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ASSESSMENT AND MANAGEMENT OF PAIN IN HEMOPHILIA PATIENTS

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REVIEW ARTICLE

Assessment and management of pain in haemophilia patients

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Summary. Haemophilia patients experience acute pain during joint bleeds and chronic pain from haemophilic arthropathy. More than 50% of haemophilia patients have painful joints that cause disability and impair quality of life. Unfortunately, only a few clinical studies have investigated the non-pharmacological or pharmacological treatments for pain or the adverse effects of pain on the health and quality of life of children and adults with haemophilia. There are no detailed algorithms or guidelines for pain management in haemophilia patients, and treatment is largely empirical. Therefore, a standardized approach to the management of pain in haemophilia patients is needed. This approach should include a close relationship between pain specialists and the staffs at haemophilia treatment centres; validated instruments specific to haemophilia for assessing pain, quality of life and disability; and stepwise algorithms/protocols for treatment of chronic vs. acute pain and prophylactic vs early treatment. A pain treatment protocol should include a definition of the problem of pain and best practices for physicians. A call to action is needed to standardize treatment approaches to pain and to develop algorithms/protocols for the management of pain in haemophilia patients. This review will highlight the prevalence and devastating impact of pain in haemophilia patients, currently available treatment options and identify the unmet needs for pain management.

Keywords: chronic pain, haemophilia, haemophilic arthropathy, pain management, pain treatment guidelines, quality of life

Introduction

Joint injury from intra-articular haemorrhage in the patient with haemophilia results in acute pain that is typically treated with mild analgesics, rest, ice, compression and elevation. For more severe pain, opioids may be necessary to provide adequate relief to aid restoration of function. Many haemophilia patients have more than one type of pain, in addition to joint pain [1]. At present, there is a limited body of both specific guidelines on managing pain in patients with haemophilia, and information on its impact on overall health, physical activity and quality of life in children [2] and adults [3] with haemophilia. Current guidelines emphasize a team approach for managing patients, but specific, well-established guidelines are necessary for properly managing episodic and chronic pain in the haemophilia population [4,5].

The purpose of this review is to highlight the prevalence and impact of pain in patients with haemophilia and to provide an expert source of treatment options. Our goal is to propose a strategic course for managing pain throughout various stages of arthropathic injury in the haemophilia patient as part of a comprehensive haemophilia treatment programme. This review also serves as a call to action for standardized approaches to managing pain in haemophilia patients.

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Materials and methods

A literature search was conducted for articles published between 1990 and 2010 about haemophilia and the effects of joint damage on occurrence of acute and chronic pain. The National Library of Medicine (PubMed) database was consulted, and the reference lists of identified articles were reviewed for additional information and original sources. Search terms included haemophilia, pain, comorbidities, drug treatment and management.

Impact of pain on patients with haemophilia

After years of repeated injury of a joint and exposure to the inflammatory and oxidant effects of haemoglobin, a complex haemophilic arthropathy ensues. The initial

effect is acute pain, swelling and decreased range of motion [6]. Recrudescent injury leads to synovial inflammation, progressive cartilage destruction and bone erosion that lead to chronic synovitis if left unmitigated [6]. Concomitant symptoms of persistent chronic pain, joint stiffness, decreased range of motion and decreased function are associated with chronic synovitis and advanced arthropathy [6].

Pain, disability and reduced quality of life are the long-term effects burdening the patient with haemophilic arthropathy. In one survey of 71 patients with severe haemophilia (mean age 43 years) and an average of four painful joints, activities of daily living were limited in 89%, mood was negatively affected in 85% and untreated persistent pain was reported by 50% of patients. Another survey of 78 adult patients (ages 18–70 years) with severe haemophilia revealed that two-thirds suffered from more than one painful joint, with the ankle being the most common site of pain. Pain was a significant factor in their functional limitations [7].

