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Results of an Italian Delphi poll to assess consensus on pain management in hemophilia

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INTRODUCTION

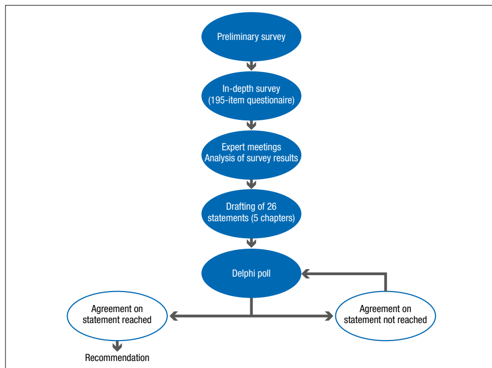
Chronic joint pain and pain flares are a major problem for persons with hemophilia (PwH). This study aimed at assessing consensus among Italian hemophilia specialists on the management of pain in PwH.

METHODS

- Following preliminary and in-depth surveys a Delphi poll (26 statements) on the therapeutic approach to pain in hemophilia was conducted among 61 specialists at 35 Italian hemophilia centres (**Figure**).
- *Agreement* on each statement was defined as 80% of ratings falling within one of the three 3-point regions of a 9-point Likert scale (1-3, 4-6, or 7-9). *Disagreement* was defined as 90% of ratings falling within one of the two extra wide regions (1-6 or 4-9).

Practical recommendations were drafted based on the poll results.

Figure. Main steps of the Haemodol Project.



RESULTS

Fifty-two/61 clinicians (85%) answered the 1st Delphi round, 51 the 2nd, and 51 the 3rd. Chapter-specific poll results indicate that:

- Clinicians should explore pain at each visit using specific quantitative scales.
- Paracetamol represents the first-line therapy for acute and chronic pain in adults and children with hemophilia. For both populations the management of flares is mainly based on steroids or non-steroidal anti-inflammatory drugs (NSAIDs) in association with paracetamol.
- Physiotherapy has an important role in the control of chronic pain.

Chapter-specific statements and poll results are reported in the following tables.

Chapter	Pain assessment and quality of life	Result
Investigate pain as a symptom	*Clinicians at hemophilia centers must investigate pain at every consultation with hemophilic patients.*	***Agreement***
Pain assessment	*Pain assessment must be carried out by using quantitative scales validated for adults (NRS or VAS) and children (Wong-Baker or FLACC Scale). For each determination, report the finding in the patient's notes specifying the scale used, so as to be able to monitor changes in the symptom.*	***Agreement***
Pain assessment	*When assessing pain it is important to distinguish between nociceptive and neuropathic pain by using the questionnaire for neuropathic pain (Pain Detect).*	***Agreement***
Pain assessment	*When assessing pain it is important to distinguish between acute and chronic pain.*	***Agreement***
Pain assessment	*In chronic pain a distinction must be made between pain perceived in a continuous and persistent manner and pain caused by flares. In the case of flares, it is necessary to measure the intensity of the pain and record its frequency and duration.*	***Agreement***
Monitoring pain as a symptom	*To monitor the frequency of pain onset, the data on the bleeding episodes contained in the infusion logs should be integrated with the data on chronic pain and episodes of acute pain, on the intensity of such episodes and the use of pain relieving drugs, if used.*	***Agreement***
Quality of life evaluation	*It is important to evaluate the impact of pain on the patient's quality of life at each check-up or in the case of significant changes in the patient's clinical condition or therapy, using the EQ-5D-5L questionnaire (Euro-QoL).*	***Reformulation and Agreement after Round three***

Chapter	ADULT PwH – ACUTE pain	Result
ADULT patient – ACUTE pain	*The non-pharmacological treatment of acute joint or muscle pain is based on limiting (not completely blocking) movement and load in the first 1-2 days after symptom onset. The application of ice (or in any case cooling of the affected area) for 10-15 minutes several times a day for the first 1-2 days after symptom onset is also indicated, provided that the ice is not applied in direct contact with the skin.*	***Agreement***
ADULT patient – ACUTE pain	*Within non-pharmacological interventions, in severe hemarthrosis of the large joints in the adult patient it may be useful to perform arthrocentesis within the first hours from the onset of the acute pain.*	***Aggregation of opinions in region 7-9 equal to 47.1%***
ADULT patient – ACUTE pain	*The pharmacological treatment of first choice for pain due to acute hemarthrosis and/or muscle hematoma in the adult patient is oral paracetamol at an effective analgesic dose of 1,000 mg every 8 hours. This should be combined with an opioid if the pain is severe (NRS>7) or there is no therapeutic response within 4 hours.*	***Agreement***
ADULT patient – ACUTE pain	*In the event of pain due to acute hemarthrosis and/or muscle hematoma in the adult patient, both oral NSAIDs + PPI and COXIB may be used for short periods as a first-line pharmacological treatment, in cases in which paracetamol is contraindicated or ineffective.*	***Agreement***
ADULT patient – ACUTE pain	*The second-line pharmacological treatment of acute pain due to hemarthrosis and/or muscle hematoma in the adult patient is paracetamol or NSAID, in combination with tramadol or codeine.*	***Aggregation of opinions in region 7-9 equal to 60.0%***
ADULT patient – ACUTE pain	*In the event of unsatisfactory pain control with the second-line therapy (paracetamol or NSAID, in combination with tramadol or codeine), pain due to acute hemarthrosis and/or muscle hematoma in the adult patient may be managed with third-line opioids (oxycodone, tapentadol).*	***Agreement***

