Review Article

Effectiveness of Physiotherapy in the improvement of the perception of quality of life in patients with hemophilia.A systematic review.

Abstract

Background. Hemophilia is a hereditary and chronic disease that mainly affects males. It is characterized by a deficiency in one of the specific clotting factors. The main clinical manifestations of hemophilia are orthopedic, as a result of bleeding in the musculoskeletal system, mainly through bleeding episodes in joints and muscles.

Aim.To assess the effectiveness of treatments of physiotherapy for the improvement in the perception of quality of life in patients with hemophilia.

Method. This review has been developed a bibliographic search in different databases: PubMed, PEDro, the Virtual Library of health and Isi Web, and in different journals: *Haemophilia*, *PhysicalTherapy* and *ManualTherapy*.

Results. We found 1091 articles of which only the article meets the inclusion criteria. This article has been passed to 2 scales: Van Tulder and Peter, for the quantitative analysis of scientific evidence.

On the other hand, is a search for 8 descriptive studies for comparison in terms of the little research of experimental studies on this topic.

Conclusions. This review shows the small number of clinical trials that assess the effectiveness of physiotherapy treatment to improve the perception of quality of life in patients with hemophilia. The literature there is no homogeneity in terms of the relationship of the age of the patients and characteristic of hemophilia with the quality of life. It is necessary clinical trials to be able to demonstrate physiotherapy treatments in the improvement of the quality of life in these patients.

Key words: Haemophilia, Arthropathy, Quality of life, Physiotherapy

Introduction

Hemophilia is a hereditary chronic disease that primarily affects males, for a recessive disorder of chromosome X. It is characterized by a deficiency in one of the clotting factors, which hinders the normal cessation of bleeding in these patients (1). There are two types of hemophilia: hemophilia A (where there is a lack of Factor VIII-FVIII) and hemophilia B (deficiency of Factor IX-FIX) (2).

Due to its low incidence, hemophilia is a disease considered rare, affecting approximately 1: 10000 (hemophilia A) and 1: 60000 (hemophilia B) (3).

The main clinical manifestations of hemophilia include bleeding in the musculoskeletal system by bleeding into muscles (hematoma) and joints (haemarthrosis) (2). Over 80% of bleeding in patients with hemophilia occurring in knee ankle and elbow (4).

Haemarthroses appear mainly to trauma, but sometimes they can also be referred spontaneously (5). The successive development of haemarthrosis in the same joint (target joint) is damaging the joint structures, manifested by severe chronic pain and resulting in clinical symptoms of joint degeneration. These degenerative changes leading to bone loss process and functionality, known as hemophilic arthropathy (6).

The final stage of joint damage is the establishment of a degenerative process known as hemophilic arthropathy. This is manifested by pain, loss of range of movement, muscle atrophy and impaired proprioception. The appearance of the first signs of hemophilic arthropathy is common to occur in the first decades of life, due to the susceptibility of articular cartilage to the damage caused by the iron component of blood (7).

The most effective treatment to prevent the recurrent haemarthrosis and hemophilic arthropathy is the regular administration (prophylactic treatment) of FVIII or FIX concentrates (8).

The progressive joint deterioration that occurs by the development of hemophilic arthropathy, makes it necessary for multidisciplinary approach that includes a

medical (prophylactic treatment), surgical (orthopaedic surgery techniques), physiotherapeutic (for functional improvement and delayed functional alterations)and psychosocial (for the effects that this produces functional impairment in psychological, social and labor aspects of these patients) approach (9).

The World Health Organization (WHO) defines physiotherapy as the "art and science of physical treatment of re-education exercise, heat, cold, light, massage and electricity" (10). Physiotherapy, like other health professions, has been developed in different fields finding a wide range of specialist areas such as neurological physiotherapy, orthopaedic, rheumatology, paediatric or geriatric (11).

The primary role of physiotherapy in hemophilia is haemarthrosis the prevention of and physical sequelae the restoration of functionality after acute bleeding episodes, and maintenance of range of motion, muscle strength and periarticular proprioception in cases of deterioration advanced joint (12).

