# Kinesiotaping for the Treatment of Haematomas in Haemophiliacs: a Case Control Study

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## **SUMMARY**

**Introduction.** Intramuscular hemorrhages are the second most common type of bleeding in patients with haemophilia. In haemophilic patients, muscle bleeding causes pain and postural defects and requires a long healing time.

Aim. The purpose of this study is to evaluate the effectiveness of kinesiotaping, in combination with functional rehabilitation and  $\mathrm{CO}_2$  laser therapy, in the healing process of MH in patients with haemophilia.

**Methods.** We recruited 39 haemophilia patients who presented with a muscle hematoma. The patients were divided into 2 groups: treatment group treated with kinesiotaping, functional re-education and  $\rm CO_2$  laser therapy, and a control group treated with functional re-education and  $\rm CO_2$  laser therapy. The evolution of the hematoma was studied ultrasonographically and some evaluation scales (NRS, FISH) were administered

**Results.** The treatment group, compared to the control group, showed significant improvements in terms of: hematoma diameter  $(2.36 \pm 3.32 \ vs \ 6.47 \pm 3.37; \ p < 0.05)$ , hematoma thickness  $(0.08 \pm 0.12 \ vs \ 0.28 \pm 0.14; \ p = 0.08)$ , pain (NRS:  $2 \pm 1.57 \ vs \ 3.53 \pm 1.37; \ p < 0.05)$  and number of days of replacement therapy (n days:  $1.3 \pm 0.48 \ vs \ 3.2 \pm 0.98; \ p < 0.05)$ . These results were shown to be superior in patients on prophylaxis. **Conclusions.** Kinesiotaping, associated with therapeutic exercise and physical therapy, can be a valuable aid in reducing the healing times of muscle hematomas in haemophilic patients, especially if already under prophylaxis.

#### **KEY WORDS**

Blood diseases; haemophilia; kinesiotaping; muscle haematomas; rehabilitation.

# INTRODUCTION

Haemophilia is an inherited disease linked to the X chromosome resulting from a deficiency of factor VII (type A) or factor IX (type B). Based on the serum levels of the corresponding deficiency factor, we can distinguish several forms: mild (< 1%), moderate (1-5%), and severe (> 5%) (1). After joint bleeding, muscle haematoma (MH) is the second

most common type of bleeding in patients with haemophilia

(2-5). In haemophilic patients, MH is more frequently localized in the iliopsoas muscle, in the quadriceps femoris, in the calf and forearm muscles (6).

Unlike hemarthrosis, MH is mostly associated with trauma, it is more common in young and athletic subjects (7). It is known that there is a relationship between hemophilic arthropathy and the tendency to develop MH, as arthropathy leads to muscular and postural imbalances and incorrect

movement patterns which increase the risk of injury, even after minor strains (6).

The development of a MH, often impairs the quality of life of patients, limiting recreational activities due to the fear and/or risk of bleeding (8).

In addition, haematomas often cause pain, fibrous scars, recurrent haematomas, and postural defects, which are related to the extent of bleeding and the tension within the muscle compartment (5).

In haemophilic patients, muscle bleeding requires a longer healing time than haemarthroses, even if the data collected in the literature are quite scant (9).

In these patients, medical treatment of MH generally relies on intravenous infusion of the deficient factor until complete resorption. If not adequately treated, haematomas can lead to irreversible muscle damage, with reduced mobility, loss of function, ossifying myositis, anemia, compartment syndrome, and compression of peripheral nerves requiring urgent surgical decompression (10, 11).

To date, advances in rehabilitation, combined with hemophilia therapy, are focused on the prevention of bleeding and bleeding-related musculoskeletal complications through targeted and specific rehabilitation programs. This allows patients with haemophilia to be more active and to participate in sports (6).

The guidelines of the World Federation of Hemophilia (WFH) on the management of MH indicate that the levels of the deficiency factor should be increased immediately, after-the first symptoms or trauma, maintaining adequate factor levels for approximately 5-7 days. The affected limb must be raised and the muscle immobilized until the pain is resolved. It is necessary to establish a balance between rest, early mobilization and load restoration, to avoid the onset of complications related to prolonged immobilization and the risk of re-bleeding. To relieve pain symptoms, ice packs applied for about 15-20 minutes, several times a day, can be useful. As soon as the painful symptoms are relieved, a rehabilitation program with isometric contractions can be undertaken, followed by concentric exercises based on a symptomatic approach (12).

