HAEMOSTASIS

Original article

Pain assessment and management in Italian Haemophilia Centres

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Background - Although the widespread use of factor VIII/IX replacement therapy has significantly reduced the severity of arthropathy in persons with haemophilia (PWH), some develop degenerative joint changes, associated with significant pain. The aim of this survey was to investigate the management and perception of pain among Italian physicians who treat PWH.

Materials and methods - Between September and October 2017, a questionnaire was distributed to 35 Italian haemophilia treatment centres (60 physicians).

Results - Fifty-three haemophilia specialists completed the survey. We found that there was good agreement (98.1%) on the need to investigate pain at each clinical visit, but there was heterogeneity in the opinions of haemophilia specialists with regards to the availability of validated guidelines (35.8%) and whether pain specialists should be a part of the comprehensive care team in daily clinical practice (58.5%). Haemophilia specialists also agreed pain should be evaluated using a rating scale validated in PWH (88.7%). Pain was mainly managed by the haemophilia specialists themselves, supported by a physiatrist and physiotherapist, while a pain specialist was only involved in 26.4% of cases. The combination of paracetamol with tramadol or codeine was the most common first-line treatment, while cyclo-oxygenase-2 inhibitors, non-steroidal anti-inflammatory drugs, and opioids were less commonly used.

Discussion - There are some unmet needs in Italy regarding pain management for PWH and the management of pain in these patients by haemophilia specialists. There is a lack of evidence-based guidelines for these specialists to use, as well as a reluctance to involve pain specialists. The lack of spontaneous reporting of pain by PWH, despite using pain relief, highlights the need for clinicians to actively ask patients about any pain they may be experiencing.

Keywords: *blood coagulation disorders, haemophilia, pain perception, pain management, surveys.*

INTRODUCTION

With an overall incidence of 1:5,000 male newborns, haemophilia is one of the most common inherited coagulation disorders[1]. Joint bleeding represents the most commonly reported type of haemorrhage in persons with haemophilia (PWH)[2-4]. Repeated bleeding episodes may lead to degenerative arthropathy, which is the most frequent complication

in both severe and moderate haemophilia[5-7]. Although the widespread use of factor VIII/IX replacement therapy has significantly reduced the onset of arthropathy, a non-negligible percentage of patients develop degenerative joint changes despite adequate prophylaxis[7,8]. As a consequence of chronic arthropathy, joint pain is the most common type of pain observed in PWH[9], with up to 50% of adult PWH having chronically painful joints that cause disability and impaired quality of life[5,10] and 89% of PWH experiencing at least one pain exacerbation episode during a 4-week observation period[11].

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage[12]. Despite the prevalence of joint pain in adult PWH, the assessment of pain and the implementation of pain management strategies are limited and inconsistent, even in comprehensive haemophilia care settings[10,13-16].

According to current guidelines[17], effective pain management in PWH is essential in order to reduce the impact of pain on the patients' daily activities and quality of life[18]. Pain management in this chronically ill population should adopt a comprehensive and multidisciplinary approach, and include physiotherapy, physical therapy, radiosynoviorthesis, surgery, psychological support, and pain medication[17]. Adequate assessment of the cause of pain is essential, and differentiating between acute and chronic pain is crucial in order to determine proper therapeutic strategies[17]. However, several reports have suggested that not enough use is made of clinical pain assessment tools in PWH[15,16].

As to the management of pain with medication[17], pain caused by acute joint or muscle bleeding should be managed mainly by means of clotting factor concentrates, whereas pain due to chronic haemophiliac arthropathy should be treated with paracetamol as a first-line drug, with cyclo-oxygenase-2 (COX-2) inhibitors, combination treatments and opioids as second choice[19, 20]. However, the use of adequate pain-relieving protocols in PWH is challenging[21] and currently available evidence[22] suggests that pain management strategies are significantly underused[23]. In this respect, recent data suggested that 33% of acute pain patients and 57% of chronic pain patients did not use any medication for their specific pain[24] and nearly 40% of PWH indicated that their pain was not well treated[15]. Furthermore, potential adverse effects of some pain medications can be exacerbated in PWH, a population with comorbidities such as liver disease, HIV infection, cardiovascular disease or chronic renal failure[21]. Thus, there is an unmet need to identify adequate pain treatment strategies and accurate tools for pain assessment in PWH. In the present study, we report results of a survey on pain assessment and management in Italian Haemophilia Treatment Centres (HTCs).

