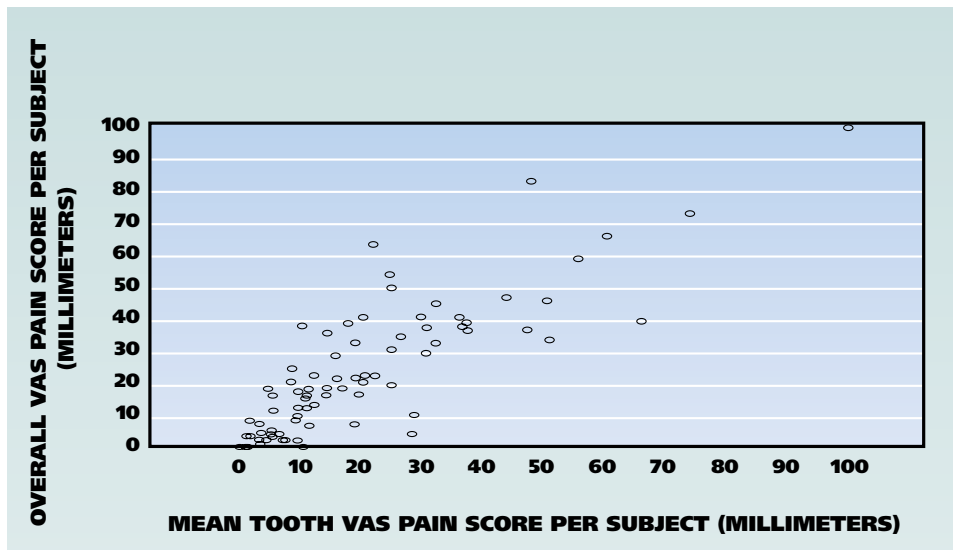


Figure 3. Scatterplot of overall visual analog scale, or VAS, pain scores versus mean tooth visual analog scale pain scores per subject. Source: Magnusson and colleagues.⁹

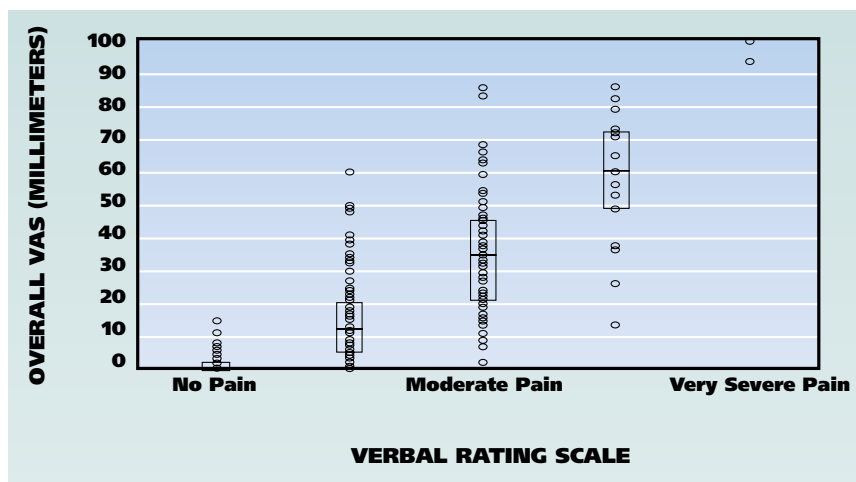


Figure 4. Box plot of pain scores on overall visual analog scale, or VAS, versus overall verbal rating scale. Sources: Jeffcoat and colleagues,⁷ Donaldson and colleagues⁸ and Magnusson and colleagues.⁹

spite of a second application of study drug ($P = .049$).

DISCUSSION

In our analyses of anesthetic efficacy data from the three placebo-controlled studies, we made two complicating observations with respect to the main outcome variable: overall pain scores. Our first observation was that there was a substantial treatment difference by center interaction in the initial two studies.^{7,8} There was a great variation across centers in VAS pain scores of subjects who received the placebo gel, with study center median ($n = 12$) scores ranging from 4.5 to 46.5

mm. Screening and enrollment of pain-sensitive subjects in the third study eliminated to a great extent the variation in VAS pain scores across centers in that study. We performed several exploratory analyses to try to identify factors that could explain the center differences, such as SRP time, pocket depth, percentage of bleeding pockets and percentage of hypersensitive teeth; however, we detected no obvious explanation. It is likely that different recruit-

ment policies and operator techniques contributed to the observed differences.

The second complicating observation we made was that, despite consistent, statistically significant treatment effects of the anesthetic gel in comparison with the placebo gel in the studies, the preplanned analysis gave numerically small point estimates of the treatment differences (8 mm in Jeffcoat and colleagues,⁷ 4 mm in Donaldson and colleagues⁸ and 10 mm in Magnusson and colleagues⁹) as compared with the “minimum clinically relevant

difference” of 15 mm assumed in the sample size calculation.

