Index of Pain Experience in Sickle Cell Anaemia (IPESCA): Development from daily pain diaries and initial findings from use with children and adults with sickle cell anaemia

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Index of Pain Experience in Sickle Cell Anaemia (IPESCA): Development from daily pain diaries and initial findings from use with children and adults with sickle cell anaemia

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Abstract

Frequent daily pain occurs in sickle cell anaemia (SCA). There is an unmet need in clinical trials for a composite pain endpoint capturing complex aspects of daily pain from pain diaries. This study introduces the Index of Pain Experience in SCA (IPESCA), which combines location, frequency, intensity and type of pain into one composite index. To validate IPESCA, it was compared with two months of pain burden recall from the Sickle Cell Pain Burden Interview-Youth (SCPBI-Y) questionnaire. During the diary period, eleven patients (21%) reported no pain and 42 (79%) reported some pain. IPESCA demonstrated the ability to detect change across SCPBI-Y pain burden categories at Month 1 ($p<0.001$) and Month 2 ($p<0.01$) and correlated with increasing age ($p<0.001$). IPESCA is a simple pain endpoint related to the social and emotional aspects of pain burden and may be promising for future trials.

Keywords: Sickle Cell Anaemia, Paediatrics, Sickle Cell Disease

Pain burden assessments are essential to evaluate the effectiveness of interventions in sickle cell anaemia (SCA) treatment trials. Number of days in pain or number of hospital admissions are commonly utilised but these measures overlook additional important clinical information captured in complex pain diaries that are challenging to quantify and summarise. We created a simple, intuitive composite index (Index of Pain Experience in Sickle Cell Anaemia [IPESCA]) reflecting frequency as well as location, intensity and type of pain.

The sample included 61 children and adults screened for the Prevention of Morbidity in Sickle Cell Anaemia (POMS) phase-II randomised controlled trial (Howard *et al*, 2018). At screening visit, patients completed a paper pain diary for 14 consecutive days, which included shading locations in pain on a body map, circling words to describe their pain and choosing a 0-10 numerical rating of pain intensity. The body map diagram (von Baeyer *et al*, 2011) was divided into 18 specific areas, and the widespread pain index (WSPi) (Zempsky *et al*, 2017) comprised total number of body locations in pain over the two-week period. Eight of 21 descriptor words were classified as 'neuropathic' **(*e.g.* aching, stabbing, numb, shooting, pricking, burning, penetrating, radiating)** (Wilkie *et al*, 2010). IPESCA is a novel summary measure, consisting of four components: WSPi, maximum persistence of pain, defined as total number of days in pain at any one location, total number of neuropathic words chosen, and mean of daily average pain intensity. The components were equally weighted using this equation:

$$f(x) = \frac{(\max\ [new] - \min\ [new])(x - \min\ [original])}{\max\ [original] - \min\ [original]} + \min\ [new]$$

and scaled to range 0-0.25 to create a summed index (range 0-1).

Patients also completed the validated Sickle Cell Pain Burden Inventory-Youth (SCPBI-Y) (Zempsky *et al*, 2013) questionnaire, which assesses the past month's impact of pain on physical, social and emotional aspects of daily function. The SCPBI-Y was completed at the screening visit and at randomisation visit 30 days later, together representing the previous two months of pain burden.

Analyses were performed using R v3.3.2 (www.r-project.org). Demographics were compared using the t-test for continuous variables, the chi-squared test or Fisher's exact test for categorical variables. IPESCA was tested for skewness and kurtosis using the R 'moments' package (Komsta & Novometsky, 2015). Internal consistency was performed by calculating Pearson's correlations to measure the strength of the linear relationship between IPESCA and the four components that comprise IPESCA. The SCPBI-Y showed evidence of a non-normal distribution so was made categorical: 'No Days', 'A Few Days', 'Some Days', 'Many Days', 'Every Day'. Due to fewer patients in severe pain categories, nonparametric Kruskal-Wallis tests were used to comparing median IPESCA across SCPBI-Y categories and post-hoc Mann-Whitney tests were used to compare median IPESCA between neighbouring categories.

Eight patients were excluded from analysis (completing less than 7 diary days [n=6], incorrectly completing the pain diary [n=2]). Across all patients, 384/708 diary days (54%) included pain. Five patients had a prescription for dihydrocodeine (three took once daily, two as required). One patient had prescriptions for co-dydramol and oromorph as required. One patient had prescriptions for carbamazepine, duloxetine and

gabapentin daily for neuropathic pain as well as seizures. Three patients had daily prescriptions for oxycodone and pregabalin for pain, fentanyl and hydromorphone for pain, and diclofenac, co-codamol, tramadol and pregabalin for pain, respectively.

Eleven patients (21%) reported no pain and 42 patients (79%) reported any pain. Of those patients who experienced pain, the mean percentage of days in pain was 52% (median: 57%), and 10 patients (24%) reported pain every day. The most frequent pain locations were the lower legs and head (Figure 1a). There were no significant differences in age, gender, presence/absence of SCI, hydroxyurea use or haemoglobin count between patients with and without pain.

