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Review

Treatment of musculo-skeletal pain in haemophilia

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ABSTRACT

Musculo-skeletal pain treatment is inadequate in many haemophilic patients. Analgesics are used only by 36% of adult patients. FVIII/FIX intravenous infusion is mainly used to lessen pain, followed in frequency by usage of NSAIDS (primarily COX-2 inhibitors). In about 30% of patients, pain continues after infusion of F VIII/IX. In acute haemarthroses pain treatment must continue until total disappearance (checked by ultrasonography) and include haematologic treatment, short-term rest of the involved joint, cryotherapy, joint aspiration and analgesic medication (paracetamol in mild pain, metamizole for more intense pain, and in a few precise patients, soft opioids such as codeine or tramadol). In the circumstance of intolerable pain we should use morphine hydrochloride either by continual infusion or a patient-controlled analgesia (PCA) pump, determined by the age, mental condition and grade of observance of the patient. Epidural blocks utilizing bupivacaine and fentanyl may be very efficacious as well. Three main strategies to alleviate chronic musculo-skeletal pain secondary to haemophilic arthropathy (joint degeneration) exist: pharmacologic management, physical medicine and rehabilitation, and intra-articular injections. As for pharmacologic management, NSAIDs (ibuprofen, diclofenac, celecoxib, robecoxib) are better than paracetamol. The advantages of tramadol or tramadol/paracetamol and non-tramadol opioids are scanty. With respect to physical medicine and rehabilitation, there is insufficient confirmation that a brace has supplementary favourable effect compared with isolated pharmacologic management. Land-based curative exercise and watery exercise have at the minimum a tiny short-run benefit. Curative ultrasound can be helpful (poor quality of evidence). The efficacy of transcutaneous electrostimulation (TENS) for pain mitigation has not been proved. Electrical stimulation treatment can procure notable ameliorations. With respect to intra-articular injections, viscosupplementation appears to be a useful method for pain alleviation in the short-run (months). The short-run (weeks) advantage of intra-articular corticosteroids in the treatment of joint pain has been shown.

1. Introduction

Haemophilia is a congenital hereditary disorder of blood coagulation characterised by recurrent painful articular bleeding episodes (haemarthrosis). The goal standard of treatment is primary prophylaxis intravenous infusion of the deficient factor: FactorVIII (FVIII) in haemophilia A, Factor IX (FIX) in haemophilia B [1–3]. However, despite primary prophylaxis subclinocal bleeding episodes may occur. Repeated haemarthrosis will cause joint degeneration (haemophilic arthropathy) accompanied by chronic articular pain in several joints (knees, ankles, elbows) [4,5]. According to Riley et al. [6], > 50% of adult people with haemophilia have painful joints that cause disability and impair quality of life (QoL). Adequate pain handling is indispensable so as to rise the patient's QoL [7,8]. Promoting analgesic usage might diminish the effect of pain on functional limitations [9].

In 2014, Young et al. [10] carried out a review of the literature and stated that studies were needed to identify optimal pharmacologic treatment for chronic articular pain in adult haemophiliacs. In another systematic review published in 2015, Humpries and Kessler [11] emphasised the importance of an appropriate pain management in adult haemophiliacs.

Efficacious pain treatment in haemophilia is crucial to lessen the affliction that pain inflicts on patients. The purpose of this review is to analyse the existing conservative strategies for the treatment of acute and chronic musculo-skeletal pain related to haemophilia.

2. Epidemiology

In 1987, Chiniere and Melzak [12] reported that in adult haemophiliacs ethnocultural factors associated with language affiliation could make a contribution to inter-individual variety in chronic articular pain perception. In 2001, Wallny et al. [7] analysed 71 adult haemophiliacs.

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On average, there were four articulations with major chronic articular pain. The most common painful joints were the ankles (45%), followed by the knees (39%) and the elbows (7%). In 29% of adult haemophiliacs, chronic articular pain continued after application of FVIII/FIX, while 12% told that chronic articular pain still persisted after usage of FVIII/IX and analgesics. In another report published in 2002, Wallny et al. [8] stated that the more intense the objective damage to articulations, the more often haemophiliacs said to have persistent chronic articular pain.

In a study published in 2006 by van Genderen et al. [9], 78 adult haemophiliacs were analysed. Two-thirds (52/78) of patients had more than one painful articulation, the ankle being notified most commonly (43/78). More than two-thirds of haemophiliacs had one or more joints with chronic articular pain.

In 2011, Wiktop et al. [13] reported that the three most frequent word descriptors for chronic articular pain were the same - achy, throbbing and tender; the most used pain medications were non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. Factor replacement was utilized for chronic articular pain treatment 38% of the time. In 2014, Kalnins et al. [14] reported that 86% of adult haemophiliacs had chronic articular pain.