The effectiveness of physical therapy in the healing process of MH has recently been evaluated in  $ad\ hoc$  studies (13-15). Among these,  $\mathrm{CO}_2$  laser therapy has resulted effective and well tolerated in subjects with haemophilia. The  $\mathrm{CO}_2$  laser is a non-invasive means, which has an anti-inflammat ry and anti-edema action. It actives biological mechanisms that increase blood circulation through a process that allows oxygen and nutrient-rich blood to flow to the target tissue area and improve mitochondrial oxidative metabolism (13). The Kinesiotaping (KT) technique is an innovative technique that guarantees a rapid and decisive result in the resorption

of the hematoma. It consists of the application of adhesive bandages in the site of the hematoma. Skin stimulation by KT determines greater recruitment of motor units and neuromuscular spindles with a consequent improvement in muscle strength and muscle tone (14, 15). It also determines an increase in blood flow and an increase in interstitial spaces, favoring vascular and lymphatic drainage (16). Finally, by decreasing the pressure on the subcutaneous nociceptors, it modulates the intensity of muscle pain by reducing it (17, 18). The purpose of this study is to evaluate the effectiveness of kinesiotaping, in combination with functional rehabilitation and CO<sub>2</sub> laser therapy, in the healing process of MH in patients with haemophilia.

# **MATERIALS AND METHODS**

At the Rehabilitation Department of the Polyclinic Paolo Giaccone hospital in Palermo, in collaboration with the Hematology unit of the same hospital, a single-center randomized control case study was conducted in the period between April 2020 and April 2021.

The study was approved by the Medical Ethics Committee of the University Hospital of Palermo, Italy (n° 3/2020); written informed consent was obtained from each patient by the Declaration of Helsinki.

The inclusion criteria were: age ≥ 18 years; diagnosis of type A or B haemophilia (mild, moderate and severe); the presence of symptomatic and/or asymptomatic superficial MH assessed during the initial physiatric evaluation; absence of signs of nervous and/or vascular compromise; prophylactic or on-demand replacement treatment for haemophilia; written declaration of consent for participation in the study. The exclusion criteria were: altered states of consciousness and the presence of permanent deformity and/or stiffness. A total of 54 haemophilic patients with muscle hematomas were sent, within 24 hours of observation by the haematologist, to the Rehabilitation unit to undertake a rehabilitation process. Of these, only 39 patients met the inclusion criteria and were deemed eligible to participate in the study. Through a randomized randomization process, using a computer-generated random number table, the patients were assigned to two groups: 22 patients were assigned to the "Treatment Group" (TG) and underwent a 10-session rehabilitation protocol, consisting of functional rehabilitation, CO, laser therapy, and application of kinesiotaping at the hematoma site; and 17 patients were assigned to the "Control Group" (CG) and underwent a 10-session rehabilitation protocol consisting of functional rehabilitation and CO<sub>2</sub> laser.

Enrolled patients were evaluated at baseline  $(T_0)$  and at the end of the 10 rehabilitation sessions, through a clinical evaluation by a physiatrist with the evaluation of demographic

characteristics and administration of evaluation scales, such

as NRS (19) and FISH (20). All patients finally underwent ultrasound assessment to confirm the diagnosis of MH and exclude another contemporary bleeding (e.g., in the retroperitoneal space, iliac cavity, anterior abdominal wall, and hip joint). The ultrasound examination was performed by a physiatrist with decades of experience in the musculoskeletal field. Initial images were obtained with a 7-10 MHz linear array probe in two planes. The haematoma area was scanned from end to end to identify the deepest part and still images of this region were saved. Ultrasound evidence of a haematoma was defined as hypoechoic or anechoic changes within the subcutaneous tissue or muscle. The diameter and depth of the haematomas were all expressed in centimeters (cm). The rehabilitation program took place in 20 sessions (from Monday to Friday) lasting 60 minutes, performed on an outpatient basis in the hospital, and had the following objectives: to resolve the hematoma, to recover/maintain range of motion, to recover/maintain strength muscle, to prevent joint deformity, to improve posture and gait. In particular, it included joint mobilization exercises, including traction, and muscle stretching. Both methods are low-load maneuvers that allow you to maintain or restore tissue (muscles and tendons), promoting correct joint movement. Muscle strength recovery was accomplished through the initial performance of isometric exercises, followed by low-load, high-repetition exercises. Having obtained good muscle control and initial recovery, we proceeded with the execution of exercises first with an open kinetic chain and then with a closed kinetic chain, followed by concentric and finally eccentric exercises. To these was also associated a proprioceptive re-education, through oscillating tables, irregular surfaces, and visual biofeedback for the recovery of the execution of the specific gesture, as well as a global postural re-education, to improve load distribution (21, 22). The lasertherapy sessions were carried out using Opton 8000 scanning laser (Mectronic Medical S.r.l., Italy), under the supervision of an expert physiotherapist. The sessions were performed at the end of each functional re-education session. Every single session lasted about 10 minutes, with a wavelength used of 10,600 nm, an emission frequency of 1-200 Hz, and a maximum power of 20 W. During the application of laser therapy, the physiotherapist and the patient wore protective goggles.