MATERIALS AND METHODS

From September 2017 to October 2017, a questionnaire was distributed to 60 haemophilia specialists from 35 Italian HTCs. All those who took part in the survey were haematologists, physiatrists, or pain specialists with experience in treating PWH. Members of the HAEMODOL Study Group are listed in *Appendix 1*.

The survey investigated different aspects of haemophilia-related pain.

- Five questions on general knowledge and perception of pain in PWH by means of a Likert scale from 1 (total disagreement) to 5 (total agreement), defining agreement when >66% of participants scored[4,5].
- Three questions assessing percentage of PWH reporting pain and using medication for pain control (<30%, 30-50%, >50%).
- One question on the type of pain usually experienced by PWH (joint, injection site, muscle, other).
- One question on the type of physician usually involved in the management of haemophilia-related pain (haemophilia specialist, pain specialist, family physician, physiotherapist, physiatrist, orthopaedic surgeon).
- Two questions on medications used for pain management in adults and children, respectively (paracetamol, paracetamol in combination with tramadol or codeine, non-steroidal anti-inflammatory drugs [NSAIDs], COX-2 inhibitors, opioids).
- One question on the overall perception of the quality of pain management in PWH (optimal, good, poor).

Calculations on the results of the survey were performed using the Office Business 365 software package for Mac (Microsoft, Redmond, WA, USA).

Ethical statement

Because this study was based on a survey of pain assessment and management in Italian HTCs, no ethical committee approval was needed.

Table I - *General knowledge and perception of pain in haemophilia patients*

Statement, % respondents[a]	Total disagreement				Total agreement
	1	2	3	4	5
It is mandatory to investigate patient pain during the medical examination	0.0%	0.0%	1.9%	15.1%	83.0%
Pain management in haemophilia patients follows specific guidelines	11.3%	24.5%	28.3%	22.6%	13.2%
An appropriate collaboration with a pain specialist is needed for a good management of symptoms	0.0%	7.5%	34.0%	41.5%	17.0%
Co-operation with a pain specialist is frequent and well established	18.9%	32.1%	32.1%	15.1%	1.9%
Pain symptoms should always be classified through a rating scale validated in haemophilia patients	0.0%	3.8%	7.5%	30.2%	58.5%

[a]Number of respondents: 53.

RESULTS

Between September and October 2017, a questionnaire was distributed to 35 Italian Haemophilia Treatment Centres (n=60 physicians). These included anaesthesiologists (n=1), haematologists (n=36), cardiovascular doctors (n=1), sports doctors (n=1), emergency doctors and surgeons (n=1), rehabilitation doctors (n=4), internists (n=6), transfusion medicine doctors (n=5), orthopaedic doctors and traumatologists (n=1), paediatricians (n=4). Fifty-three (88%) of the 60 physicians in Italian HTCs invited to take part completed the survey. Results are summarised in **Tables I-V**.

The first section, including five questions on general knowledge and perception of pain in PWH, showed good agreement on the need to investigate pain at each clinical visit, as well as on the need to evaluate pain using a validated haemophilia-specific rating scale (**Table I**). In contrast, there was wide variability in the perception of availability of validated guidelines on pain management in PWH, the presence of pain specialists in the comprehensive care team in daily clinical practice, and the need for co-operation with a pain specialist (**Table I**).

In most cases (96.2%), pain is handled by a haemophilia specialist, while a pain specialist is involved in only 26.4% of cases (**Table II**).