3. Haemarthrosis (acute pain)

The following five features need to be taken into account if adequate management of acute joint bleeding is to be accomplished [15]: Haematologic treatment (intravenous infusion of FVIII/FIX), in preference within 2 h from the beginning of joint bleeding, till a plasma level not < 30–50% of the insufficient factor is attained, short-run repose of the affected articulation, local criotherapy, joint aspiration (arthrocentesis) of blood, and analgesic medication.

3.1. Haematologic treatment

The main step is substitution therapy with the insufficient coagulation factor (ideally within 2 h from the start of symptoms) [16,17]. That is why it is advised that the patient must have coagulation factor concentrates at home so that treatment is not postponed. The aim is to get corrective coagulation factor levels (30–50 IU dL^{-1}) [16]. This signifies that a patient with severe haemophilia will have to be treated with 15–25 IU Kg^{-1} of FVIII and 30–50 IU Kg^{-1} of FIX, even though in patients with severe haemarthrosis more intense management protocol could be required. For significant haemarthroses, a more vigorous treatment is needed to preclude advance to synovitis, repeated articular haemorrhages and eventually advanced haemophilic arthriopathy. Besides early substitution treatment with the insufficient clotting factor, these sorts of haemarthroses require joint aspiration (arthrocentesis) till total disappearance of blood on ultrasonography [18–20]. The latter needs 10–30 days substitution treatment with the factor concentrate.

3.2. Rest

We must emphasise that a determining benchmark next to the beginning of haemarthrosis is the immobilisation of the implicated joint.

3.3. Cryotherapy

Local cryotherapy is efficacious for intense articular bleeds. Cryotherapy, at brief yet repeated interludes, can also lessen swelling and alleviate pain due to its vasoconstricting impact.

3.4. Joint aspiration (arthrocentesis)

Taking into account that there is a duration and dose-dependent association among cartilage contact to blood and chondrocyte death, when there is a large increment in the volume of intra-articular blood

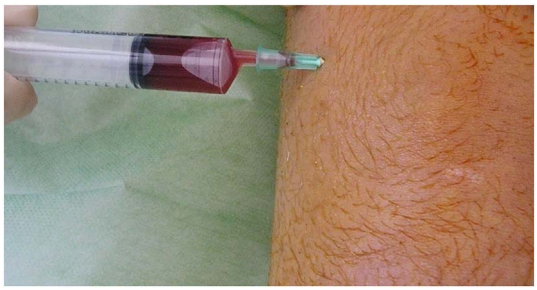

Fig. 1. Arthrocentesis (joint aspiration) of the knee: This must be performed in acute and voluminous cases to relieve the pain and avoid the risk of future joint damage, although always with suitable haemostatic cover.

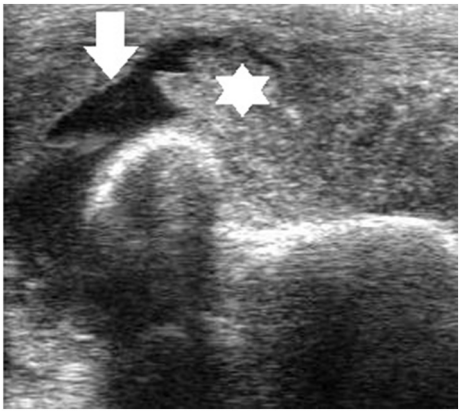

Fig. 2. Ultrasonography (saggital plane) of the elbow of a haemophilia patient showing acute haemarthrosis (arrow). Synovitis (synovial villi) is also present (asterisk).

joint aspiration should be carried out in 2 days to preclude long-run joint impairment [21] (Fig. 1). Speedy arthrocentesis must be performed with the patient secured with coagulation factor levels of 100 IU dL^{-1}. When there is doubt as to whether haemarthrosis is present, it is advised to perform ultrasonography (Fig. 2).

3.5. Analgesia

The appropriateness of a particular analgesic treatment will be determined by the severity of pain and on the peculiarities of the patient [22,23]. From the pharmacological viewpoint, one may differentiate among three distinct grades of pain severity in children. In mild pain, use of paracetamol is almost always effective (Table 1). For more strong pain, a more strong analgesic should be utilized, like metamizole. In a few precise patients, soft opioids such as codeine or tramadol may be employed as well. In the circumstance of atrocious pain, the optimal medication must be morphine hydrochloride (continuous infusion or a PCA pump), based on the age, mental condition and grade of acceptance of the patient. Epidural blocks with bupivacaine and fentanyl may be very operative as well.

4. Haemophilic arthropathy (chronic pain)

Three main strategies to alleviate chronic musculo-skeletal pain

Table 1
Main characteristics of paracetamol.

Analgesic and antipyretic action. Antinociceptive mechanism of action at central level (COX-3 and serotonine release) and at peripheral level
Good relationship between dose (1 g/6 h) and analgesic response
Excellent tolerability. It can be used in patients with renal insufficiency, lactating children, pregnant women and children > 11 years