Pain Intensity Variability and Its Relationship With Quality of Life in Youths With Juvenile Idiopathic Arthritis

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Objective. To describe variability of pain intensity experienced by youths with juvenile idiopathic arthritis (JIA) and examine factors related to within-day patterns of pain and the relationship between magnitude of pain variability and quality of life.

Methods. Pain intensity was self-reported on a visual analog scale (VAS; range 0–100) by 112 youths with JIA ages 8–18 years using electronic diaries 3 times per day for 7 days. Average absolute change in pain (AAC) was computed as a measure of the magnitude of pain variability for each participant. Logistic regression was used to examine the relationship between demographic and disease characteristics and the probability of having high pain variability (AAC ≥10 VAS units). Linear regression was used to examine the relationship between quality of life (assessed by the Pediatric Quality of Life Inventory) and AAC. The generalized estimating equations approach was used to examine the relationship between the time of day and pain intensity.

Results. The mean ± SD AAC was 15.6 ± 10.5. The majority of youths (65%) had high AAC (≥10 VAS units). Disease severity predicted high pain variability (β = 0.02, P = 0.044). Higher AAC predicted lower quality of life (adjusted R² = 0.194, β = −0.59, P = 0.003). Within-day patterns of pain intensity varied by JIA subtype and sex.

Conclusion. This study characterized the pain intensity variability experienced by youths with JIA. Pain variability throughout the day was common, varied by JIA subtype and sex, and was related to quality of life. These findings have implications for future pain research, patient education, and development of clinical interventions for this population.

INTRODUCTION

Juvenile idiopathic arthritis (JIA), one of the most common chronic disabling diseases of childhood (1), can be associated with an unpredictable course of pain and long-term disability (2). Pain negatively impacts quality of life (3,4) and participation in school and social activities (5,6). Although youths with arthritis display a wide range of clinical presentations, daily pain is reported by most (7,8).

Pain associated with JIA comes and goes or fluctuates in intensity both within and across days (5,7,9). Monitoring variations in pain intensity in a clinical setting may be useful to identify possible triggers of pain aggravation and, consequently, help develop alleviating interventions (10). Variability in pain may reflect the influences of variables that fluctuate either systematically in a pattern that is repeated regularly (e.g., a daily pattern) or irregularly (e.g., nonrepeating fluctuations). Pain variability can be described quantitatively by the magnitude of changes in pain or qualitatively by the shape, frequency, or period of the pattern (11). In adults with fibromyalgia, interindividual differences in pain variability are predictive of the response to pharmaceutical intervention (12). Quantitative differences in pain variability in JIA may represent previously unrecognized interindividual heterogeneity that may be useful for predicting treatment response.

Within-day pain patterns are a qualitative description of pain variability that may be an important distinguishing characteristic. Pain intensity in adults with arthritis shows systematic variability (repeating daily patterns), and the within-day pain patterns differ by the type of disease...
Significance & Innovations

- Within-day patterns of pain intensity differ by juvenile idiopathic arthritis (JIA) subtype and sex.
- The majority of youths with JIA (65%) have changes in pain intensity ≥10 units on a 0–100-unit visual analog scale from one time point to the next when pain is measured 3 times daily for 1 week.
- The magnitude of pain variability within and between days has a negative relationship with quality of life.

(13,14). For example, morning pain is characteristic of rheumatoid arthritis (RA), while osteoarthritis pain tends to peak in the evening (14). The differences underlying disease processes are indicated as a potential cause of the distinct within-day patterns of pain intensity between these 2 subtypes of arthritis (13).

Within-day variability of pain intensity, interference of activities caused by pain, stiffness, and fatigue has been observed in adolescents with JIA (7,15,16). However, variability of pain intensity among youths with JIA has not been thoroughly analyzed or examined for potential contributing factors. A better understanding of variability in pain intensity will expand knowledge of the pain experience for youths with JIA. In addition, the relationship between pain variability and quality of life is not known.