Chapter	ADULT PwH – CHRONIC pain	Result
ADULT patient - CHRONIC pain	*The non-pharmacological treatment of chronic joint or muscle pain (and/or peripheral neurological pain) in the adult patient consists of physical therapy (land- and water-based exercise therapy) prescribed by the Physiatrist and/or Orthopedic surgeon.*	***Agreement***
ADULT patient - CHRONIC pain	*In the event of chronic arthropathic pain in the adult patient, the first-line treatment is oral paracetamol at a dose of 1,000 mg every 8 hours or the combination of paracetamol and tramadol or an opioid other than tramadol (codeine or buprenorphine).*	***Agreement***
ADULT patient - CHRONIC pain	*In the event of chronic arthropathic pain in the adult patient, both oral NSAIDs + PPI and COXIBs may be used as a first-line pharmacological treatment, for short periods due to their side effects, in cases in which paracetamol is contraindicated or ineffective.*	***Aggregation of opinions in region 7-9 equal to 54.9%***
ADULT patient - CHRONIC pain	*When planning the first-line pharmacological treatment of chronic arthropathic pain in the adult, oral cortisone or oral NSAIDs or COXIBs may be used for short periods as anti-inflammatories in combination with paracetamol in the event of flares.*	***Agreement***
ADULT patient - CHRONIC pain	*The second-line pharmacological treatment of chronic arthropathic pain recommended for the adult patients is paracetamol or NSAIDs in combination with tramadol or an opioid other than tramadol (codeine or buprenorphine).*	***Aggregation of opinions in region 7-9 equal to 64.7%***
ADULT patient - CHRONIC pain	*In the adult patient, in the event of chronic arthropathic pain negatively affecting quality of life and refractory to second-line treatment (paracetamol or oral NSAIDs or COXIBs in combination with tramadol or an opioid other than tramadol – codeine or buprenorphine) other opioids may be used as a third-line strategy (fentanyl, oxycodone, tapentadol).*	***Agreement***

Chapter	PEDIATRIC PwH –ACUTE pain	Result
PEDIATRIC patient - ACUTE pain	*The non-pharmacological treatment of acute pain due to hemarthrosis or hematoma, whether spontaneous or traumatic, in children consists of the application of ice (or in any case cooling of the affected area) for 10-15 minutes several times a day for the first 1-2 days after symptom onset, provided that the ice is not applied in direct contact with the skin.*	***Agreement***
PEDIATRIC patient - ACUTE pain	*In acute pain due to hemarthrosis and/or hematoma in children, the first-line pharmacological treatment is oral paracetamol at a dose appropriate for the child's weight (15 mg/kg) every 8 hours. For children weighing > 26 kg the dose is 500 mg every 8 hours.*	***Agreement***
PEDIATRIC patient - ACUTE pain	*In planning first-line pharmacological therapy for acute pain due to hemarthrosis and/or hematoma in children, oral cortisone or NSAIDs may be prescribed in combination with paracetamol.*	***Aggregation of opinions in region 7-9 equal to 61.2%***

Chapter	PEDIATRIC PwH –CHRONIC pain	Result
PEDIATRIC patient - CHRONIC pain	*Non-pharmacological treatment of chronic pain in children consists of physical therapy (land- and water-based exercise therapy) prescribed by the Physiatrist and/or Orthopedic surgeon, to be initiated as soon as possible.*	***Agreement***
PEDIATRIC patient - CHRONIC pain	*In the event of chronic arthropathic pain in children, the first-line treatment is oral paracetamol at a dose appropriate for the child's weight (15 mg/kg) every 8 hours. For children weighing > 26 kg the dose is 500 mg every 8 hours*	***Agreement***
PEDIATRIC patient - CHRONIC pain	*In the first-line pharmacological treatment of flares of chronic arthropathic pain in a child receiving prophylaxis, cortisone may be used for short periods in combination with paracetamol.*	***Reformulation* Aggregation of opinions in region 7-9 equal to 68.1%***
PEDIATRIC patient - CHRONIC pain	*In the first-line pharmacological treatment of flares of chronic arthropathic pain in a child receiving prophylaxis, an oral NSAID (ibuprofen) may be used for short periods in combination with paracetamol.*	***Reformulation* Aggregation of opinions in region 7-9 equal to 42.6%***
PEDIATRIC patient - CHRONIC pain	*If the first-line strategies prove ineffective, in the pharmacological treatment of chronic arthropathic pain in a child receiving prophylaxis it is possible to use, as a second-line strategy, tramadol in addition to paracetamol.*	***Reformulation* Aggregation of opinions in region 7-9 equal to 50.0%***
PEDIATRIC patient - CHRONIC pain	*If the first-line strategies prove ineffective, in the pharmacological treatment of chronic arthropathic pain in a child over the age of 12 years receiving prophylaxis it is possible to use the combination of paracetamol and codeine as a second-line strategy.*	***Reformulation* Aggregation of opinions in region 7-9 equal to 70.2%***

** The 4 reformulated Statements are based on the original formulation of the 2 following statements:*

PEDIATRIC patient - CHRONIC pain	*In planning the first-line pharmacological treatment, in the event of flares of chronic arthropathic pain in children, oral cortisone or NSAIDs (ibuprofen) may be used as anti-inflammatories for short periods in combination with paracetamol.*
PEDIATRIC patient - CHRONIC pain	*In planning the pharmacological treatment of chronic arthropathic pain in children, in the event that the first-line strategies prove ineffective, tramadol may be used in addition to paracetamol. As an alternative, the combination of paracetamol and codeine is indicated in children aged over 12 years.*

CONCLUSIONS

Pain is still an issue in PwH. Hemophilia treaters have to explore and quantify pain to deliver the best therapy to control it. The constitution of a multidisciplinary team is also important for the correct management of pain.