Patients with haemophilia and haemophilic arthropathy experience substantially more disability and morbidity than the general population [8,9]. A study in Italy of 52 patients (aged 15–64 years) with severe haemophilia with inhibitors found that 81% were disabled and 27% had chronic synovitis [10]. Quality-of-life assessments identified pain in 71% of patients and extreme pain in 4%. Physical functioning, bodily pain and role-physical scores were lower than in the general population [10]. Among 1066 patients (median age, 36 years) with moderate haemophilia surveyed in the Netherlands, 73% reported a joint bleed in the past year, 43% had joint impairment, 27% were disabled and 15% reported chronic pain [11].

A survey in the United Kingdom of 68 patients (mean age, 41 years) with severe haemophilia A or B found that more frequent pain correlated with negative thoughts about pain (e.g. anger, fear, isolation-seeking behaviour and anticipating catastrophes) and increased concern about using pain medication [1]. Finally, an evaluation of 209 men with haemophilia A or B concluded that intensity of pain was the primary influence on physical quality of life, and negative thoughts about pain affected mental quality of life [3]. Thus, pain and its associated effects are common components of the lives of haemophilia patients.

Management and assessment of pain

The increased use of prophylactic treatment haemophilia patients has reduced the overall burden of acute and chronic pain. However, early recognition and intervention to reduce hypertrophy in epiphyseal growth plates in paediatric patients is still essential to decrease the long-term effects of recurrent bleeding. In the adult patient, properly treated episodes of bleeding in childhood can lead to improved work performance, productivity, mobility, quality of life and psychosocial elements [2].

Studies on the effects of pain in patients with haemophilia conclude that effective pain management, including interventions to increase pain acceptance and reduce negative thoughts about pain, will improve quality of life. More frequent use of analgesics can reduce the functional limitations caused by chronic joint pain [3,7,12].

Specific training and guidelines analgesic use is critical for good management of chronic pain patients. The current recommendations for appropriate use of opioids are often given limited attention at the expense of the patient. A substantial body of information is readily available for treating and monitoring patients in need of improved pain control with opioids. However, an equally daunting amount of time and effort is required to comply with the concerns of good pain control, meeting regulatory requirements and making reasonable efforts to prevent the drug diversion that causes public safety concerns.

Assessment of pain

When considering treatment of the chronic pain associated with haemarthropathy, guidelines and precautions from the general pain literature are especially relevant for the haemophilia population. First and foremost would be observation of the established universal precautions of pain management (Table 1) [13].

A comprehensive management approach should involve all members of the healthcare team, including haematologist, orthopaedic surgeon, physical therapist, nurse, psychologist, counsellor and pharmacist [5]. Training and the use of consistent guidelines and open communication are essential to optimizing treatment outcomes. A key component of pain management is establishing specific goals for each patient. However, a recent study in 1004 children and 2383 adults at 20 European haemophilia centres found that a comprehensive treatment approach is not followed at most centres [14]. Pain specialists are rarely consulted, and 25% of patients manage pain themselves. Pain management

Table 1. Universal precautions of pain management [13].

1. Make a diagnosis with appropriate differential
2. Psychological assessment, including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Preintervention and postintervention assessment of pain level and function
6. Appropriate trial of opioid therapy ± adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the 'four A's' of pain medicine: analgesia (pain relief), activities of daily living (psychosocial functioning), adverse effects and aberrant drug behaviour
9. Periodically review pain diagnosis and comorbid conditions including addictive disorders
10. Documentation

practices were highly variable, highlighting the need for evidence-based guidelines.

When assessing pain among haemophilia patients, the character, location, intensity, frequency and duration of pain and aggravating and relieving factors are important to document throughout the management of a patient to guide treatment [5]. A critical element to evaluate is joint range of motion, which can be adversely affected by pain specific to synovitis and joint arthropathy. Pain assessment is an essential component of adequate care, and some examples that are more applicable to the haemophilia patient are included (Table 2) [15–19].

Non-pharmacologic management

More than 80% of the world's population uses some type of complementary or alternative medicines (CAMs). The cost of CAMs in the US healthcare system was estimated to be $34 million in 2009, with 38.1 million American adults using CAM at least once [20]. Complementary or alternative medicines can be utilized with or outside of conventional therapy.

