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Orthodontic pain trajectories in adolescents: Between-subject and within-subject variability in pain perception

Satpal S. Sandhu[a] and George Leckie[b]
Ferozepur, Punjab, India, and Bristol, United Kingdom

Introduction: The objective of this study was to assess the effects of age, sex, and the age-sex interaction on mean pain trajectories and individual variations in the pain experienced by adolescents after orthodontic separator placement. **Methods:** We included 115 subjects (mean age, 14.99 years; SD, ±1.90 years; 56 boys, 48.7%; 59 girls, 51.3%) in this study. Orthodontic separators were placed in the mesial and distal contact points of the maxillary and mandibular first molars. A 100-mm visual analog scale was used for pain assessment at 11 prespecified times: 1 hour and 2, 4, 12, 24, 36, 48, 72, 96, 120, and 144 hours. A mixed-effects location scale model was used for the data analysis to directly model between-subject and within-subject variabilities in pain in addition to the usual modeling of mean pain as a function of age, sex, and time. **Results:** Mean initial pain after 1 hour of separator placement for the 12- to 15-year-old male group was 13.52 mm on the visual analog scale, which initially increased rapidly (linear estimate, 9.16; $P = 0.000$; 95% confidence interval [CI], −8.65 to 9.67) but decelerated with time (quadratic estimate, −0.95; $P = 0.000$; 95% CI, −1.0 to −0.90), suggesting an inverted U-shaped mean pain trajectory. Age, sex, and age-sex interaction effects did not significantly influence initial pain. Compared with the 12- to 15-year-old male group, the 15- to 18-year-old female group reported the steepest rise in pain (estimate, 8.55; $P = 0.00$; 95% CI, 7.40 to 9.70) and, as a result, experienced the most overall pain. The 12- to 15-year-old male group reported minimum between-subjects variations (SD, ±4.6 mm) as well as within-subjects variations (SD, ±5.5 mm). The between-subjects variations were highest for the 12- to 15-year-old female group (SD, ±9.8 mm), whereas the within-subjects variations were highest for the 15- to 18-year-old female group (SD, ±10.1 mm). **Conclusions:** The 12- to 15-year-old boys reported the lowest mean average pain intensity and a minimum subjective variation in between-subject and within-subject variances. The 15- to 18-year-old girls experienced maximum mean pain intensity and the highest daily fluctuations in pain intensity. The 12- to 15-year-old girls were the most different from one another in their overall pain experience. (Am J Orthod Dentofacial Orthop 2016;149:491-500)

Orthodontic force application during tooth movement induces complex biologic responses in and around the periodontium, resulting in the release of inflammatory mediators such as prostaglandin-E_2, interleukin 1-beta (IL-1β), and substance P. These substances, which are essential for bone remodeling during tooth movement, also cause pain.[1,2]

[a]Professor, Department of Orthodontics and Dentofacial Orthopedics, Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab, India.
[b]Senior lecturer in Social Statistics, Centre for Multilevel Modelling, Graduate School of Education, University of Bristol, Bristol, United Kingdom.
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Address correspondence to: Satpal S. Sandhu, Department of Orthodontics and Dentofacial Orthopedics, Genesis Institute of Dental Sciences & Research, Ferozepur–Moga Road, Ferozepur–152002, Punjab, India; e-mail, drsatpalsandhu@yahoo.co.in.
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Pain is both patient- and time-dependent, resulting in substantial heterogeneity in patients' reported pain trajectories over time.[3] Put differently, pain is both a between-subject and a within-subject phenomenon. Evidence shows that most orthodontic patients report that pain commences during the first few hours after orthodontic force application, reaches peak intensity after 1 day, and eventually declines to almost pain-free levels after 7 days.[4-7]

Bergius et al[5,6] reported that the experience of pain varied substantially among subjects after elastic separator placement, suggesting between-subject variations in orthodontic pain perception. They further reported that the patient's sex had a significant influence on orthodontic pain perception. A recent study highlighted the fact that patients' age and sex have strong interaction as well as direct effects on orthodontic pain perception.[4]

Describing pain trajectories would improve our understanding of how orthodontic pain conditions develop over time, and whether patients differ in pain perception. This understanding would then enable better management of orthodontic pain. In orthodontics, no study has ever been undertaken in this direction to understand pain trajectories. Importantly, previous studies have largely ignored between-subject and within-subject variations of pain and how these distinct sources of variation may depend on the patients' characteristics. For example, do younger subjects tend to vary more in the overall average pain they experience (between-subject variation) than older subjects? Do female patients tend to report more fluctuating (ie, erratic or volatile) pain trajectories (within-subject variation) than male patients?