As to the type of pain usually encountered in PWH, 96.2% of haemophilia specialists agreed on the large prevalence of joint pain, followed by muscle pain (**Table III**).

Regarding patient-reported pain (**Table IV**), the large majority of physicians replied that both acute and chronic

Table II - *Specialists involved in pain management of haemophilia patients*

% respondents[a]	Specialist[b]
Haemophilia specialist	96.2%
Pain specialist	26.4%
General practitioner	28.3%
Physical therapist	45.3%
Physiatrist	52.8%
Orthopaedic surgeon	11.3%

[a]Number of respondents: 53.
[b]Respondents were allowed to select multiple specialists.

Table III - *Types of pain reported by haemophilia patients*

% respondents[a]	Type of pain[b]
Joint	96.2%
Infusion-related	3.8%
Muscle	35.8%
Other	0.0%

[a]Number of respondents: 53.
[b]Respondents were allowed to select multiple responses.

Table IV - *Pain reporting and use of medication for pain control by haemophilia patients*

Statement, % respondents[a]	<30%	30-50%	>50%
How many of your haemophilia patients report acute pain without prompting or questioning?	35.8%	43.4%	20.8%
How many of your haemophilia patients report chronic pain without prompting or questioning?	32.1%	41.5%	26.4%
How many of these patients are treated with analgesics?	5.7%	20.8%	73.6%

[a]Number of respondents: 53.

pain are reported in <50% of PWH, but >50% of them are currently receiving treatment for pain control.

The questions on the medications used for pain management showed that paracetamol is the drug of choice both for acute pain and chronic pain management in children, with the combination of paracetamol and tramadol or codeine, and NSAIDs being used in a limited number of cases. Interestingly, COX-2 inhibitors were not used as drug of choice for acute pain and were used in <4% of cases for chronic pain. Opioids were described as "never used as a drug of choice" (**Table V**).

In the adult setting, different methods of pain control were chosen. The combination of paracetamol with tramadol or codeine was the most frequent first option both for acute pain and for chronic pain. Comparing acute and chronic pain, COX-2 inhibitors were more often used as first choice for chronic pain than for acute pain (41.5% *vs* 18.9%), whereas NSAIDs and opioids were less frequently used (3.8% *vs* 5.7% and 3.8% *vs* 7.5%, respectively) (**Table V**). Interestingly, 81.1% of haemophilia specialists judged the level of pain management as adequate (71.7% good and 9.4% excellent), whereas only 18.9% rated it as poor.

DISCUSSION

Here we report the results of a survey of pain assessment and management in Italian HTCs.

The haemophilia specialists showed good agreement on the need to investigate pain at each clinical visit. The Italian government has approved specific rules to standardise the clinical assessment and management of pain[25], and the level of agreement found in our survey may reflect the influence of these rules on clinical practice. The results of our survey are in line with those reported by the European Haemophilia Therapy Standardisation Board (EHTSB). The EHTSB carried out a literature review and a survey of 22 HTCs throughout Europe that care for 1,678 children and 5,103 adults[13] with the aim of reviewing the evidence and investigating current clinical practice in pain assessment and management in PWH. In the EHTSB survey, the presence, intensity, duration and frequency

Table V - *Treatment choice for haemophilia patients*

Statement, % respondents[a]	Paracetamol	Paracetamol + other analgesic (tramadol, codeine)	Non-selective NSAIDs	COX-2 selective NSAIDs	Opioid: morphine, oxycodone, buprenorphine	Other or NA
Which is your drug of choice for treating acute pain in children?	86.8%	5.7%	1.9%	–	–	5.7%[b]
Which is your drug of choice for treating chronic pain in children?	66.0%	17.0%	7.5%	3.8%	–	5.7%[b]
Which is your drug of choice for treating acute pain in adults?	24.5%	37.7%	5.7%	18.9%	7.5%	5.7%[c]
Which is your drug of choice for treating chronic pain in adults?	5.7%	39.6%	3.8%	41.5%	3.8%	9.4%[d]

