
Open issues in the assessment and management of pain in juvenile idiopathic arthritis

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ABSTRACT

Pain is the major symptom of children with juvenile idiopathic arthritis (JIA) and its reduction is a key goal of treatment. It is widely agreed that assessment of pain is a fundamental component of the rheumatology evaluation and should be carried out at each clinic visit. However, so far there has been insufficient attention to the impact and causes of pain in children with chronic arthritis in both clinical practice and research. Quantitative measures of pain are seldom used regularly in daily care and pain assessment has not been incorporated in the most popular composite outcome measures for JIA, including the criteria employed to measure improvement in therapeutic trials. A recent advance in the development of pain tools involves mobile devices, particularly smartphones, and the internet to collect real-time self-reported data via electronic diaries. Concern has been raised by the recent observations of persistence of pain in some children with JIA despite adequate treatment with the modern biologic medications and good disease controls. These findings underscore the need of large-scale studies of the prevalence and determinants of pain in patients treated with contemporary care. In addition, the reasons that explain the persistence of pain after the resolution of the inflammatory process should be investigated through research on neurobiological mechanisms of pain and by addressing the role of factors external to the disease, such as mood, anxiety, and pain sensitisation and coping.

Introduction

Pain is the most common and distressing symptom of juvenile idiopathic arthritis (JIA) (1, 2). High levels of pain disturb sleep, limit normal activities, disrupt school attendance, and can have profound impact on psychosocial

functioning. Just a minimum decrease in pain intensity was found to have an appreciable effect on children's well-being (3).

Several studies have shown that pain is more prevalent in JIA than previously thought and that a sizeable proportion of patients continue to report pain long after disease onset (4). Recently, considerable concern has been raised by the observations of persistent pain in some children with JIA despite adequate treatment with biologic medications and good disease control (5-7). Thus, reduction of pain remains a key goal in the management of JIA. Notably, pain control has been included in a proposed set of quality measures for the process of care in JIA (8).

It is widely agreed that quantitative assessment of pain is an essential part of the rheumatologic examination and should be performed at each clinic visit. It has been recommended that pain be assessed with age-appropriate, reliable and valid tools (9). Information about the child's pain is typically obtained by a parent (most often the mother) or the child him/herself, if considered mature enough to provide a reliable self-report. A variety of tools, either unidimensional or multidimensional, are available for parent's or child's assessment of pain in JIA (2). The unidimensional tools measure one aspect of pain, namely intensity, whereas the multidimensional tools address various dimensions of the pain experience, which includes sensory, affective, and evaluative components.

In this article, we provide a brief summary of the tools that are traditionally used for pain assessment in routine care of children with JIA and of the newer methods that enable real time data collection through the internet and mobile devices. In addition, we discuss the reasons why pain is frequently neglected as outcome measure in JIA and

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emphasise the need of including pain among the outcome endpoint in future clinical trials.

Traditional pain measures used in routine clinical practice

Visual analogue scales

The 100-mm (or 10-cm) visual analog scale (VAS), which is the prototype of the unidimensional tools, has long been used for assessing pain intensity in children with JIA for both clinical purposes and research. It is a continuous horizontal line anchored at the two ends with the words “no pain” and “worst pain imaginable”. The VAS has been well validated in paediatrics and is recommended for self-report in patients aged 8 years and older (10).

We have proposed a 21-numbered circle VAS as an alternative to the horizontal line VAS (11) (Fig. 1). It was found to be simpler and more feasible and to have the potential to increase the accuracy of ratings. In particular, the new VAS may help to overcome the phenomenon of the relative aversion to extremes seen when using a traditional linear VAS. Indeed, often very low values (0.1 or 0.2 cm) are obtained when the parent or the patient really intended to mark the end of the line. Happy and sad faces were added to the anchor words at the 2 extremes of the VAS because in preliminary testing some assessors misinterpreted the score rule by interpreting the score 10 as the best and the score 0 as the worst (as in the Olympic games). After adding the faces, misinterpretation was no longer observed.

