Pain interferes with daily activities, emotions and sleep in adults with severe, moderate and mild haemophilia : a national cross-sectional survey

Reference:
Chantrain Valérie-Anne, Lambert Catherine, De Smet Patrick, Lobet Sébastien, Foubert Anthe, Meeus Mira, Hermans Cedric, Roussel Nathalie.- Pain interferes with daily activities, emotions and sleep in adults with severe, moderate and mild haemophilia : a national cross-sectional survey
Haemophilia / World Federation of Hemophilia - ISSN 1365-2516 - 29:2(2023), p. 521-529
Full text (Publisher's DOI): https://doi.org/10.1111/HAE.14747
To cite this reference: https://hdl.handle.net/10067/1935650151162165141

Pain interferes with daily activities, emotions and sleep in adults with severe, moderate and mild haemophilia: A national cross-sectional survey

Short running title: Pain interferes with daily activities, emotions and sleep in adults with haemophilia

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Word count

Abstract, 248/250
Script, 2963/3000
References, 38/40

Introduction: Pain is a major issue in people with haemophilia (PwH). Few studies comprehensively assessed pain in PwH using biopsychosocial framework and studies in mild PwH are lacking.

Aim: To assess pain prevalence, pain interference and their relationship with health-related quality of life (HR-QoL) in male adults with haemophilia.

Methods: A survey was initiated by the Belgian national member organisation. Pain in the last 24h, pain severity (BPI-PS) and pain interference (BPI-PI) scores were obtained with the Brief Pain Inventory short-form (BPI). HR-QoL was evaluated with the EQ-5D-3L, giving the health utility index (EQ-HUI). Associations between EQ-HUI, BPI-PS and BPI-PI were analysed using Pearson's correlation test. A multiple regression analysed the relationship between HR-QoL and BPI-PS, with age and haemophilia severity as confounding factors.

Results: Within 185 respondents (97, 31 and 57 respectively severe, moderate and mild PwH), 67% (118/177) reported pain. In severe, moderate and mild PwH, respectively 86% (79/92), 71% (22/31) and 32% (17/54) reported pain. Median [IQR] BPI-PS, BPI-PI and EQ-HUI scores were respectively 1.5 [0.0; 4.0], 1.6 [0.0; 3.6] and 0.81 [0.69; 1.00]. PwH reported pain interference with general activity (56% (99/176)), psychosocial factors such as mood (53% (93/175)), and sleep (51% (90/177)). Moderate correlations were found between EQ-HUI, BPI-PS and BPI-PI. After adjusting for age and haemophilia severity, BPI-PS explained 14% of HR-QoL variance.

Conclusions: Pain is a major issue amongst PwH, including people with mild haemophilia. Pain interferes with activities, emotions, sleep and HR-QoL, arguing for a comprehensive biopsychosocial approach of pain.

Keywords: blood coagulation disorders, biopsychosocial, pain assessment, quality of life, daily living, survey

Introduction

Unprecedented improvements in the care of people with haemophilia (PwH) have led to a decrease in annual bleeding rate and raised life expectancy[1]. Nevertheless, a substantial proportion of PwH still suffers from debilitating joint pain. It decreases their functional ability and interferes with daily activities and quality of life[2]. Measuring and interpreting pain are challenging in any clinical context, and even more so when considering the additional implications for bleeding disorder management. Both PwH and therapists experience for example difficulties in differentiating bleeding-related versus arthropathy-related pain[3]. Pain is however a complex phenomenon influenced by multiple factors, highlighting the importance of a comprehensive assessment from a broad biopsychosocial perspective[4,5].

While several studies examined the prevalence of pain in people with severe or moderate haemophilia[6], studies assessing pain in people with mild haemophilia are lacking. However, preliminary data suggest that pain might also be a burden in individuals with mild haemophilia[7].