COX-2: cyclo-oxygenase-2; NA: not available; NSAID: non-steroidal anti-inflammatory drugs. [a]Number of respondents: 53. [b]NA n=3 (n=2 do not treat paediatric patients; n=1 does not prescribe drugs). [c]Corticosteroid n=1; NA n=2 (n=1 does not treat adult patients; n=1 does not prescribe drugs).
[d]Paracetamol + selective NSAID n=2; depending on aetiology, from physiotherapy to therapy with paracetamol + codeine (usually), acupuncture to control migraine n=1; NA n=2 (n=1 does not treat adult patients; n=1 does not prescribe drugs).

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of pain and analgesic use were regularly assessed at check-ups and when the patient complained of pain[13].

In our survey, responses regarding the availability of validated guidelines on pain management in PWH varied between haemophilia specialists (35.8% agreement). These data are consistent with previous studies; for example, in the EHTSB survey only five centres had institutional, non-haemophilia-specific pain management guidelines[13]. There is little evidence available on the pharmacological pain management of PWH, and clinical practice is largely empirical and varies widely[10,13,18,22,26]. Even the World Federation of Haemophilia guidelines devote limited space to pain management[17], and there are no evidence-based guidelines on pain management in PWH.

There was a wide variation in response to the survey with regard to the presence of pain specialists in the comprehensive care team in daily clinical practice and the need for co-operation with pain specialists. These data, which may be influenced by the availability of pain specialists at the centres, are in line with the literature[13,21,27]. The EHTSB survey found that most centres fail to adopt a comprehensive treatment approach, with only two centres arranging regular consultations with pain specialists, despite most of them having access to a pain consultant (21 centres)[13]. A report from the 14th meeting of the Members of the Zürich Haemophilia Forum also highlights a lack of collaboration with pain specialists among PWH themselves and the HTCs providing their care[21]. Finally, a report of The Knowledge and Attitudes Survey of Bleeding Disorders Providers Regarding Pain (KASBD) of 152 US-based HTCs conducted by Witkop *et al.* in the spring of 2012 advocated for a comprehensive approach utilising multidisciplinary specialists and non-pharmacological therapies as well as pharmacological approaches[27].

In our survey, there was a strong agreement with regards to the need for evaluating pain through a rating scale validated in haemophilia patients. Pain assessment is an essential component of proper care and it is crucial that the pain assessment tools used in clinical trials of PWH be appropriate for the age of the patients[10,14]. Although the importance of having objective tools is recognised, most centres in the EHTSB survey used a verbal description of pain while only eight (36%) used a defined scale, namely a numeric rating or visual analogue scale (VAS)[13]. In a survey conducted in 2015 by Tagliaferri et al. of 44 Italian haemophilia specialists, only 50% reported using a pain rating scale such as a VAS, the Numeric Rating Scale, or, for children, the Wong-Baker Faces[28].

While it is recognised that pain management in PWH should be multidisciplinary[17], the results from our survey highlight that pain is mostly managed by the haemophilia specialists themselves, followed by a physiatrist and a physiotherapist; a pain specialist is involved in only 26.4% of cases. This is consistent with the results from the EHTSB survey[13] and from the US-based National Pain Study (NPS), which was conducted over a 28-month period from 2007 to 2009 in patients with bleeding disorders[15]. In these surveys, 2-7% of cases were managed by a pain specialist or pain centre. In contrast, results of the survey by Tagliaferri *et al.* showed that 61% of the Italian clinicians reported collaborating with other specialists[28].