All the KT tape bonding procedures were performed by a physiotherapist, in possession of the K-Taping certificate. K-Active Tape Classic, 50 mm × 17 m (NittoDenko Corporation, Japan) was used. These are elastic adhesive tapes 5 cm wide, made of 100% cotton, and covered with hypoallergenic acrylic glue applied for 3 days with the technique lymphatic drainage. The applications were carried out at the

end of each rehabilitation session. Before applying the tape, the skin was cleaned, freed from moisture and grease, and, if necessary, shaved. The length of the tape was measured individually, based on the affected muscle district. The tape application procedure began with the formation of an anchor at the root of the limb, above the relevant regional lymph node stations. Further strips were attached sequentially along with the lymphatic collectors in the direction of lymphatic drainage, taking care not to create excessive tension (figure 1).

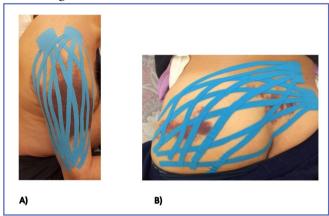


Figure 1. Technique lymphatic drainage of kinesiotaping.

Finally, a health worker took a photograph of the muscle haematoma at  $T_0$  and  $T_1$ , in order to visually show its progress.

We used the NRS scale for pain assessment. This is a quantitative rating scale by which patients are asked to rate their pain on a defined scale, from 0 to 1 (19).

The FISH scale is a valid and reliable tool for assessing the autonomy of a patient with haemophilia in carrying out activities of daily living (ADL) including self-care and transfers. Each activity is assigned a score from 1 to 4, based on the level of independence and assistance required. The score ranges from 8 to 32, where higher scores indicate a better ability to perform ADL (20).

The primary endpoints evaluated were: the resolution of the haematoma, in terms of diameter and thickness, and the reduction of pain associated with haematoma.

The secondary endpoints were: the trend of the FISH scale and the number of days of treatment with coagulation Factor VIII or IX during the acute phase of the haematoma.

## Statistical analysis

The data obtained were indexed on an Excel sheet and the subsequent statistical analysis was performed using the R

software (R Foundation for Statistical Computing, Vienna, Austria). The descriptive analysis was performed based on the mean and standard deviation. For the statistical modeling we used the classic linear regression model to evaluate the effect net of any confounding variables. P-values < 0.05 were considered statistically significant

### **RESULTS**

The general characteristics of the patients, 39 male subjects, of mean age of  $37.13 \pm 13.51$  years, are summarized in **table** I. No statistically significant differences were noted between the two groups at baseline between the collected data.

The mean diameter of the haematomas was  $15.33 \pm 6.9$  cm, and the mean thickness of  $0.49 \pm 0.25$  cm. Patients reported an average pain of  $5.13 \pm 1.38$ , according to the NRS scale (**table II**). All patients had at least one MH at the time of the initial clinical evaluation. 6 (15.4%) patients had three MH at the time of initial clinical evaluation, 19 (48.7%) had two, and 14 (35.9%) patients had only one. The most common muscle localization of the haematoma was represented by

the quadriceps femoris (23.1%), forearm muscles (20.5%), calf (15.5%), deltoid (12.8%), hand muscles (10.2%), biceps brachialis (7.7%), gluteus maximus (7.7%) and large pectoral (2.5%).

**Figure 2** shows the evolution of hematomas from  $T_0$  to  $T_1$ , following treatment (**figure 2**).

The differences in the outcomes of the variables analyzed between the treatment group and the control group at  $T_1$  are shown in **table III**.