Pain fluctuations may be distressing for young patients who may interpret pain as a sign of disease aggravation or tissue damage, or may be frustrated by the interference of activities caused by pain. Likewise, youths with lower quality of life may be more sensitive to various biologic, psychological, social, or environmental triggers and therefore may experience greater variability in symptoms than peers with higher quality of life. It is important to understand the range of variations in the pain experience to effectively support and reassure young patients with arthritis and their families of the expected symptom experience. Systematic variability (repeating daily patterns of pain) would also be a source of measurement bias for recalled measures of pain that do not standardize for the time of day (TOD) of measurement, since the intensity of pain at the time of recall has a known biasing effect on recalled pain scores (17,18).

There were 2 objectives for this study. The first objective was to describe the within-day patterns (qualitative variability) of pain intensity in youths with JIA and to examine the factors related to pain patterns. We hypothesized that the TOD would be a significant predictor of pain intensity and that this relationship would differ by the subtype of disease and by sex. Pain patterns are expected to vary by disease subtype due to disease differences in pain patterns in adults with arthritis (14). Sex differences are expected because previous research has revealed that female individuals with arthritis reported greater frequency of worst pain in the morning than male individuals (15). The second objective was to describe the quantitative pain variability in youths with JIA and to examine the relationship between pain variability and quality of life. We hypothesized that greater pain variability would be related to lower quality of life.

MATERIALS AND METHODS

Data from 2 prospective observational studies (7) were analyzed using generalized estimating equation (GEE) procedures. Youths were invited to participate if they were diagnosed with JIA, were between ages 8 and 18 years, and attended 1 of 2 university-affiliated pediatric rheumatology clinics in Toronto, Ontario, Canada between January and December 2005. A total of 112 adolescents were recruited. The participants completed a multidimensional pain survey on an electronic diary (19) 3 times daily for up to 3 weeks (upon waking, after school, and before bedtime). The first week of data was analyzed; therefore, each participant provided a single time series of repeated measures of pain intensity data with up to 21 time points (3 times per day for 7 days).

Research ethics approval was obtained from the University of Saskatchewan for the data analysis. Data were analyzed using PASW Statistics 17 (SPSS). Data were first examined for missingness and cases were included in the analysis based on 2 criteria for completeness. Time series were required to have an overall completeness of 70% (at least 15 of 21 time points), as well as morning, afternoon, and evening cell frequencies of 57% (at least 4 of 7 time points). Cases were removed if the participant reported no pain (pain score 0) over the observation period. A total of 85 time series were included in the final analysis, yielding a selection rate of 76% (n = 85 of 112) of eligible time series from the original data set.

Measures. The pain intensity question, which was part of a multidimensional survey on the electronic diary (19), was worded “Touch the mark and move it to show how much PAIN or HURT you have right now.” The participants recorded responses on 5-cm sliding visual analog scales (VAS) with anchors of “no pain” at the far left and “very much pain” at the far right. The construct validity of this diary has been described previously (7). Pain intensity measured on an electronic VAS has demonstrated high test–retest reliability in adults with upper extremity injuries (intraclass correlation coefficient 0.96) (20).

Participants completed the Pediatric Quality of Life Inventory (PedsQL; version 4), a 23-item questionnaire used to assess health-related quality of life in youths with rheumatic disease (21) that demonstrated good internal consistency (Cronbach’s α = 0.88–0.90) and sensitivity to change in disease status over time (21). The PedsQL is a continuous scale ranging from 0 (lowest quality of life) to 100 (highest quality of life).

Physician global assessment of disease severity (PGADS) was assessed by the participant’s pediatric rheumatologist on clinical examination and scored on a 10-cm VAS. Age and disease duration were obtained from clinical records and recorded in years. Disease duration was determined from the date of diagnosis. The subtype of JIA was determined by the pediatric rheumatologist.
Statistical analyses. GEEs were computed to examine data for TOD effect on pain with demographic and disease characteristics as covariates in the model (22). The GEE can be used to model correlated repeated-measures data when the dependent variable is not necessarily normally distributed and produces population mean estimates of changes in responses (23, 24). To avoid errors with the estimates, Stokes et al recommend at least 5 observations per level of the dependent variable per level of the variables in the model (24). Since 21 observations were collected from 85 participants, this study had sufficient data for the selected analytical methods. Because this was a secondary data analysis, an a priori sample size and power calculation was not conducted for regression analyses; rather, the precision of confidence intervals (CIs) was interpreted. Model building strategies were based on Kleinbaum et al (25).