Mixed-effects models, also known as multilevel models and hierarchical linear models, can be used to analyze the evolution of subjects' individual outcome trajectories over time; and to relate variations in these trajectories to subjects' time-invariant characteristics such as age and sex of individual.[8,9] Mixed-effects models can also incorporate time-varying subject characteristics to model occasion-to-occasion deflections or departures from subjects' trajectories. Thus, mixed-effects models provide a popular way not only to estimate overall mean relationships, but also to quantify and then explain the degrees of between-subject and within-subject variations in patients' outcomes over time.[8,9]

Recently, Hedeker et al[10] and Hedeker and Nordgren[11] extended the standard 2-level random-intercept mixed-effects model to additionally model as a function of the covariates both the between-subjects variations in trajectories about their overall mean trajectory and the within-subjects variations in their observed measurements about their own trajectories. They called their model the "mixed-effects location scale model," where "location" refers to the usual modeling of the mean response, and "scale" refers to the new direct modeling of the between-subjects and within-subjects response variability. They implemented their model in the standalone program MIXREGLS.[11]

The objectives of this clinical research were to evaluate the overall mean orthodontic pain trajectory and the between-subjects and within-subjects variations about this over the week after orthodontic separator placement and to examine the influences of age, sex, and the age-sex interaction on the overall means, and the between-subjects and within-subjects variances using mixed-effects location scale models.

MATERIAL AND METHODS

The sample size calculation was based on a power analysis concept used in a recent study in which the authors investigated the age-sex interaction effect on mean average orthodontic pain perception.[4] Briefly, in this approach, which is based on the power analysis for a 2 × 2 factorial design, sample size is estimated for either of the binary coded groups (sex or dichotomized age) assuming that interest lies in detecting the same effect size for each binary group and then doubling the estimated sample size to detect the interaction effect.[4,12]

The parameter estimates (including time function regression coefficients, and between-subjects and within-subjects variances, and so on) required for the power analysis were obtained from the authors of the previous study.[4] Based on these parameters, the power analysis for the quadratic trend analysis was undertaken to determine the sample size, as recommended for the mixed-effect model for binary coded groups (eg, male and female).[13] The standardized Cohen d effect size for a mixed-effects analysis is defined as d = slope coefficient/√ (between-subjects variance + within-subjects variance), where the slope coefficient may be for any polynomial function of time such as linear, quadratic, and so on.[13]

Power analysis based on a study design with 1 baseline and 10 follow-up repeated measurements per subjects, an attrition rate of 10%, and a moderate effect size (Cohen d = 0.5) for the difference in slopes among the groups at a significance level of 0.05 and a power level of 0.80, showed that 60 participants (30 in each group) were required. Therefore, the total sample size required to detect the age-sex interaction effect on the mean response was 120 subjects (30 in each of the 4 groups).

The Cohen medium effect size for mean difference (d = 0.5) value corresponds to the Cohen medium effect size for correlation (r = 0.30), which can be used to find matching values for the regression coefficients in terms of 9% (R^2 = 0.09) variance explained, which could be rounded to approximately 10%.[14] Therefore, the sample size in this study was also calculated to be sufficient to detect a 10% difference in the variance among the groups.

The participants were consecutive patients who visited the private office of the first author (S.S.S.) for orthodontic treatment and were enrolled in the study if all inclusion criteria were satisfied, and informed consent was obtained. In total, 120 orthodontic patients were included in this study. The study protocol was approved (July 24, 2013) by the ethics committee of the Indian Medical Association, Jalandhar, Punjab, India.

The inclusion criteria were (1) 12- to 18-year-old adolescent boys and girls who required fixed orthodontic treatment, (2) erupted permanent first and second molars and no posterior open bite and interdental spaces, (3) no