Regarding the diameter of the haematoma, at  $T_1$  we demonstrated a significant improvement in the treatment group compared to the control group (2.36  $\pm$  3.32 vs 6.47  $\pm$  3.37; p < 0.05) (**table III**).

The thickness of the haematoma at  $T_1$  also showed a significant improvement in the treatment group compared to the control group (0.08  $\pm$  0.12 vs 0.28  $\pm$  0.14; p = 0.08) (table III).

A significant improvement was also demonstrated in the extent of pain associated with haematoma in the treatment group compared to the control group  $(2.00 \pm 1.57 \text{ } vs \text{ } 3.53 \pm 1.37; p < 0.05)$  (table III).

Table I. Characteristics patients at baseline.

Characteristics	Total (n = 39)	Treatment Group (n = 22)	Control Group (n = 17)	P-value
Age, mean (%)	$37.1 \pm 13.5$	$38.4 \pm 14.2$	$35.4 \pm 13.3$	0.50
Gender, n (%)				
Men	39 (100)	22 (100)	17 (100)	0.99
Woman	0 (0)	0 (0)	0 (0)	
Diagnosis of Emophilia, n (%)				
Type A	34 (87.2)	19 (98.4)	15 (88.2)	0.24
Type B	5 (12.8)	3 (9.1)	2 (11.8)	
Severity forms, n (%)				
Mild	11 (28.2)	7 (31.8)	4 (23.6)	
Moderate	4 (10.2)	2 (9.1)	2 (11.7)	0.52
Severe	24 (61.6)	13 (59.1)	11 (64.7)	
Type of Treatment, n (%)				
Prophylaxis	23 (58.9)	12 (54.5)	11 (64.7)	0.36
On Demand	16 (41.1)	10 (45.5)	6 (35.3)	
Sport, n (%)				
Yes	20 (51.3)	12 (54.5)	8 (47.1)	0.28
No	19 (48.7)	10 (45.5)	9 (52.9)	
Hystory of emarthrosis, n (%)				
Yes	17 (43.6)	9 (40.9)	9 (52.9)	0.81
No	22 (56.4)	13 (59.1)	8 (47.1)	
Arthropathy, n (%)				
Yes	23 (58.9)	13 (59.1)	10 (58.8)	0.67
No	16 (41.1)	9 (40.9)	7 (41.2)	
FISH, mean ± SD	$29.8 \pm 6.4$	$28.8 \pm 5.6$	29.3 ± 6.1	0.79

Table II.	Characteristics	of	hematomas	at baseline
Table II.	Characteristics	OT	nematomas	at paseline

Characteristics	Total (n = 39)	Treatment Group (n = 22)	Control Group (n = 17)	P-value
Diameter, mean ± SD	$15.3 \pm 6.9$	$17.8 \pm 7.6$	$13.8 \pm 7.1$	0.10
Depth, mean ± SD	$0.49 \pm 0.25$	$0.59 \pm 0.28$	$0.43 \pm 0.31$	0.09
NRS, mean ± SD	$5.13 \pm 1.38$	5.21 ± 1.5	$5.13 \pm 1.25$	0.86
Muscle localization, n (%)				0.31
Quadriceps femoris	9 (23.1)	5 (22.7)	4 (23.5)	
Forearm	8 (20.5)	5 (22.7)	3 (17.7)	
Calf	6 (15.5)	3 (13.7)	3 (17.7)	
Deltoid	5 (12.8)	2 (9.1)	3 (17.7)	
Hand	4 (10.2)	2 (9.1)	2 (11.6)	
Biceps brachialis	3 (7.7)	2 (9.1)	1 (5.9)	
Gluteus maximus	3 (7.7)	2 (9.1)	1 (5.9)	
Large pectoral	1 (2.5)	1 (4.5)	0 (0)	



Figure 2. Muscle haematoma evolution after kinesiotaping application.

Finally, no statistically significant difference in FISH scores at  $T_1$  was noted between the treatment group and the control group (28.3  $\pm$  2.31 vs 27.7  $\pm$  1.88; p = 0.40) (table III).

Analysing the number of days of treatment with recombinant Factor VIII or IX during the acute phase of the

haematoma, we observed a significant reduction in the number of days of taking recombinant Factor VIII or IX in the treatment group compared to the control group (n days:  $1.3 \pm 0.48 \ vs \ 3.2 \pm 0.98$ ; p < 0.05) (table III).