An average absolute change in pain (AAC) score was computed for each individual by summing the absolute difference scores between consecutive time points in the time series and dividing by the number of changes. A time series with no missing data points \((n = 21\) observations) would produce 20 change scores. A 2-category classification of pain variability was created for logistic regression. Participants were classified as high variable if the AAC would produce 20 change scores. A 2-category classification with no missing data points \((n = 21)\) would produce 20 change scores. A 2-category classification of pain variability was created for logistic regression. Participants were classified as high variable if the AAC was ≤ 10 units on the VAS or low variable if the AAC score was < 10 units on the VAS. The equation for AAC in pain is as follows:

\[
(\sum_{i=1}^{n} |P_{t1} - P_{t2}| + |P_{t2} - P_{t3}| + \ldots + |P_{tn-1} - P_{tn}|)/n - 1
\]

where \(P\) = the self-reported pain intensity score, \(t_1\ldots t_n\) = consecutive time points in the time series with nonmissing values, and \(n\) = the number of nonmissing observations in the time series.

Binomial logistic regression was conducted to determine if demographic or disease factors predicted the probability of belonging to high or low variability pain intensity categories. The following factors were examined on univariate analysis: illness severity (PGADS), illness duration, age, sex, and diagnostic subtype. Linear regression was conducted with quality of life (PedsQL) as the dependent variable to examine the relationship between pain variability (AAC) and quality of life, controlling for the influence of illness severity (PGADS), illness duration, age, sex, and diagnosis.

RESULTS

Data from 27 participants were not included in the final analyses. Five participants did not report pain during the observation period and 22 participants had insufficient data based on our criteria for inclusion. Demographic and disease characteristics of participants included in the analysis and excluded cases (insufficient data and no pain groups combined) are shown in Tables 1 and 2. Nonparametric chi-square tests and \(t\)-tests revealed no differences in diagnosis, age, disease duration, disease severity, or quality of life between the cases included and those excluded from analysis.

The characteristics of pain intensity reports are shown in Table 3. The large proportion of zero scores (27.5%) gave the pain intensity data a bimodal distribution with both discrete properties (pain/no pain) and continuous properties when pain was reported as present (range 1–100). Given that these data were not normally distributed and resistant to transformation (26), the pain intensity data were converted to an ordinal categorical variable for the GEE analysis. VAS scores of 0 were categorized as no pain, between 1 and 30 as mild pain, between 31 and 70 as moderate pain, and greater than 71 as severe pain. The boundaries of the categories were based on those used in previous studies (27–31).

An independent working correlation matrix was selected for all GEEs (32). Cumulative logits were modeled on ordinal logistic models with pain as a categorical variable. The main effects tested in the univariate analysis for the GEE analysis and excluded cases (insufficient data and no pain groups combined) are shown in Tables 1 and 2.
were combined for analysis, resulting in 4 diagnostic categories for separate analyses; therefore, diagnostic subtypes other time throughout the day.

Participants had a significantly higher probability of having moderate or severe pain in the morning, dropped slightly in the afternoon, and rose again in the evening. The absolute change scores ranged from 0–100; the individual AAC scores ranged from 0.7–47.6. The mean ± SD AAC for all 85 participants was 15.6 ± 10.5. High variability (AAC ≥10) was observed in 55 (65%) of 85 participants. The mean ± SD group AAC for youths categorized as low variability was 5.4 ± 2.9, and the mean ± SD group AAC for youths categorized as high variability was 21.1 ± 9.0.

With 55 cases demonstrating high variability, there were sufficient data for the inclusion of 5 variables in the logistic model without the risk of overparameterization (33). The addition of PGADS to a logistic regression model containing age and sex was statistically significant, indicating that disease severity was a significant predictor of the probability of having higher pain variability (β = 0.022 [95% CI 1.001, 1.044], P = 0.044).

The addition of pain variability (AAC) to a linear regression model containing illness severity, illness duration, age, and sex was a statistically significant predictor of quality of life (adjusted R² = 0.194, β = −0.585 [95% CI −0.965, −0.205], P = 0.003). This indicated that pain variability had a statistically significant negative relationship with quality of life in that higher pain variability was associated with lower quality of life, controlling for the effects of illness severity, illness duration, age, and sex on quality of life (Table 4).