Tender joint count

The physician is usually not asked to rate the intensity of the child's pain on a VAS or another quantitative scale, but to assess and register the presence of pain in each individual joint in the context of the standard joint examination. A joint is defined as painful if it shows either tenderness on digital pressure or pain on motion. The sum of the joints with tenderness/pain on motion makes up the tender joint count. As per the rules of joint count calculation in JIA, the sole presence of tenderness/pain on motion is not sufficient to classify a joint as “active”. For a joint to

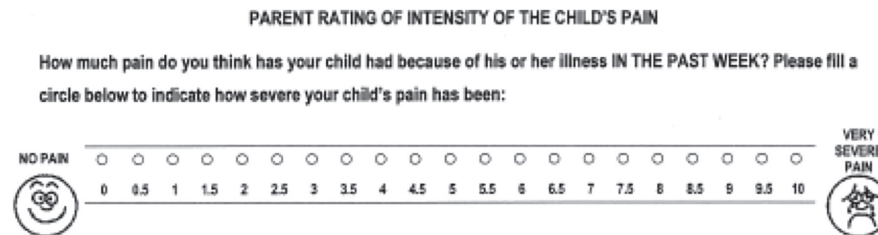


Fig. 1. 21-numbered circle visual analog scale for parent's rating of pain in children with juvenile idiopathic arthritis.

be defined as “active”, a joint must be swollen, or have both tenderness/pain on motion and limited motion. Only the presence of swelling is sufficient alone to define a joint as active (12,13).

Assessment of pain through electronic diaries

Taking advantage of the recent advances in technology, the use of internet and mobile devices, particularly smartphones, has been explored to collect real-time self-reported data via electronic diaries (e-diaries). E-diaries facilitate collection of repeated pain measures within and across days and have been found to improve the quality of self-reported data through prompts and automatic time-stamping (14-17). The use of smartphones for capturing self-reported pain and via e-diaries has been validated in children with arthritis and was found to capture effectively current symptom reports (18-21).

Examples of e-diaries developed for JIA include the e-Ouch multidimensional pain diary for adolescent with arthritis (18), the Standardised Universal Pain Evaluations for Paediatric Rheumatology Providers (SUPER-KIDZ) pain assessment tool (22), and the Pain-QuILT™ (23). The characteristics and performances of these tools have been reviewed recently (2).

An example of the analysis of pain in children with JIA through e-diary reports is provided by the study of Bromberg *et al.* (17). These authors evaluated the temporal relationships between pain, daily symptoms, and daily functional outcomes in children with JIA using self-reported data from e-diaries completed 3 times during the day (morning, afternoon, and evening) on a smartphone (T-Mobil Dash). The 3 daily surveys were completed

for a total of 28 days. Data were automatically uploaded from the phone to a password-secured internet server through the phone's wireless data plan. E-diary measures included current pain intensity on a horizontal VAS, pain location in 7 body areas (*e.g.* head, hands, arms, hip and knee, feet), pain duration on a 4-point ordinal scale (from “a few minutes” to “more than 4 hours”), and pain unpleasantness on a horizontal line with the anchors of “not bothering me at all” to “bothering me a lot”. The 59 children included in the study completed a total of 3,258 e-diary entries. Children reported having pain (VAS score ≥ 3 of 100) on 72% of all diary days, and no children were entirely pain-free throughout the reporting period. The mean pain intensity ratings across the morning, afternoon, and evening entries were not significantly different. An important finding was that the intensity of pain did not vary appreciably in relation to the medication class. In particular, children prescribed biologic agents had pain intensity scores comparable with those of children who were not receiving these medications.

Pain in JIA composite outcome measures

Despite being a key symptom of inflammatory arthritis, pain has been largely neglected in the construction of most composite outcome measures for JIA. For example, pain assessment is not included in the criteria for clinical inactive disease (24, 25) and minimal disease activity (26), and is not part of the items of the Juvenile Arthritis Disease Activity Score (27, 28). Furthermore, it is also not included in the American College of Rheumatology Pediatric (ACR Pedi) response criteria (29), which have been used to measure

improvement in all recent clinical trials for registration of biologic medications in JIA. By contrast, pain has been incorporated, together with parent/child rating of overall well-being, physical function, and health-related quality of life (HRQOL), in parent-centered and child-centered composite disease assessment indices for JIA, named the Juvenile Arthritis Parent Assessment Index (JAPAI) and the Juvenile Arthritis Child Assessment Index (JACAI), respectively (30).

Several reasons may explain why pain has received insufficient attention by researchers in JIA metrology. First, the intensity of pain is thought to be largely reflected by the parent's global assessment of the child's overall well-being, which is known to be heavily influenced by pain symptoms. Notably, the scores of children's overall well-being and pain VAS ratings by the parent have been found to be consistently correlated at high level (*i.e.* with Spearman's $r > 0.80$) across different stages of JIA, either early, advanced or longstanding (31).