Several studies have evaluated the efficacy of different Physiotherapy techniques in the treatment of hemophilic arthropathy observing significant improvements in range of movement (using techniques hydrotherapy) (13), muscle strength and proprioception (home programs with active exercise) (14, 15) and the perception of joint pain (using manual therapy techniques) (16)

The perception of quality of life (QoL) cannot be an independent assessment and goes with the proportion of welfare of a person in relation to his physical condition, emotional state, family, love, social life and the direction that attributed to his life among other things (17). Have been developed various scales to measure QoL depending on the age of subjects and specific to various diseases (18).

For the evaluation of the perceived quality of life in children and adolescents with hemophilia the Haemo-QoL questionnaire (19) was created. It consists of 8 dimensions (physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). In this questionnaire two different variables are obtained: the QoL depending on physical condition (physical QoL), and depending on psychosocial state (mental QoL).

The QoL may be influenced by factors such as disease and its treatment. In patients with hemophilia, the main factors that negatively influence the perception of QoL are restrictions on physical activities, concern about bleeding, development of hemophilic arthropathy, the need to perform orthopaedic surgical procedures and fear of transmission of infectious diseases (20).

The aim of this review was to assess the effectiveness of Physiotherapy treatments for improving the perceived quality of life in patients with hemophilia. Also seeks to identify what techniques of Physiotherapy produce a greater effect on the psychosocial variable and observe the influence of the physical variables affected by bleeding complications, in the perception of quality of life for patients with hemophilia.

Material and Method

Design of the study

Systematic review, conducted between October and November 2013, with a last update in April 2014.

Documentary sources

We have developed a literature search in different databases in order to identify all articles that describe physiotherapy intervention, using as dependent variable the perception of quality of life in patients with hemophilia.

The databases consulted were: PubMed, PEDro, the Biblioteca Virtual de Salud (BVS) and Isi Web of Knowledge. Similarly, we conducted a search in three journals: *Haemophilia, Physical Therapy* and *Manual Therapy*.

Search strategy.

The medical subjects heading included “hemophilia” AND “quality of life” AND “physical therapy” OR “physiotherapy” OR “rehabilitation” in the article, and specialised electronic magazines were consulted: *Haemophilia, Physical Therapy* and *Manual Therapy*. Two authors reviewed the abstracts and full texts of the studies found in the databases and journals, and if in doubt, the eligibility of any of the articles was determined by consensus.

Criteria for selection of articles

The studies selected met the following criteria: (I) the articles must be published; (II) they use physical therapy treatments; (III) they include at least one treatment group with pre-test and post-test evaluations; (IV) the size of the sample in the post-test is a minimum of five individuals per group.

The articles were excluded who: (I) case studies, descriptive articles or systematic reviews; (II) articles where subjects were not diagnosed with hemophilia A or B; (III) studies in which the methodology of physiotherapy treatment and measures of evaluation used is not detailed; (IV) abstract or communications to Congress; (V) and studies of Physiotherapy after surgery where no detail physiotherapy treatment protocol employed.

We did not put any time limit on the date of publication of the articles: the study had to have been published prior to April 2014. Likewise the studies included are restricted to those in Spanish, French, English, Italian, and Portuguese.

Qualitative analysis of the level of scientific evidence

It has made a qualitative analysis of the level of evidence in the study selected using two scales: the Van Tulder (21) and PEDro (22) scale.

After making the different search strategies described earlier in the databases and journals indicated, 1096 articles were obtained. Only one of these articles [35] met all the inclusion criteria. Figure 1 shows the flow chart of the search performed.

Results

After the search, only 81 articles were preselected, but only one carried out anPhysiotherapy treatment with an experimental group and a control group, and the pre and post evaluation assessed the perceived quality of life of patients in both groups.

Therefore, the methodology and the level of scientific evidence analysis of this review focused on the study of von Mackensen et al. (23), who conducted a physiotherapy treatment in an aquatic medium using joint mobilization techniques, stretching exercises, joint stability, and gait training and posture in patients with hemophilia.

Table 1 shows the main sample and methodological characteristics of the selected study.