**Table IV** shows, within the treatment group, the differences in the outcomes of the variables analyzed between patients in prophylactic therapy and those in on-demand therapy (table IV).

Patients in the treatment group in prophylactic therapy were 12, while those in on-demand therapy were 10. It was observed that patients belonging to the treatment group undergoing prophylactic therapy, compared to those undergoing on-demand therapy, showed greater benefit both in terms of diameter (1.2  $\pm$  0.7 vs 5.2  $\pm$  3.05; p < 0.05), and in thickness (0.09  $\pm$  0.10 vs 0.17  $\pm$  0.12; p = 0.12) and both for the FISH scale score (28.9  $\pm$  1.14 vs 27.2  $\pm$  2.34; p < 0.05) (table IV).

However, the improvement in pain appeared to show no significant differences in patients on prophylactic therapy compared to those on on-demand therapy (2.17  $\pm$  1.47 vs 1.8  $\pm$  1.75; p = 0.42) (table IV).

# **DISCUSSION**

Even today there is no standardized treatment protocol for the most appropriate management of MH in patients with haemophilia. This could be due to the lack of knowledge of the signs indicating that the bleeding has stopped and the scant data on treatment of MH in patients with haemophilia (5).

This study aimed to evaluate the clinical effectiveness of kinesiotaping associated with therapeutic exercise and CO<sub>2</sub> laser therapy in the healing process of muscle hema-

< 0.05

0.40

the control gloup.				
Characteristics (n = 39)	Treatment Group (n = 22)	Control Group (n = 17)	P-value	
Diameter	$2.36 \pm 3.32$	$6.47 \pm 3.37$	< 0.05	
Depth	$0.08 \pm 0.12$	$0.28 \pm 0.14$	0.08	
VAS	2 ± 1.57	$3.53 \pm 1.37$	< 0.05	

 $3.2 \pm 0.98$ 

 $27.7 \pm 1.88$ 

**Table III.** Effects of treatment with kinesiotaping, laser therapy and therapeutic exercise in the treatment group compared to the control group.

Table IV. Treatment group: differences between patients in prophylactic therapy and patients in on-demand therapy.

Characteristics (n = 22)	Prophylactic Therapy (n = 12)	On-demand Therapy (n = 10)	P-value
Diameter	$1.2 \pm 0.7$	$5.2 \pm 3.05$	< 0.05
Depth	$0.09 \pm 0.10$	$0.17 \pm 0.12$	0.12
NRS	$2.17 \pm 1.47$	$1.8 \pm 1.75$	0.42
FISH	$28.9 \pm 1.14$	$27.2 \pm 2.34$	< 0.05

tomas in patients suffering from haemophilia, to increase knowledge in the rehabilitation field

 $1.3 \pm 0.48$ 

 $28.3 \pm 2.31$ 

Number of days of treatment

with F-VIII FISH

MH is common in people with haemophilia it occurs in 10-23% of cases and can cause irreversible clinical consequences and psychosocial problems (5, 6). The potential long-term consequences of MH in haemophilia (myositis ossifying, abscess, pseudotumor, chronic nerve injury) are serious and disabling (6).

It, therefore, appears clear the importance of preventing and managing these haematomas, to improve the clinical conditions of patients.

The results of our study showed how the synergy between instrumental physical therapy ( $\mathrm{CO}_2$  laser therapy), kinesiotaping, and therapeutic exercise represents an effective therapeutic strategy in the resolution of MH, in terms of diameter and thickness, allowing to avoid possible complications. At the end of the 10 rehabilitation sessions provided, the pain associated with haematomas also showed a clear reduction in pain, reducing the burden of the disease on patients.

Often these haematomas cause severe pain due to the increase of muscle tension, with consequent functional limitation and significant negative psychological impact. Furthermore, as a consequence of the accumulation of polymorphonuclear cells and mononuclear phagocytosis, fibrous repair tissue is formed with progressive mechanical reduction of muscle function and consequent limitation of normal joint function (5).

Over the years, attention has increased on the psychosocial problems of haemophilic patients following a bleeding

episode. Participation in physical activities in haemophilic adults and children is often complicated by the risk of developing haematomas with a tendency to avoid physical activity (7, 8). Study B-HERO-S (23) found a negative impact on participation in recreational activities, regardless of the severity of haemophilia. The main reasons for the interruption of activities were fear/risk of bleeding or contact bleeding.