Non-pharmacologic therapy for pain management in haemophilia patients has been a mainstay of conservative treatment (Table 3) [21–27]. One approach is expressed by the acronym RICE, for Rest, Ice, Compression and Elevation (Table 4) [28]. However, herbal remedies are difficult, if not impossible, to endorse due to the dearth of valid scientific data supporting their use in the United States. In addition, questions about the quality of products and/or veracity of marketing claims are not subject to US Food and Drug Administration (FDA) scrutiny or rigorous testing standards.

Pharmacologic treatments for pain

Patients with haemophilia utilize a wide variety of pharmacologic treatments from over-the-counter and prescription sources. These therapies may be part of a stepped-care progression from topical anaesthetics to mild analgesics to opioids—although no evidence-based guidelines or protocols are available that establish a stepwise treatment of pain with haemophilia. Some haemophilia patients may be reluctant to use analgesics. In one study, only 36% of haemophilia patients with pain were taking analgesics [7]. The authors concluded that promoting treatment with analgesics among haemophilia patients might decrease the effect of pain on functional limitations. As part of a comprehensive care programme,

Table 2. Examples of instruments used for assessing pain in the haemophilia patient.

Instrument	Purpose
Haemophilia Pain Coping Questionnaire [15]	Measures pain frequency, intensity and coping strategies
Haemophilia Joint Health Score [16]	Assesses joint health over time, including swelling, muscle atrophy, strength and joint range of motion, crepitus, axial alignment, joint pain and gait
Pain Coping Strategies Questionnaire [17]	Measures cognitive and behavioural strategies related to pain coping strategies
Knee Society Score [18]	Rates pain, stability and the knee's range of motion and a functional score that rates a patient's ability to walk and climb stairs
Western Ontario and McMaster Universities Index [19]	Assesses patients with hip or knee osteoarthritis using 24 parameters, including pain

Table 3. Non-pharmacologic interventions for pain management in patients with haemophilic arthropathy.

Intervention	Description
Acupuncture	Traditional form of Asian medicine. Treatment is applied with needles at specific sites along pathways associated with particular physiological systems and internal organs [21]
Biofeedback	Uses a sensory signal in proportion to a biological process (e.g. breathing) to provide feedback. Goals are to perform self-relaxation as needed to minimize distress and discomfort
Cognitive behavioural therapy	Deals with how thoughts influence feelings and behaviour, and how changing thoughts can improve mood. Requires active participation from the patient to reframe thoughts, unlearn emotional and behavioural patterns and modify and reconfigure beliefs and expectations
Distraction	Techniques include reading a book or magazine, talking with friends, watching a movie, playing computer or board games or other activity that distracts attention from pain
Exercise or fitness programme	Physical activity and sports improve quality of life and physical conditioning, increase strength and lower risk of haemophilic atrophy [22]
Guided imagery	Uses sight, sound or a combination of senses to imagine a state different than what currently exists [23]
Herbal therapy	Herbal therapy is not regulated by the FDA; thus, there is a potential for mislabelling. Strengths of products often vary [24]. Many herbs, including feverfew, garlic, ginger, gingko or Asian ginseng, can increase the risk for bleeding.
Hydrotherapy	Useful for painful or stiff joints and muscles after acute haemarthrosis, muscle bleed, chronic arthropathy and synovitis and after long periods of bed rest [22]
Hypnosis	Involves complete physical and mental relaxation to minimize stress by creating an altered state of consciousness characterized by profound relaxation [25]
Integrative therapy	Incorporates traditional non-pharmacologic and pharmacologic therapies and non-traditional therapies (i.e. biofeedback) into pain management structured to meet individual needs [26]
Physical therapy	Goals are improved muscular strength, reduced stress on joints and decreased risk of joint damage [22]
Therapeutic massage	Manipulation of the body to normalize soft tissues. Increases blood circulation, reduces muscular tension or flaccidity, enhances tissue healing, increases ease and efficiency of movement and aids in relaxation
Transcutaneous electrical neurostimulation (TENS)	Applies a low intensity electrical impulse to stimulate peripheral nerves, which inhibits transmission of pain information along nerves and may result in the release of endorphins [27]

Table 4. Components of RICE for management of pain [28].