In terms of qualitative analysis of the level of scientific evidence, the results of the analysis with the Van Tulder and PEDro scales are detailed in tables 2 and 3.

Finally, the analysis of the 8 descriptive studies (1, 18, 24-29) which we have made in this review is detailed in table 4.

Discussion

The results of this review show the scant literature about the effect of physiotherapy in the treatment of patients with hemophilia. However, descriptive and observational articles found in this review, indicate the appropriateness of acting on physical variables affected by haemorrhagic processes characteristic of these patients.

1. *Characteristics of the selected article*

- *Type of study*

The study that met the inclusion criteria (23)was a nonrandomized, prospective and longitudinal clinical study.

- *Sample*

The number of patients who started the study was 28: 13 were assigned to the experimental group (EG) and 15 to the control group (CG). Patients were recruited from two hospitals in Hamburg and were assigned to each group according to their availability. The mean age of the 28 patients at baseline was 40.68 years (SD: 12.7, range 22-64), with no significant differences between groups (GE: 42.54 years, GC: 39.07 years).

The majority of patients (78.5%) had a medical diagnosis of hemophilia A and 64.2% had a viral infection as a result of pharmacological therapy. Just the 28.5% of patients were on prophylaxis at baseline, while none of them had antibodies to FVIII / FIX (inhibitors).

92.8% of subjects were administered pharmacological treatment in their own home (self-treatment) and just over half of them (53.5%) already had a target joint.

Of the 28 patients who started the study, only 21 were subjected to post treatment evaluation. For various reasons 7 patients dropped out (4 in the experimental group and 3 in the control group).

- *Intervention*

This study was conducted over a period of 12 months and no follow up assessment was performed. The treatment applied to patients enrolled in the experimental group consisted of exercises which contained mobilizations and strengthening the full range of joint movement. According to the physical conditions of patients with hemophilia, along the 12 months of treatment was modified and adapted the training program. Devices were used to increase strength and be more effective in the training of muscle strength, such as weights of water and pool tables.

Each exercise was carried out with 20 repetitions, which would be less in the case of muscle fatigue appeared by training.

- *Measuring Instruments*

Before beginning treatment, at 6 months and after the end of the same, assessed 3 main dependent variables: physical performance, the orthopaedic status and perceived quality of life of patients. For measuring the QoL the measuring instruments used in this study were as SF-36 and Haem-A-QoL questionnaires.

The SF-36 (30) is the generic questionnaire most widely used in the assessment of perceived quality of life. This scale consists of 36 items that assess physical function, restriction of activities related to physical problems, pain, vitality, general health perception, social relations and activity restriction.

The Haemo-QoL-A (31) questionnaire was designed to assess the perceived quality of life in adult patients with hemophilia. It consists of 46 items comprising 10 dimensions (physical health, feelings, vision, sports and leisure, work and school, boarding, processing, future, family planning, and relationship / couples).

- *Results*

At 6 months of starting the study and after the period of treatment of 12 months, the paper's authors evaluated the different variables of the study, finding improvement in orthopaedic joint health.Concerning QoL they watched no

significant difference between the scores of the patients in both groups; neither as a result of the treatment period there were differences between subjects in the same group. This lack of variations in the QoL was observed in subjects in both groups, regardless of the analyzed questionnaire.

2. *Qualitative analysis of the level of scientific evidence*

In both scales the result was 3 points. This score is small, mainly because of the lack of randomization of study subjects to experimental and control groups. Similarly, the non-realization of an intention to treat analysis and no blinding of assessors or patients decreases the score.

The homogeneity at baseline between the experimental and control groups, the development of inclusion and exclusion criteria for recruitment of patients, and the validity of the outcome measures used in the pre and post assessment of the dependent variables, are the items that justify this score.

3. *Quantitative analysis of the selected article*

- *Variables of treatment and of the patients*

The total study duration was 12 weeks with an intensity of 1 hour a week and a magnitude of the treatment applied to patients in the experimental group 12 hours. The mean age of the 28 patients who took part in the study was 40.68 years (with a standard deviation of 12.7 and an age range of 22-64 years).