As to the type of pain usually encountered in PWH, 96.2% of haemophilia specialists agreed on the large prevalence of joint pain. Pain, disability, and reduced quality of life are the long-term effects suffered by the patient with haemophilic arthropathy[13]. Similar data are reported in a study by Rambod *et al.* investigating the assessment and management of pain in children and adolescents with bleeding disorders in the UK and Iran, in which 87.4% of the participants with pain reported joint pain[29]. That study reported that knees and ankles were the most painful joints; a finding which was also reported by van Genderen *et al.* in their survey in 78 adults with severe haemophilia in the Netherlands. They found that the ankle was considered the most painful joint[30].

Our survey showed that most physicians thought that <50% of PWH spontaneously report acute or chronic pain; however, the large majority of physicians report that >50% of PWH are currently receiving medication for pain. This discrepancy indicates that PWH have difficulty spontaneously reporting their pain, which is nonetheless present given that they use analgesic therapy. Similar findings were seen by Tagliaferri *et al.*; in their study, clinicians reported a lower prevalence of patients with pain (46%) compared with 61% of patients reporting pain[28]. This discrepancy was also observed in an online survey of pain perception and management in adolescents and young adults with haemophilia or von Willebrand disease conducted by Lambing et al. which aimed to determine

agreement/disagreement between patients, caregivers and health care providers[24]. The authors suggest that it is possible that patients may self-report pain more frequently in an anonymous survey than during an "official" visit with their health care provider, leading to some of the noted misperceptions[24].

Because the systematic evaluation of pharmacological therapies for chronic pain in PWH is limited, the recommended approach to analgesia has been extrapolated from guidance for other forms of chronic pain, with adaptations to limit any increased risk of bleeding or other complications specific to this population; this is based on the World Health Organization's Analgesic Ladder[31]. While this approach has not been validated in the haemophilia population, the typical first-line therapy for chronic pain consists of a non-opioid analgesic medication such as paracetamol or an NSAID. In our survey, the combination of paracetamol with tramadol or codeine was the most frequent first option for both acute and chronic pain in adults (37.7% and 39.6%, respectively). The use of COX-2 inhibitors was more frequent in chronic pain, whereas NSAIDs and opioids were less frequently used in this setting. The results of our survey are in line with the EHTSB survey, where the combination of paracetamol or NSAIDs with a weak opioid was the preferred option for acute pain and the use of COX-2 inhibitors was preferred in young adults with chronic pain[13]. In contrast, in the survey conducted by Tagliaferri *et al.*, paracetamol was prescribed as first-line therapy in adults by 89% of clinicians, NSAIDs by 7%, and COX-2 inhibitors by 4%[28]. The differences seen between our survey and that of Tagliaferri *et al.* may be due to very recent improvements in pain management in clinical practice, with the use of weak opioids and COX-2 inhibitors as a first-line approach. Other research, including two reports of the NPS study[15,16] and a retrospective study conducted by Wang *et al.*[32] using data from a single haemophilia centre in Canada, all showed that different pharmacological strategies for pain management are commonly utilised in PWH, with the most commonly used medications being similar to those seen in our survey. Furthermore, in the Wang *et al.* study, most patients were using more than one form of pain relief[32].

Only a limited number of studies investigating pain in children and adolescents with inherited bleeding disorders have been conducted, despite DeKoven *et al.* noting that children's pain is one of the biggest problems parents have to deal with and constitutes a significant burden[33]. In our survey, paracetamol was the first choice for acute (86.8%) and chronic (66%) pain in children. The combination of paracetamol with tramadol, codeine or NSAIDs was not commonly used, and COX-2 inhibitors and opioids were not used as a first choice. Like in adult populations, different pharmacological strategies for pain management are also commonly used in paediatric PWH. In the EHTSB survey, paracetamol was the preferred first-line treatment for children with acute pain, while paracetamol or NSAIDs were the preferred first-line treatment for chronic pain. Beyond first-line treatment, there was little consensus on pain management[13]. In a study conducted by Rambod *et al.* in 154 children and adolescents with a bleeding disorder, 20.8% experienced pain. The most frequently used pain management strategies in children and adolescents were administration of clotting factor and rest[29]. Finally, in a study conducted by Lambing *et al.* in 89 adolescent or young adult PWH (age 13-25 years), the most common medications used for acute pain were coagulation factor concentrates and acetaminophen and, for chronic pain, coagulation factor concentrates and NSAIDs. More patients than providers reported using opioids for chronic pain: 21% of patients and 13% of providers reported using short-acting opioids, while 11% and 6%, respectively, reported using long-acting opioids[24].