Rest
Rest affected area
Avoid weight-bearing activities
Use splints and crutches, if necessary
Ice
Produces
Superficial vasoconstriction leading to pain reduction and reduced metabolic rate
Local anaesthesia by a reduction in rate of conduction of sensory nerves
Change in local circulation
Apply ice for no longer than 20 min at a time, four to eight times per day
Use crushed ice, a cold pack or frozen bags of peas or corn
Compression
Prevents or reduces swelling
Use elastic wrap or compression bandage (not wrapped too tightly)
Wrapped area should not hurt or throb from the bandage
Elevation
Elevate the extremity as often as possible
Elevate the injury above the level of the heart with pillows, etc
Reduces swelling

encouragement and guidance from a trusted provider may have a profound impact on a patient's willingness to utilize more aggressive pharmacologic therapy, thereby improving overall function and quality of life.

In the previously cited UK survey [1], more than one-third of the 68 patients with severe haemophilia expressed concerns about becoming dependent on prescription analgesics and, to a lesser extent, use of illicit drugs and drug-related liver damage. The study also found that the use of analgesics was related to the frequency of pain [1]. Better education through haemophilia centres with regard to risk vs. benefit of medications is clearly needed to overcome barriers to adequate pain control, which are founded largely on misconceptions of patients and providers.

Initial steps in pain management include the use of over-the-counter analgesics such as acetaminophen, ibuprofen or non-steroidal anti-inflammatory drugs (NSAIDs). A survey of European haemophilia treatment centres found that acute and chronic pain was most often managed with acetaminophen or NSAIDs [14].

Acetaminophen

Randomized clinical studies of acetaminophen in patients with haemophilia have not been conducted. Despite decades of use as an analgesic, acetaminophen should be used with caution. Acetaminophen is the most common cause of acute liver failure in the United States, and almost half of those cases are due to an unintentional overdose [29]. The risk of hepatotoxicity is increased by chronic alcohol use, malnutrition and drug interactions with cytochrome (CYP) P450 inducers. An acetaminophen dosage of 4 g day^{-1} for 14 days was associated with significant elevations in hepatic transaminase levels to three times the upper limit of normal in more than 30% of 145 healthy subjects [30].

Analgesics: NSAIDS and COX-2 inhibitors

A rational process for analgesic selection utilizes a stepwise approach (Table 5) [4]. Despite their widespread use, NSAIDs are associated with a risk of gastrointestinal (GI) complications, including ulcers, bleeding and perforation [31–36]. Mortality from upper GI bleeding and perforation has increased over the past decade among people taking NSAIDs or aspirin compared with the general population [37]. NSAIDs with a long half-life or slow-release formulations have a greater risk of upper GI bleeding or perforation [32]. Due to the risk for bleeding, NSAIDS and medications containing acetylsalicylic acid should not be used by haemophilia patients during bleeding episodes [5]. New preparations of transdermal NSAIDs may permit improved pain relief in subcutaneous joints such as the knee and ankle with fewer systemic side effects, although studies in the haemophilia population are not available.

The cyclo-oxygenase-2 (COX-2) inhibitors have a lower risk of GI complications than traditional NSAIDs [32,36,38] and may be used with caution during bleeding episodes [5]. Cyclo-oxygenase-2 inhibitors also are associated with lower rates of hospitalization and perforated peptic ulcer than NSAIDs [39]. However, the beneficial GI effects of COX-2 inhibitors are offset by a significantly greater risk for cardiovascular (CV) diseases such as myocardial infarction, stroke, heart failure and hypertension [40]. The risk is greatest in people with a history of CV disease or CV risk factors. Celecoxib is the only COX-2 inhibitor currently available in the United States. In addition, both NSAIDs and COX-2 inhibitors are associated with a heightened risk of acute renal failure within the first 30 days of therapy [41].