Besides, pain interference - the consequences of pain on relevant aspects of persons' lives and its impact on social, cognitive, emotional, physical and recreational activity as well as sleep and enjoyment of life[8] - is largely under-evaluated in PwH[6]. This contrasts with other chronic musculoskeletal conditions such as osteoarthritis or chronic low back pain, where evaluating the interference of pain with emotions, cognitions or sleep is done in clinical routine[9]. It is acknowledged that integrating the different domains included in the biopsychosocial model of pain enhances pain evaluation and optimizes treatment targets[4].

Therefore, this study aimed to investigate the prevalence of pain and pain severity amongst adults with severe, moderate and mild haemophilia. Furthermore, the interference of pain with activities, emotions and sleep will be evaluated. Finally, the relationship between health-related quality of life (HR-QoL) and pain (i.e., pain severity and interference) will be examined.

Methods

Survey methodology & participants

For this cross-sectional study, a survey was initiated and conducted by the Belgian national member organization (NMO) of PwH (representing approximately 53% of the expected national haemophilia population). All members received a postal survey in which the Brief Pain Inventory short-form (BPI), the EuroQol-5-Dimensions-3-Levels (EQ-5D-3L) and questions about haemophilia were included. To be included in the study, respondents had to be adult men with severe (FVIII|FIX activity <1%), moderate (FVIII|FIX activity 1%-<5%) or mild (FVIII|FIX activity 5-40%) haemophilia A or B. Approval of the ethics committee and informed consent was legally covered by the special provisions stated in §31 of the Belgian Act on Experiments on the Human Person[10].

Brief Pain Inventory short-form (BPI)

The BPI is a self-administered questionnaire evaluating *the prevalence of pain* in the last 24 hours and its *interference* with daily life*,* i.e. *activities* (walking, general activity and work), *emotions* (relation with others, enjoyment of life and mood) and *sleep*[11]. The BPI was shown to be valid and reliable in PwH[12]. Pain variability over the last 24 hours (i.e., "worst", "least", "average" and "now") is captured on a 10 points numeric rating scale (NRS), with higher scores indicating higher pain severity. Averaging the 4 items results in the pain severity score (BPI-PS, 0–10). Pain interference with general activity, mood, walking ability, work, relation with others, sleep and enjoyment of life was rated on a 10 points NRS. Higher scores indicate higher interference of pain, and the mean of the 7 items gives the pain interference score (BPI-PI, 0–10). In case of missing data, official guidelines were used to compute the scores[11]. The BPI also includes a body diagram on which subjects were asked to indicate whether they suffered from painful elbows, knees and ankle joints, as they are the most painful joints in PwH[13].

EuroQol-5-Dimensions-3-Levels (EQ-5D-3L)

The EQ-5D-3L was used to evaluate *HR-QoL* in PwH[14]. The first part comprises a descriptive system of 5 dimensions (i.e., mobility, selfcare, daily activities, pain and anxiety and depression) rated as: no, some or extreme problems. Provided that all items are rated, a health utility index (EQ-HUI) (range, -0.33–1.00) is derived using a specific value set, higher scores indicating better health status. No Belgian value set being available, the Dutch one was used[15]. The second part is a visual analogue scale (EQ-VAS) labelled from 0: "worst imaginable health state", to 100: "best imaginable health state" on which subjects rate their overall health.

Statistical analysis

Data were computed using IBM® SPSS® Statistics v.27. We performed descriptive analyses of pain outcomes and HR-QoL for all PwH but also for severe, moderate and mild PwH separately. Descriptive data were presented as median [IQR] (min - max) (due to the low number of PwH in the subgroups). Categorical variables were reported as frequencies and percentage frequencies (N (%)). Second, the relationships between pain severity (BPI-PS), pain interference (BPI-PI) and HR-QoL (EQ-HUI) were analysed by scatter plots to visually inspect for nonlinearity. A Pearson's correlation test was used to analyse relationships. Correlations were considered low, moderate, high, or very high with coefficient of 0.30–0.49, 0.50–0.69, 0.70–0.89 and ≥0.90, respectively[16]. A multiple regression analysis with HR-QoL (i.e., dependent variable) and pain severity (i.e., independent variable) was performed. Age and the severity of the disease were included as confounding factors, seen their impact on HR-QoL in PwH[17]. Statistical significance level of the regression analysis was set at p-value ≤0.05. After the regression analysis, normality of the residuals and homoscedasticity were visually checked. Missing data were addressed in presenting accurately the number of respondents for items and scores through the manuscript.