Interestingly, 81.1% of the haemophilia specialists involved in our study judged the level of pain management as adequate, whereas only 18.9% rated it as "poor". In our survey, we cannot compare these results with the patients' point of view. Several other studies have demonstrated that patients are not satisfied with their pain control. In a report of the NPS, 39% of PWH reported that their pain was insufficiently treated and over 50% see their HTC providers for pain management[15]. The KASBD noted knowledge deficits in pharmacology and highlighted that it is vital for HTCs to have adequate education on pain management in PWH. It also advised that HTCs recognise their limitations and consult with pain specialists when needed[27].

CONCLUSIONS

This survey provides a picture of the management and

perception of pain among Italian haemophilia specialists. The limitations of this study could be the fact that it does not explore the patients' point of view and that specific questions about the use of non-pharmacological approaches to pain (prophylaxis, physiotherapy) are lacking. However, it has identified some unmet needs for haemophilia specialists, such as evidence-based guidelines. Chronic pain can heavily affect the patients' quality of life. Therefore, it is important that haemophilia specialists as well as referring physicians are increasingly involved in all aspects of pain management, including involving a pain specialist, physiatrist and physiotherapist in the comprehensive management of pain. Moreover, it is recommended always to ask patients about any pain they may experience and to listen carefully when they report symptoms.

As a further development, the survey results provided the basis for the study group to define the statements for a Delphi consensus survey, with the objective of developing guidelines for pain management in PWH for Italian HTCs.

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ETHICAL APPROVAL

Because this study was based on a survey of pain assessment and management in Italian Haemophilia Centers, no Ethical committee approval was needed.

INFORMED CONSENT

The participants to the survey were haemophilia specialists. No patients were involved and individual patient data were not discussed, therefore, written informed consent was not needed.

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AUTHORSHIP CONTRIBUTIONS

MNDDM and CS contributed equally to this study. All Authors contributed to study design, read and approved drafts. MNDDM, CS, and BA performed the analyses. MNDDM, CM and CS drafted the manuscript and made critical revisions.

DISCLOSURE OF CONFLICTS OF INTEREST

MNDDM has received grants and honoraria from Bayer, Pfizer, Sobi, and Novo Nordisk. CS has acted as a paid consultant to Bayer, Shire, Pfizer, Sobi, Novo Nordisk, Roche, Novartis, and Amgen. GDM has acted as a paid consultant to Novo Nordisk, Pfizer, Kedrion, Bayer, CSL Behring, and Roche. MEM has acted as a paid consultant to Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Sobi/Biogen, Bioverativ, Roche, Octapharma, Grifols, and Kedrion. ACM has acted as a paid consultant to Bayer, CSL, Kedrion, Novo Nordisk, Pfizer, Roche, Shire, and Sobi, and as a paid invited speaker for Bayer, CSL, Novo Nordisk, Shire, and Sobi. AR has acted as a paid consultant to Bayer, CSL Behring, Kedrion, Shire, Novo Nordisk, Pfizer, Sobi, and Roche, and as a paid invited speaker for the same companies. RCS has acted as a paid consultant to Bayer, Shire, Sobi, Roche, and CSL Behring. AT has acted as a member of advisory boards for Bayer, Novo Nordisk, and Roche, and as a paid invited speaker for Novo Nordisk. CM has acted as a paid consultant to Sobi, Merck, Sandoz, and Grünenthal. The other Authors report no conflicts of interest.

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APPENDIX 1: HAEMODOL STUDY GROUP

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