Even though 15 mm commonly is used as the clinically significant treatment difference in other pain conditions, little information can be found in the literature that is applicable to our analyses. Some support for our choice of a 15-mm treatment difference being a minimum clinically relevant difference is given in a study of patients who have arthritis, in which a clinically relevant reduction in VAS pain score was shown to be 6 mm.¹⁰ In another study of patients who had acute pain resulting from trauma, it was 13 mm.¹¹ Generalization from one clinical pain setting to

another, however, must be made with caution.

In the three studies we examined, the investigators did not establish a baseline pain score in each subject in association with, for example, SRP of a quadrant, since conditions in the clinical study setting would differ from those at baseline. Two different quadrants then would have had to be instrumented, one for screening and one for treatment. In this case, the difference in extent, severity or both of periodontal disease would have been a confounding factor.

Thus, data on changes in pain intensity from baseline to the period of treatment with the study drug are not available, and, consequently, the size of a meaningful difference in pain intensity in each subject was difficult for us to assess. The previously described considerations also applied when Magnusson and colleagues⁹ chose to select pain-sensitive subjects from among those who were sensitive to pain on probing rather than among those who were sensitive to pain during SRP.

We based the preplanned analysis of treatment effects in terms of differences in overall VAS pain scores between the anesthetic gel and the placebo gel in the individual studies on an additive or shift model with a common treatment effect difference, assuming a constant treatment effect over the entire range of possible VAS values. In the individual studies, the HL estimates of treatment difference ranged from 4 to 10 mm and were, in pooled data, 7 mm. Also, when enrolling pain-sensitive subjects, the treatment difference, in overall VAS pain score, was less than the established minimum clinically relevant difference of 15 mm.

We were surprised by the considerably lower VAS pain score of 27 mm during SRP among pain-sensitive subjects treated with the placebo gel, compared with a VAS pain score of 64 mm in the same subjects on probing in the screening phase. The results suggest that pain on probing differs from pain during SRP. For example, the vehicle may reduce some of the discomfort during instrumentation.

Linear regression analysis on a center level suggested that the treatment effect was better described in terms of a ratio instead of a treatment difference. The estimated treatment ratio according to the alternative analysis is 50 per-

cent. In other words, treatment with the anesthetic gel reduced pain by 50 percent as measured by VAS, compared with treatment with the placebo gel. This analysis implies that to observe treatment differences of 15 mm or larger, the placebo-group VAS pain level has to be about 30 mm or more. However, the pain scores in subjects who received the placebo gel were low. The median center VAS pain scores were in the order of 10 mm in approximately 40 percent of the centers, and overall 75 percent of all VAS pain scores were lower than 36.5 mm, accounting for all subjects in both treatment groups.

From a general point of view, it seems more appropriate to model the pain-reducing effect as a ratio rather than as a numerical difference when overall VAS pain score is used to assess pain. This is especially true when VAS values in subjects who received the placebo gel reach fairly low levels.

The use of a VAS for evaluating subjects' perceptions is simple, reliable and valid.^{12,13} The pain during SRP is a procedural pain in which each scaling stroke elicits pain that subsides once scaling is withheld and elicited again at each subsequent stroke. In the three studies we examined, we used the overall

VAS pain score to reflect the pain on completion of SRP of the study quadrant. We also found that there was a very good correlation between subjects' median VAS pain scores based on VAS scores from individual teeth and subjects' overall VAS pain scores after treatment of one quadrant of the mouth.

There usually is a good correlation between VAS pain scores and VRS ratings; this also was true in our analysis of the series. Extrapolation of these data suggests that subjects' perceptions of moderate pain would correspond to VAS pain scores of approximately 35 mm, with the 25th percentile at 22 mm and the 75th percentile at 46 mm. As we expected, there was a wide interindividual variation in the perception of pain.

Our alternative analyses show that the treatment effect in terms of the main outcome variable—the overall VAS pain scores—is described most appropriately as a ratio. Other studies support this finding. In a pooled analysis of 2,724 patients with neuropathic pain, the investigators found that higher baseline scores necessitated

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larger raw change scores to achieve the same level of a patient's global impression of change.¹⁴ We concluded that in studies with no minimum baseline pain requirement, clinical relevance should be defined in terms of percentage change. In our analysis, we considered a reduction of pain from baseline of 30 percent to be clinically relevant, defined as overall status much improved. Studies of migraine and dental surgery patients have shown that low pain scores at baseline required less raw change to be judged as meaningful pain relief by the patient, whereas relative (percentage) change was the same regardless of baseline pain.^{15,16}

CONCLUSION

When evaluating the anesthetic efficacy during SRP, we found that we could describe treatment effects of the anesthetic gel relative to placebo more appropriately by means of ratios instead of absolute differences. In this series of 337 subjects, we found that that pain was reduced by 50 percent when subjects received the anesthetic gel as compared with the placebo gel. This difference was statistically significant ($P < .0005$). ■

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