Our rehabilitation protocol aims to interrupt the vicious circle of haematomas-hemarthrosis and its related complications that distinguish this setting of patients. A history of arthropathy was present in about 60% of the patients examined, reflecting the high frequency of joint involvement in haemophilic patients. This supports the relationship between arthropathy and the tendency to develop MH (6). In the literature, the protocol for the management of MH in patients with haemophilia is based on the combination of rehabilitation and replacement therapy (6).

Hematological therapy is carried out with infusion of recombinant coagulation factors deficient at 50-70% of normal during the first 5-7 days and subsequent infusion with lower doses until complete recovery (5). In our study, it was observed that the adopted protocol was able to reduce the number of days of treatment with the recombinant deficient factor during the acute phase

The rehabilitation of MH, through therapeutic exercise and the use of physical therapy, is useful in accelerating the hematoma healing process in haemophilic patients. It aims to control the joint and restore ROM, strength and normal physical performance (24, 25).

Potential benefits of physical activity for people with haemophilia include reduced joint pain and increased muscle strength and joint flexibilit, as well as psychological benefits such as decreased anxiety and improved self-esteem and social interactions (8).

After the acute phase, therapeutic exercise should be introduced, to prevent joint blockages and counteract hypotonotrophy, weakness, and muscle retractions typical of these patients. An aspect that should not be underestimated is the prevention of MH. Adequate overall physical performance helps reduce the risk of exercise-related muscle injury as deficits in muscle strength can increase the risk of muscle bleeding during physical activities. Accordingly, it is essential to perform tailored physical exercise in order to increase muscle power through resistance training (26).

De Martis *et al.* conducted a pilot study to evaluate the safety, efficac, and tolerability of laser therapy in hemophilic patients with chronic arthropathy. The laser treatment showed a significant analgesic effect, allowing rapid pain control to be achieved after only a few applications. The results obtained by them allow us to consider laser therapy as a possible alternative to painkiller drugs, due to its analgesic effect (27). Also in our study, laser therapy showed high safety and tolerability (no adverse reactions were registered in treated patients).

In patients with haemophilia, deficient coagulation factor prophylaxis is the standard of care for the treatment and prevention of bleeding episodes and in surgery (12). Several studies have shown that replacement therapy offered in prophylactic form offers the best results for the patient, in terms of joint health, improvement of quality of life, and reduction of bleeding episodes, compared to on-demand treatment at any age. However, adherence to continuous intravenous therapy with the deficient factor is challenging and requires good patient compliance, with the possibility of breakthrough bleeding during prophylaxis (28-31).

The results of our study appear to be in line with the data in the literature. In our study, patients undergoing our rehabilitation on prophylaxis showed better results, in terms of size and thickness, than patients in on-demand treatment. Moreover, in patients undergoing prophylactic treatment with the deficient recombinant factor, our rehabilitation protocol resulted in an improvement in the performance of daily life activities.

At our knowledge, this is the first case-control study to evaluate the effectiveness of the combination of func-

tional rehabilitation, physical therapy, and kinesiotaping, compared to standard rehabilitation treatment, in the healing process of MH in patients with haemophilia. However, our study is not without limitations. Primarily, the small sample of patients, due to the rarity of the disease and the difficulty in identifying subjects who met our inclusion criteria, doesn't allow us to generalize the obtained results. A further limitation of our study was the failure to evaluate the protective effect of therapeutic exercise on the prevention of muscle hematomas. This is due to the lack of long-term follow-up investigating this effect.

## **CONCLUSIONS**

Despite the advances in haematology and rehabilitation, the management of MH in patients with haemophilia is still matter of debate, due to the long period required for their resolution.

Kinesiotaping, associated with therapeutic exercise and physical therapy, can be a valuable aid in accelerating the healing process of MH in haemophilic patients, especially if they are on prophylactic therapy.

This opens up new scenarios in the prognosis of these patients, strengthening the role of rehabilitation in the management of these patients.

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None.

#### DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

## **CONTRIBUTIONS**

FV: conceptualization, investigation and writing - original draft preparation. DS: methodology and writing - review and editing. GLM: validation. GP: formal analysis. GP and FA: resources. MN and MV: data curation. SS and GLM: supervision. All authors have read and agreed to the published version of the manuscript.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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