Results

Participants and disease characteristics

Of the invited 842 PwH members of the NMO, 224 returned the survey resulting in an overall response rate of 26.6%. Thirty-nine respondents were excluded because of age (i.e., <18y). In total, 185 out of the 722 adult members replied to the survey (response rate, 25.6%). The response rate in severe, moderate and mild PwH of the NMO was as follows: 38.0% (97/255); 22.5% (31/138); 17.3% (57/329). Participants' characteristics are summarized in Table 1.

Pain prevalence, pain interference and HR-QoL

Results of all PwH (n = 185)

BPI and EQ-5D-3L data are presented in Tables 2 and 3. Sixty-seven percent of all PwH (118/177) reported pain in the last 24 hours. Median [IQR] (range) BPI-PS and BPI-PI scores were respectively 1.5 [0; 4] (0-7.5) and 1.6 [0; 3.6] (0-10). Pain interference was most reported with general activity (56%, (99/176)), walking (62%, (109/176)) and work (57%, (101/177)). Pain interference was also reported with mood (53%, (93/175)), relation with others (39%, (69/177)), pleasure in life (47%, (84/177)), and sleep (51% (90/177)). When analysing PwH that reported pain in the last 24 hours (118/177), 70% (81/115) reported pain interference with sleep on the BPI (3 missing values). While 30% (54/181) of PwH reported 2–3 painful body regions, 28% (51/181) indicated to suffer at more than 3 locations.

Regarding the EQ-5D-3L, 72% (129/180) of PwH obtained EQ-HUI lower than 1 and median [IQR] (range) was of 0.81 [0.69; 1] (-0.11–1). EQ-VAS showed a similar trend.

Severe and moderate haemophilia (n = 129)

Among subjects with severe and moderate haemophilia, 82% (101/123) reported pain in the last 24 hours (Table 2). Pain interference was most reported with activities (i.e., walking, work and general activity) (Figure 1). Pain also interfered with emotion-related items and sleep (Figure 1). On the body chart, 13% (17/126) reported no painful location, but 49% (62/126) indicated 1–3 painful regions and 37% (47/126) more than 3. Regarding the synovial joints, 41% (52/126) reported at least one painful elbow, 43% (54/126) one painful knee and 63% (79/126) one painful ankle (Figure 2).

Results of the EQ-5D-3L showed a large distribution of EQ-HUI and EQ-VAS (Table 3). Respectively 89% (86/97) and 70% (21/30) of severe and moderate PwH obtained EQ-HUI inferior to 1.

Mild haemophilia (n = 57)

In adults with mild haemophilia, 32% (17/54) reported pain in the last 24 hours (Table 2). Pain interfered most with walking, work, and general activities (Figure 1). Also, 60% (33/55) reported no painful locations and 33% (18/55) reported between 1–3 painful locations. A minority reported at least one painful joint (i.e., 13% (7/55) elbow, 20% (11/55) knee and 9% (5/55) ankle joint.

Correlation and regression analyses (n = 185)

The correlation analysis of the whole sample (i.e., subjects with severe, moderate and mild haemophilia) showed moderate negative correlation between HR-QoL and pain severity (r = -0.511), and HR-QoL and pain interference (r = -0.666) (Table 4). A high negative correlation was observed between pain severity and interference scores (r = 0.690). No significant correlation was found between pain severity and age (r = 0.163).

In the regression analysis, HR-QoL was not significantly associated with age (Table 5). After adjusting for age, haemophilia severity explained 18% of HR-QoL variance. Once age and haemophilia severity were forced into the regression model, the effect of pain explained 14% of the variance of HR-QoL. The entire model explained 33% of HR-QoL variance.