DISCUSSION

This study describes the within-day pain variability experienced by youths with JIA. Disease severity was a significant predictor of the probability of having higher pain variability (AAC ≥10). Although the CI was sufficiently narrow (95% CI 1.001, 1.044) to provide confidence in the

| Table 2. Age, disease duration, disease severity, and quality of life characteristics* |
|---------------------------------|-----------------|-----------------|
| Participants included (n = 85) | Participants excluded (n = 27) |
| Age, years                      | 13.1 ± 2.4 (8–17) | 13.0 ± 2.8 (9–17) |
| Disease duration, years         | 4.8 ± 4.4 (0.1–14.8) | 4.8 ± 3.9 (0.2–16.0) |
| Disease severity (PGADS, 100-mm VAS) | 30.7 ± 24.0 (5.5–89.0) | 29.6 ± 28.2 (1.0–90.0) |
| Quality of life (PedsQL score)  | 71.0 ± 19.2 (22.7–100.0) | 73.7 ± 18.2 (31.5–97.8) |

* Values are the mean ± SD (range). PGADS = Physician global assessment of disease severity; VAS = visual analog scale; PedsQL = Pediatric Quality of Life Inventory.

Table 3. Characteristics of pain intensity reports from the sample (n = 85)*

<table>
<thead>
<tr>
<th>Total sample pain intensity</th>
<th>Individual range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>1,564 (87.6)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23.9 ± 27.9</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>14.0 (36.0)</td>
</tr>
<tr>
<td>Range</td>
<td>0–100</td>
</tr>
<tr>
<td>Skewness (SE)</td>
<td>1.13 (0.06)</td>
</tr>
<tr>
<td>Kurtosis (SE)</td>
<td>0.16 (0.12)</td>
</tr>
</tbody>
</table>

* IQR = interquartile range.
estimate of association between disease severity and pain variability, the clinical relevance of this association was only estimated with larger increments of change in disease severity. For every 10-unit increase in PGADS, there was
The unpredictability of pain has a negative impact on life activities as well as on anxiety and distress related to symptoms. In a qualitative interview-based study of 15 youths with JIA, Ostlie et al examined the impact of symptom irregularity on activity participation (35). The respondents described how they often had to modify physical and social activities, schooling, and occupational choices because of unpredictability and fluctuations of pain and fatigue. The youths reported frequent disappointment due to last-minute changes in planned activities because of symptom flares and an increased dependency on parents for completion of activities of daily living. Youths that experience greater fluctuations in pain throughout the day may be impaired by the unpredictability of symptoms, which may impact quality of life.

The factors associated with lower quality of life may also predispose youths with JIA to be more vulnerable to the triggers of their symptoms. Schanberg et al found that more negative mood was associated with higher pain intensity (5). Feldman et al found a bidirectional relationship between pain and mood in a daily diary study of adults with chronic pain, in which a lagged analysis showed that higher pain resulted in next-day negative (angry) mood, and that depressed mood resulted in next-day increased pain (36).

The present study demonstrated that pain intensity varied by the TOD, revealing within-day pain patterns. As hypothesized, the pattern of pain variability differed by disease subtype and sex. On average, female participants exhibited a U-shaped within-day pattern of pain, with the highest probability of having moderate or severe pain occurring in the morning and evening. For male participants, the probability of having moderate or severe pain was higher in the morning than at any other TOD. Male and female participants did not significantly differ in their probability of having moderate or severe pain in the morning or afternoon, but diverged in their probability of having moderate or severe pain in the evening (Figure 1). To our knowledge, this is the first study to demonstrate within-day patterns of pain in youths with arthritis.