Only a few studies have investigated the use of NSAIDs or COX-2 inhibitors for pain among haemophilia patients. A multicenter case–control study was conducted to determine the rate of upper GI bleeding among haemophilia patients [42]. Forty-two of 2285 patients followed for a mean of 17.4 months experienced a GI bleeding episode. The risk for bleeding

Table 5. Stepwise approach to use of analgesics for pain control in haemophilia patients [4].

Step	Medication	Dosage and administration
1	Acetaminophen or NSAID	Acetaminophen: up to 650 mg dose^{-1} and 3250 mg day^{-1}
2	COX-2 inhibitor	Celecoxib: 100–200 mg once or twice daily
3	Acetaminophen + codeine or Acetaminophen + tramadol	10–20 mg up to six times daily or 50–100 mg, three to four times daily
4	Morphine or equivalent	Slow-release formulation: 20 mg twice daily; allow rescue dose of rapid release 10 mg, four times daily. Increase slow-release dose if rapid release is used >4 times daily

NSAID, Non-steroidal anti-inflammatory drug; COX-2, Cyclo-oxygenase-2 inhibitor.

with the first month of use was significantly increased with traditional NSAIDs, but not with COX-2 inhibitors. In addition, clinical studies with the COX-2 inhibitors that are not available in the United States have shown that these agents have a factor-sparing effect, relieve chronic synovitis and pain and control joint bleeding [43–45]. Thus, COX-2 inhibitors appear to have increased GI safety compared with traditional NSAIDs in haemophilia patients.

Opioids

Clinical data have not been reported for guiding the use of opioids for pain management in haemophilia patients. Instead, guidance may be taken from recommendations by professional pain and haemophilia organizations and anecdotal experience [5,46,47]. Although recommendations in 2005 from the World Federation of Hemophilia discourage use of opioids in the haemophilia population [5], current expert guidelines encourage case-by-case risk evaluation to determine if chronic opioid therapy may be helpful in reducing pain and maintaining function [47]. By becoming adept in mechanisms of pain and pharmacology of pain medications and keeping abreast of risk assessment and regulatory requirements, healthcare providers may help develop and maintain optimal pain management strategies with the patient's best interest at heart.

Opioids are effective for relief of short-term pain and chronic non-cancer pain [46,47]. Their long-term effectiveness (≥6 months) depends on the specific opioid [46]. According to an evidence-based guideline of long-term pain applications, transdermal fentanyl and sustained-release morphine exhibit moderate efficacy (Level II-2: evidence from well-designed cohort or case–control analytic studies), oxycodone exhibits limited efficacy (Level II-3: evidence obtained from multiple time series with or without the intervention), and hydrocodone and methadone have indeterminate efficacy (Level III: the opinions of respected authorities based on clinical experience, descriptive studies, case reports or reports of expert committees).

Typically, opioids are prescribed using the morphine equivalent dose (Table 6) [4]. Equianalgesic dosing should be used with caution as the possibility of incomplete cross-tolerance in a patient may actually reduce the need for a strict conversion of the medication when transitioning to other opioids. Expert guidelines recommend a 25–50% reduction in the 'equianalgesic' dose during opioid rotation, particularly when converting to methadone [47]. It is important to note that equianalgesic conversion is an incomplete science, and differences in drug metabolism and tolerance to opioids, in general, as well as side effects, must always be monitored in the individual.

Methadone is a potent and inexpensive synthetic opioid analgesic; however, it has a long half-life (up to 150 h), is extensively metabolized and accumulates in the body with repeated dosing [48]. Methadone is metabolized primarily by CYP3A4 and secondarily by CYP2D6, CYP1A2, CYP1B2 and CYP2B6 [48]. Grapefruit juice or a number of commonly used drugs can increase methadone serum levels by inhibiting metabolism via intestinal CYP3A4. Drugs with the potential to increase methadone levels include fluconazole, ciprofloxacin, diazepam, fluoxetine, paroxetine and sertraline. Drugs such as rifampin that are CYP3A4 inducers may decrease methadone levels [48]. Methadone is associated with a small, but significant increase in QT interval prolongation that may result in potentially fatal torsades de points [47].