Discussion

Sixty seven percent of PwH reported pain in the last 24 hours, confirming that pain is still a major issue amongst PwH. Importantly, also 32% of mild PwH reported pain in the last 24 hours. The majority of PwH suffer from pain at multiple locations. Pain interferes with activities, emotions, sleep and HR-QoL, arguing for a more comprehensive biopsychosocial approach of pain in PwH.

The high prevalence of pain in PwH is in line with previous studies[13,18]. While the burden of pain is well known in people with severe/moderate haemophilia, our results demonstrate that a significant part of mild PwH report pain during the 24 h preceding the survey. The lack of studies performed in people with mild haemophilia do not allow to compare our data[6]. However, a study using non-validated questionnaires found acute and chronic pain in respectively 67% and 59% of 102 mild PwH, which was higher in comparison with a control group[7]. Altogether, those data suggest pain is prevalent in PwH including those with mild haemophilia.

Furthermore, 58% of severe to mild PwH reported suffering from 2 or more locations. The ankle was mentioned as most painful joint in 46% of PwH, followed by knee (36%) and elbow (27%), consistent with the results of a sample of PwH from the United States[18].

Regarding pain interference, the mean BPI-PI score is in line with previous results observed in a population of 381 severe to mild PwH (3.2 ± 2.7) in the United States[19]. Another study observed a positive correlation between pain interference and anxiety and depression amongst 102 severe, moderate and mild PwH, even after controlling for age and education[20]. They showed that pain interference was the only dimension of pain associated with anxiety (OR = 1.397, p = 0.011) and depression (OR = 1.347, p = 0.037)[20]. Assessing the interference of pain, beside the pain severity and the number of painful locations, is therefore absolutely necessary to better understand someone's pain experience. This needs to be integrated in clinical consultations[21]. Since the BPI is easy and quick to administer, it might be a suitable tool.

While activity limitation in PwH is commonly linked to haemophilia as a disease[22], results of pain interference with activities-related items emphasize the role of pain on activities. As a result of improved treatments, PwH can now more easily engage in low-risk activities[23] but adults with severe haemophilia still present lower physical activity levels in comparison with their peers[24]. This was also revealed in the current study, since 62% of PwH reported that pain interfered with walking. Factors such as fear of injury, pain and wrong beliefs on exercising are known to be important barriers to physical activity in PwH[25]. Further research should explore how these barriers can be tackled, in light of the large benefits of being physically active for PwH, including functional improvements, pain reduction and enhanced quality of life[26,27].

In our sample, pain interference was also reported with mood, relations with others and enjoyment of life. This underlines the necessity to assess pain from a biopsychosocial framework, given the bidirectional relationships between pain and emotions, commonly observed in musculoskeletal conditions[4] and increasingly mentioned in PwH[28]. In a study assessing exclusively PwH with pain, similar pain interference with emotions was reported (i.e., pain interference with mood (72.6%), relation with others (56.1%) and enjoyment of life (70.1%))[18]. Recently, Ucero-Lozano et al. reported the link between perceived painful experiences of patients with haemophilic arthropathy and factors involved in the emotional and cognitive pain process such as catastrophizing, kinesiophobia and trait anxiety (i.e., factors involved in negative feelings)[28]. They emphasized the interplay between pain and psychosocial factors amongst PwH. Evaluating psychological factors in those with chronic joint pain is of major importance because of the bidirectional relationship between emotions and pain. Psychosocial issues are not only consequences but might also be predisposing factors to pain and its chronicization[9]. For this reason, further longitudinal research should investigate these bidirectional relationships in PwH.