The different relationship between the TOD and pain intensity between male and female participants may be due to prevalence differences in JIA subtypes between sexes. For example, oligoarticular JIA and polyarticular JIA have a much higher prevalence among females, whereas enthesitis-related arthritis has a higher prevalence among males (37). Indeed, youths in this sample differed according to this subtype prevalence between sexes, as expected, with females comprising 80.6% of the sample with systemic, oligoarticular, and polyarticular (rheumatoid factor–positive and –negative) subtypes, and only 44.4% of the sample with psoriatic, enthesitis-related, or undifferentiated subtypes. These subtypes differ in TOD effects on pain, which may explain the differences in daily pain patterns between the male and female participants. A previous study by Sällfors et al found sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized β</th>
<th>P</th>
<th>95% confidence interval for β</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>98.656</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGADSD</td>
<td>−0.279</td>
<td>0.002†</td>
<td>−1.06, −0.0453</td>
</tr>
<tr>
<td>Illness duration, years</td>
<td>−1.031</td>
<td>0.030†</td>
<td>−1.958, −0.104</td>
</tr>
<tr>
<td>Age, years</td>
<td>−0.896</td>
<td>0.319</td>
<td>−2.676, 0.884</td>
</tr>
<tr>
<td>Sex</td>
<td>5.224</td>
<td>0.243</td>
<td>−3.611, 14.059</td>
</tr>
<tr>
<td>AAC</td>
<td>−0.585</td>
<td>0.003†</td>
<td>−0.965, −0.205</td>
</tr>
</tbody>
</table>

* PGADSD = Physician global assessment of disease severity; AAC = average absolute change in pain.
† Statistically significant (P < 0.05).
differences in the frequency of morning pain in youths with arthritis (15). This study used paper diaries to collect pain intensity scores 4 times per day for 1 week, and found that female youths with chronic arthritis reported more days with worst pain in the morning compared to males. Comparisons in pain intensity across the rest of the day were not reported, and only morning proportions of worst pain were reported; therefore, this study was not able to comment on whole-day pain patterns with advanced statistical methods that take into account dependency of responses within individuals (15).

Although the causes of different pain patterns between disease subtypes are not fully understood, several influences vary systematically throughout the day and may contribute to the observed patterns. Biochemicals that are known to affect nociception, including cortisol and proinflammatory cytokines, have predictable circadian variability (38). Endogenous cortisol down-regulates immune and inflammatory responses (39). In healthy individuals, cortisol displays a circadian rhythm with an early morning peak and a steady decline throughout the day (40). The absence of the normal early morning peak production of cortisol has been proposed as a possible explanation for the early morning peak of symptoms in adults with RA (13). Further research is needed to determine if youths with active JIA demonstrate abnormal circadian rhythms in hypothalamic-pituitary-adrenal axis function, cortisol production, or inflammatory cytokine production and whether pain patterns are predictive of treatment response or long-term disease outcomes.

The relationship between the TOD and pain intensity is relevant to studies in which recalled pain scores are collected on one occasion or once daily. Since present pain has a known biasing effect on recalled pain scores (18), researchers utilizing recalled measures of pain are advised to determine the underlying pain pattern and standardize by the TOD or statistically control for the time of measurement. Given the extensive within-day variability observed in this study, researchers are advised to consider pain variability as a source of population heterogeneity and weigh the benefits and costs of more frequent assessment of pain in order to capture and examine the relationships between pain variability and relevant outcomes.

This study characterized variability of pain intensity experienced by youths with JIA. Pain and interference of activities caused by pain are distressing components of JIA that youths may find difficult to understand (35). Youths may find it reassuring to know that the typical pain experience includes frequent fluctuations. Further research is needed to determine whether pain education and coping strategies that incorporate information on adaptation to pain fluctuations are beneficial to symptom management.

This study has several limitations. The analysis was restricted to variables collected in the original study. Further research is needed to determine if factors such as physical activity, mood, or depression contribute to pain variability. Model fit statistics cannot be produced for GEEs with polytomous outcomes (23). The case selection was limited to youths who reported pain at least once during the 7-day observation period; therefore, these results can be generalized only to youths who experience pain as a component of their disease.

Despite a growing knowledge of the pathophysiology of pain, little is known about the temporal dynamics of pain. This study contributes to the knowledge of the variability of the pain experience for youths with JIA. Pain intensity varied within and between days for youths with JIA and patterns of fluctuations varied by subtype of disease and sex. These results have implications for both research design and clinical education. Since recalled pain scores are biased by pain intensity at the time of reporting, researchers performing studies employing recall measures of pain intensity are advised to standardize the TOD of measurement. Clinicians can utilize these findings when educating patients and their families that daily fluctuations in pain intensity are expected.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Tupper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Tupper, Rosenberg, Stinson.

**Acquisition of data.** Stinson.

**Analysis and interpretation of data.** Tupper, Rosenberg, Pahwa, Stinson.

**REFERENCES**