- *Methodological Variables*

The sample size of the experimental group at baseline was 13 patients, and at the end of treatment of 9 patients with hemophilia. In the control group, of the 15 patients recruited 12 were assessed in the evaluation after the study period of 12 months. The differential mortality after treatment period was 25% (7/28), being 30.7% in the experimental group and 20% in the control group.

4. *Assessment of descriptive studies*

We analyzed eight observational studies that throughout the selection process we discard for not to make a Physiotherapy treatment. These articles assessed criteria quality of life and physical variables. Table 4 shows the most important characteristics indicated respect of the samples analyzed in the same, the measurements and the results described. In the studies analyzed 975 patients with

hemophilia were enrolled with a great variability of sample size. 4 articles (18, 24, 28, 29) used between 20 and 96 subjects, in 3 (1, 26, 27) the sample was over 100 patients, and in only 1 article (25) the sample size was less 13.

The analyzed studies evaluated patients with different age ranges. More than half of the articles choose a range of young ages, between childhood and adolescence (4 yrs - 26 yrs), six articles recruited patients with a wider range of age (2 yrs - 65 yrs), and only one study does the analysis in patients of all kinds of ages with a range from 7 months to 81 years.

All of them measure the quality of life as well as other physical variables such as postural balance, muscle and joint status and the perception of pain. The most commonly used for assessing the perception of QoL are the SF-36 and HaemoQoL questionnaires. Although some authors (1, 32, 26, 27) also use other tools for measure this variables (SF-12, EQ-5D, PedsQL40 and HAQ).

5. Limitations of the study

In this study we found significant limitations. On one hand the results of the search threw only one study that met the inclusion criteria.

Similarly, the existence of a small number of experimental articles, that demonstrate the effectiveness of physiotherapy in relation to the improvement of the sequelae of hemophilia, is an inconvenience for the analysis of scientific evidence. If in addition our aim is evaluate specific variable such as QoL the results are even scarcer.

Finally, the heterogeneity regarding of the large number of questionnaires used to assess the QoL complicates the measurement and analysis of this variable.

6. Relevance of the study for clinical practice.

Despite the poor results obtained from this systematic review, are opened different working lines.

The demonstration of physical therapy techniques as an effective tool for improving the perception of QoL in patients with hemophilia, requires the need to conduct randomized clinical trials which evaluate the perception of these patients in clinical practice when they perceive the physical improvements.

The assessment of QoL before and after a physiotherapy treatment to assess this variable will help the clinician to assess their treatment more widely, responding to a true multidisciplinary treatment.

Finally, given the divergent conclusions of descriptive studies, we can state that physical therapy is important in the treatment of haemarthrosis and to prevent or delay the onset of hemophilic arthropathy, and will be according to this clinical evolution as we can actually act on the QoL of the patients.

7. Future lines of research

Future studies who assessing the effectiveness of a Physiotherapy treatment regarding the perceived quality of life for patients with hemophilia, should take particular account of methodology. It is necessary to carry out well-designed randomized clinical trials, to provide us with information about what treatment techniques significantly influence the perception of QoL.

Similarly, the use of properly validated outcome measures, detailed programs of Physiotherapy and a methodology that includes at least assessor blinding, the homogeneity among of study groups, an analysis by intention to treat and follow-up periods would help to counteract the predictable low sample size, due to the low prevalence of hemophilia.

In the study analyzed in this review has been employed a very detailed physiotherapy treatment. However, it would be appropriate to conduct a randomized clinical trial with the same program, but with a greater magnitude of treatment to ratify the physical improvements obtained. Also would help to confirm the efficacy of this therapeutic tool with respect to the quality of life for patients with hemophilia.

Finally, it would be appropriate to apply physiotherapy techniques that have proven effective regarding physical variables most affected in patients with hemophilia. The treatment of pain and deficit of the range of movement, muscle strength and proprioception in patients with hemophilia has been studied in several studies, using techniques of electrotherapy (33), hydrotherapy (34) or strength exercises against resistance (35). It would be interesting in future studies to assess the relationship of these techniques to the perception of QoL of patients, thereby to

increase the scientific evidence between Physiotherapy and quality of life of patients with hemophilia.