With respect to pain interference with sleep, it was reported in 51% of PwH. Moreover, when considering only PwH suffering from pain during the last 24h, 70% reported that pain interfered with sleep. Few studies assessed sleep problems in PwH, but available data indicate that 55% of PwH report sleep disturbance because of pain[29] and that 65% report pain interference with sleep on the BPI[18]. Also, the third subtheme related to physical alteration induced by pain in haemophilia was found to be “disturbance in sleep quality” in a qualitative study[30]. In the aforementioned studies, sleep was not the primary outcome, was not evaluated with disease-specific tools and was barely discussed. Nevertheless, this problem is well known in those with chronic pain. A meta-analysis reported a prevalence of insomnia of 72% amongst chronic pain patients[31]. For this reason, best practices in pain management advise to include sleep evaluation and management into the multimodal approach to address to pain[9]. Sleep management should be included in pain management given their bidirectional relationship: experiencing chronic pain might induce sleep disturbances, but sleep deprivation or poor sleep quality decreases pain tolerance. Using fMRI, Krause et al. found that sleep deprivation enhanced pain responsivity within specific cerebral regions in charge of pain modulation[32]. In addition, poor sleep quality is linked to psychological issues, themselves reinforcing the downward spiral of persistent pain. In haemophilia, experimental research assessing the relationship between pain and sleep disorders is lacking. Sleep disturbances in PwH with pain should therefore be investigated.

Regarding the EQ-5D-3L, our results confirm the findings of studies performed in European countries (i.e., EQ-HUI medians of 0.82, 0.78, 0.69 respectively in severe, moderate and mild participants[33]). As expected, moderate negative correlations were observed between EQ-HUI and pain scores, highlighting the relationship between HR-QoL and pain in PwH. This confirms the results of previous studies reporting correlations from 0.34 to 0.74 between pain interference and the different domains of the EQ-5D-5L within severe, moderate and mild PwH[34]. Unlike previous findings[17], age was not associated with pain severity in the current study. But in the study of Kempton et al., only patients with a history of joint pain or bleeding were recruited implying the recruitment of participants suffering from more severe forms of the disease. Taking into account the low number of young adults (i.e., <40 years) suffering from mild hemophilia, the possible relation with age should be evaluated in future studies. A moderate and linear correlation was observed between pain severity and interference. In other chronic pain populations, a non-linear relationship was observed showing that when a certain degree of pain is reached, patients report more disproportionate interference on their daily function[35]. This was not observed in the current study. In mild participants, mean EQ-HUI was 0.74 ± 0.27, which seems lower than the Belgian norms of 0.87[36]. Altogether, these results suggest that pain and reduced HR-QoL might be present in a subgroup of adults with mild haemophilia, meriting further clinical and scientific attention.

Strengths and limitations

The survey was initiated and conducted by a NMO. Haemophilia treatment centres are regularly involved in research initiatives, however our study demonstrates that NMO are aware of the current need of their members and emphasizes their important role in initiating such study. Moreover, the use of valid questionnaires enables further comparisons for reviews or meta-analysis. Also, data were presented by haemophilia severity, providing accurate data that are lacking in the literature. However, some limitations must be considered. The low response ratio of the study is considered usual when addressing large groups[37] and seems similar to a recent survey in PwH[38]. An overall response ratio in regards of the Belgian PwH population could not be calculated, as no Belgian registry is available. This hampers us to provide an overall Belgian response ratio. This latter point, as well as nonresponse to the survey (including non-response of <40y old mild PwH) may be interpretated as selection bias and prevents to interpret prevalence data. Implementing a control-group in the study design would have been an added-value. Finally, despite its validity and common use in PwH, the BPI does not discriminate between acute and chronic pain. Studying the interference according to the type of pain (i.e., acute vs chronic pain) should be done in future studies assessing pain in PwH.

Conclusion

Pain is a major issue amongst PwH and a significant part of mild PwH also report pain. The interference of pain with activities but also with emotions and sleep shows the complexity of evaluating pain. Recognizing the interplay between those factors and pain, a more comprehensive biopsychosocial evaluation of pain is needed within PwH. The BPI seems to be a promising screening tool to propose in clinical practice. Finally, the inverse relationship observed between pain and HR-QoL emphasizes the need to assess systematically pain in PwH.

Acknowledgements

This study was conducted with the help of Patrick Finders-Binje (†), vice-president of the Belgian NMO at the time of the study. We would like to thank Sietske De Keyser for helping with the data collection.

Data availability statement

Data available on request from the authors.

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