All 11 patients with no pain during the two-week pain diary period also reported 'No Days' on SCPBI-Y at Month 1 and 10/11 patients reported 'No Days' at Month 2. No patients in this study scored 'Every Day'. There was a significantly different distribution of SCPBI-Y categories between patients reporting no pain and pain at Month 1 ($p<0.001$) and Month 2 ($p=0.024$) (Table 1).

IPESCA was relatively symmetric (skewness=0.36) and was found to be strongly correlated with WSPi ($r=0.79$, $p<0.0001$), maximum persistence of pain ($r=0.92$, $p<0.0001$), number of neuropathic words ($r=0.82$, $p<0.0001$) and average pain intensity ($r=0.76$, $p<0.001$). There was a significant correlation with age ($r=0.524$, $p<0.001$). There was no significant difference in IPESCA by sex or as a function of hydroxyurea use and no significant correlation with haemoglobin.

Median IPESCA values were numerically increasing across SCPBI-Y categories and significantly different at Month 1 ($p<0.001$) and Month 2 ($p<0.01$). In a post-hoc analysis, IPESCA was significantly different between mild to moderate pain categories at Month 1 ('Mostly No Days' < 'A Few Days', $p=0.028$; 'A Few Days' < 'Some Days', $p=0.023$) and significantly different between moderate to severe pain categories at Month 2 ('Some Days' < 'Many Days', $p=0.032$) (Figure 1c).

Complex pain diaries in sickle cell anaemia were characterised for the first time using IPESCA, a comprehensive index reflecting information about daily pain frequency, location, intensity and type over two weeks of pain diaries. IPESCA demonstrated the ability to detect change across increasing SCPBI-Y pain burden categories consistently over two months; however, IPESCA should complement, rather than replace the SCPBI-Y interview questions, which gauge the social and emotional burden of pain and can be administered by phone at intervals when long periods requiring daily questionnaires may reduce compliance.

Limitations

IPESCA was not defined *a priori* in POMS and requires complete validation in an independent cohort. The SCPBI-Y is validated in patients in SCA up to 21 years of age, and this is used here to validate IPESCA in patients up to age 63 years. There were only 14 days of diaries, and estimations of pain profiles over long periods of time was not possible. Further work on the psychometric properties of the index will be required before widespread use in clinical trials.

Acknowledgments

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data, CAC, FJK and CL conceived the research and edited the manuscript. All authors report no conflicts of interest. AS is a statistical consultant for the Department of Anesthesiology at Virginia Mason Hospital in Seattle, WA; she reports no significant financial conflicts of interest.

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	No Pain (n=11)	**Pain (n=42)**	
Age mean ± sd (range)	13.9 ± 2.9 (8.5-17.3)	20.7 ± 13.1 (8.0-63.9)	t = 3.06, p=0.004**
Gender	4 F 7 M	20 F 22 M	p=0.735[a]
Hydroxyurea	7 HU- 4 HU+	22 HU- 20 HU+	p=0.725[a]
Haemglobin count mean ± sd	87.3 ± 10.4	90.0 ± 15.0	t = 0.698, p=0.492
SCPBI-Y Month 1	11 No Days 0 A Few Days 0 Some Days 0 Many Days 0 Every Day	11 No Days 18 A Few Days 6 Some Days 7 Many Days 0 Every Day	p<0.001[a]***
SCPBI-Y Month 2[a]	10 No Days 1 A Few Days 0 Some Days 0 Many Days 0 Every Day	14 No Days 17 A Few Days 3 Some Days 4 Many Days 0 Every Day	p=0.024[a]*
[a]Fisher's exact test; [b]SCPBI-Y Month 2 missing for n=4 patients; *p<0.05, **p<0.01, ***p<0.001			

Table 1. Demographics

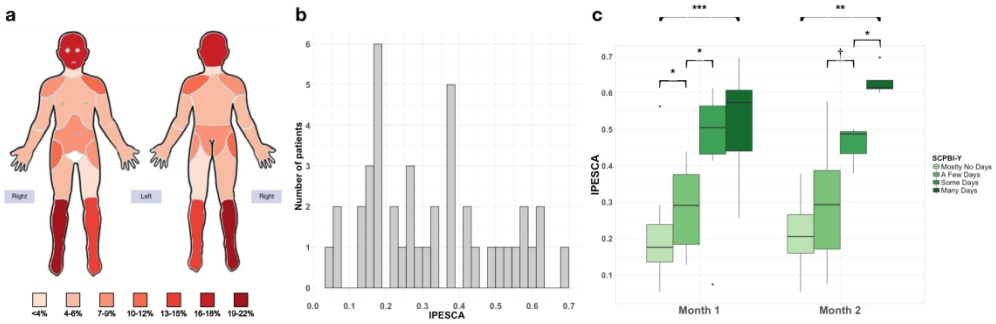

Figure 1. In n=42 patients who reported pain during pain diary period, a) Heatmaps of pain frequency (number of days in pain at that location divided by total number of days), b) IPESCA histogram, c) IPESCA was significantly different between SCPBI-Y categories at Months 1 and 2. Post-hoc analyses showed significant differences in IPESCA between mild and moderate pain categories at Month 1 and between moderate to severe pain categories at Month 2.

269x86mm (300 x 300 DPI)