A small percentage of patients with chronic pain are at risk for addiction to opioids [49]. The staffs at haemophilia treatment centres should be aware of these risks and develop a proactive approach to recognition and management that includes early referral for addiction counselling in patients determined to be at risk [5].

Table 6. Morphine equivalent dose for selected opioids (all doses except fentanyl are based on oral comparisons to IV morphine) [4].

Oral opioid	Approximate equianalgesic dose compared to IV morphine 10 mg
Morphine	30 mg
Codeine	200 mg
Fentanyl transdermal	12.5 mcg h^{-1}
Hydrocodone	30 mg
Hydromorphone	7.5 mg
Methadone	4 mg
Oxycodone	20 mg
Oxymorphone	10 mg

Surgical interventions

Patients who continue to bleed into a joint despite treatment usually develop chronic, unremitting pain for which surgical intervention may be needed. Synovectomy can be performed to manage recurrent bleeding episodes in patients with chronic synovitis and permits rapid return of function. Removal of the hypertrophied synovium can reduce chronic pain due to recurrent bleeding [6]. Patients with advanced joint disease (i.e. severely narrowed joint space, decreased range of motion and pain) are less likely to benefit from synovectomy than patients with moderate disease.

If less invasive surgical procedures fail to relieve pain from haemophilic arthropathy, total knee or hip replacement offers a long-term approach. Total knee or hip arthroplasty produces at least two-fold improvements in joint pain, range of motion, knee function scores, physical activity and quality of life [50–53]. These benefits have been observed during follow-up studies over more than 10 years [51]. In addition, a reduction in the use of coagulation factors has been demonstrated after both hip and knee arthroplasty [53].

Joints that cannot be replaced due to bone loss, infection or soft tissue consideration can often be fused. This procedure sacrifices motion for pain relief and stability. Removing the mobile joint and synovial lining should eliminate bleeding. This procedure has been especially well tolerated in the ankle and hind foot. Thus, surgical intervention offers effective relief of joint pain and disability for patients with chronic pain that is not relieved by conservative management.

Limitations of current practice

Perhaps the most important limitation in the treatment of haemophilia-associated pain is the absence of evidence-based treatment guidelines or best practices. As few controlled trials of non-pharmacological or pharmacological therapy have been conducted, pain management in haemophilia patients is largely empirical. There are no treatment guidelines with specific recommendations for children, adults and the elderly, for the treatment needs of chronic vs. acute pain or for the relative benefits of prophylactic vs. early treatment of bleeding as a strategy for managing pain. In addition, only a few validated instruments are available for assessing pain, quality of life and disability in haemophilia patients.

The utility of some of the treatments used for pain and disability in haemophilia patients is also limited. The risk for GI bleeding with NSAIDs is especially problematic for haemophilia patients. Finally, the efficacy and safety of many of the non-pharmacologic approaches to pain management have not been demonstrated in randomized, controlled clinical trials.

Given these limitations, healthcare providers need expert knowledge of the risks and benefits of non-pharmacological and pharmacological approaches to pain that can be individualized to each patient. Clinicians also need to understand that pain management is not just about prescribing a drug, but that it involves comprehensive patient evaluation and selection of a multi-modal treatment approach that will result in effective long-term pain relief.

Summary

A call to action is needed to standardize treatment approaches and to develop algorithms/protocols for the management of pain in haemophilia patients. The majority of haemophilia patients will experience acute and/or chronic joint pain that is often debilitating and diminishes their quality of life. Healthcare providers should recognize and understand the importance of effective pain management for these patients. Pain management should emphasize a close relationship between haemophilia treatment centre staff and pain specialists. These approaches should include a definition of the extent of problem (i.e. the prevalence, severity and impact on patient) and a summary of best practices for physicians.

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