Another explanation could be the multifactorial nature of pain, which makes it an imperfect indicator of disease activity in JIA. Although the presence of active arthritis and disease severity tend to associate closely with joint pain and are among the most common predictors of pain, they have been shown to account for only 6.5 to 28% of the variance in pain (32-34). On the other hand, joint inflammation is known to be painless in a sizeable proportion of children with JIA, particularly in the oligoarthritis subset (35).

Pain ratings may also be affected by mechanical pain, that is, pain related to irreversible functional and structural damage to joints, and not due to active disease. This type of pain is more common in patients with long disease duration.

A further potential confounder of pain assessment is the presence of a pain amplification condition, such as fibromyalgia. In our experience, fibromyalgia complaints are frequent in paediatric rheumatic illnesses, especially in adolescent girls and in patients with longstanding disease.

Persistence of pain in children treated with contemporary therapies

In the past two decades, the introduction of biologic disease-modifying antirheumatic drugs (DMARDs) has revolutionised the management of JIA. In a number of randomised controlled trials, these medications have been found to be markedly efficacious in improving disease symptoms (36). However, only a few studies of biologic DMARDs in JIA have reported their efficacy in controlling pain (37, 38). This scarcity of data might partly depend on the above-discussed absence of inclusion of pain in the traditional outcome end points used in therapeutic studies in JIA.

Recently, considerable concern has been raised by the reports of persistence of clinically significant pain in some children treated with biologic DMARDs, even when good disease control was achieved (5-7, 17). In a pain diary study, Lomholt *et al.* (5) found that, on average, children treated with anti-TNF agents experienced comparable degrees of pain to children receiving the standard treatment. Although more children in the anti-TNF group reported no pain in the pain diary, a similar percentage of children in each group reported pain on every day of the study period. Among children who reported pain in the diary, the intensity of pain was greater in the anti-TNF group. These findings contrasted with the lower level of disease activity in the patients on anti-TNF therapy. In the above-mentioned analysis of Bromberg *et al.* (17), pain intensity and frequency were remarkably similar to those of a study published 11 years earlier (39) despite the large number of patients in the recent study who were prescribed biologic DMARDs compared to the previous sample. In a longitudinal investigation of children who had received etanercept for a median of 8.5 years, Anink *et al.* (7) found that chronic pain remained more prevalent than expected in the presence of low levels of disease activity and disability. Altogether, these observations indicate that pain continues to be a significant concern for a subgroup of children with JIA treated with contemporary therapies, and underscore the need for continuous monitoring of pain

and its determinants during treatment with biologic DMARDs.

Conclusions and future directions

Despite the key relevance of pain in JIA and the widely recognised importance of its proper evaluation and management, several unmet needs remain in this area of clinical practice and research.

Regarding assessment, it is common view that the use of a 10-cm VAS as a single self-reported or proxy-reported measure of pain intensity, although adequate, is insufficient. Pain perception in children with chronic arthritis is multifactorial, and results from the integration of biological processes, psychological aspects, and sociocultural contexts (40). Assessment of pain should, therefore, address its impact on a broad range of factors, including physical, social and school activities, family and peer interactions, cognitive functioning, emotional distress, mood, behaviour, and pain-coping strategies (4). These issues make it clear that a reliable appraisal of pain in children with JIA requires the use of well-validated and developmentally based paediatric pain-assessment tools that can capture the multifaceted character of the pain experience. However, most of the instruments proposed so far have been extensively employed in research, but are seldom incorporated in standard clinical practice, partly due to their length and complexity. To foster the regular assessment of pain in routine care there is a need of tools that are simple and easy to apply. The recent positive experiences with the use of smartphones to collect real-time self-reported data via electronic diaries (e-diaries) have opened a modern, attracting and potentially feasible avenue to capturing self-reported pain. However, these e-tools have been so far evaluated only in research settings and their applicability and effectiveness should be tested in routine care before their widespread use can be recommended.

It is a matter of concern that pain remained a considerable problem for some children with JIA despite apparently adequate treatment with biologic DMARDs and good disease control. This matter highlights a need for large-

scale investigations of the prevalence and determinants of pain in patients treated with contemporary care. To gain further insights into the effectiveness of the new medications, future therapeutic trials, post-marketing surveillance studies and long-term follow-up surveys should include a thorough assessment of pain through the application of well established and validated tools. In parallel with these efforts, there is the need to enhance neurobiology research aimed to elucidate the causes of pain persistence beyond the resolution of the inflammatory process. Future studies should also investigate the impact of non-disease-related factors, such as mood, anxiety, pain sensitisation, and pain coping, in the maintenance of pain.

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