Conclusions

This review reveals the limited number of scientific articles that assess the effectiveness of a physiotherapy treatment to improve the perception of quality of life in patients with hemophilia.

A treatment of joint mobilization techniques, stretching exercises, joint stability training, gait training and the posture of 12 weeks, does not significantly improve the perceived quality of life for patients with hemophilia, although obtained improved orthopaedic joint health.

In the literature there is no uniformity regarding the relationship of age patients and the hemophilia (type, severity, type of treatment), with the perceived quality of life of these.

Randomized clinical trials are needed to demonstrate how Physiotherapy treatments are effective in improving the perceived quality of life of patients with hemophilia.

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428 Table 1. Characteristics of the article selected in this review.

Article	Type	R	Nexp	Ncont	Age	D	Treatment	F	Variables	Measuring instruments	Results
Von Mackensen et al. 2012	Clinical prospective longitudinal study	NO	N_{pre}:13 N_{post}: 9	N_{pre}:15 N_{post}: 12	EG: 42.54±13.5 CG: 39.07±12.3	12	-Joint mobilization techniques. . -Muscle stretching exercises. -Training of joint stability. -Training of gait and posture.	NO	- Quality of life. -Physical performance. - Status orthopedic joint.	-SF-36. -HaemoQoL. -HEP-Test-Q. -OJS.	No significant differences in QoL

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430 Type: tye of article; R: randomization; Nexp: number of patients in experimental group; Ncont: number of patients in control group; Npre: number of
431 patients at baseline; Npost: number of patients at the end of treatment; EG: experimental group; CG: control group; D: duration of the treatment
432 (weeks); Treatment: Treatment of Physiotherapy; F: Follow up period.

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435 Table 2.Analysis of the methodological quality of Von Mackensen et al.'s study, by
436 Van Tulder scale.
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Ítems	Von Mackensen et al 2012
Was the method of randomization adequate?	NO
Was the treatment allocation concealed?	NO
Were the groups similar at baseline regarding the most important prognostic indicators?	YES
Was the patient blinded to the intervention?	NO
Was the care provider blinded to the intervention?	NO
Was the outcome assessor blinded to the intervention?	NO
Were co-interventions avoided or similar?	NS
Was the compliance acceptable in all groups?	NO
Was the drop-out rate described and acceptable?	YES
Was the timing of the outcome assessment in all groups similar?	YES
Did the analysis include an intention-to-treat analysis?	NO

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441 Table 3.Analysis of the methodological quality of Von Mackensen et al.'s study, by
442 PEDro scale.
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Items	Von Mackensen et al 2012
Eligibility criteria were specified	1
Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	0
Allocation was concealed	0
The groups were similar at baseline regarding the most important prognostic indicators	1
There was blinding of all subjects	0
There was blinding of all therapists who administered the therapy	0
There was blinding of all assessors who measured at least one key outcome	0
Measures of at least one key outcome were obtained from more than 85% of the Subjects initially allocated to groups	0
All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	0
The results of between-group statistical comparison s are reported for at least one key outcome	1
The study provides both point measures and measures of variability for at least one key outcome	1

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445 Table 4.Analysis of observational studies found in the review

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Article	Type	N	Duration	Age	Variables	Measuring instruments	Results
Solovieva 2001	Observacional study	150	36	43±15 (range:16-73)	-Bleeding frequency -Physical activity -Pain -Disability -QoL	-HAQ score -SF-36 questionnaire -VAS scale	-Qol worse depending on the age and the severity of haemophilia
Tusell et al.2002	Observacional study	70	12	29.6 (range: 16-26)	-QoL -Physical activity -Radiological joint deterioration	-SF-36 questionnaire -Gilbert score -Pettersson score	-Patients with hemophilia have worse QoL than healthy controls, regardless of pharmaceutical expenditure and of the treatment regimen.
Fischer et al.2005	Observacional study	96		28,6±11.5 (range: 13-54)	-QoL -Radiological joint deterioration	-SF-36 questionnaire -Pettersson score	-The greater the age and radiological joint deterioration, worse QoL (especially in physical function).
Van der Net et al.2006	Observacional study	13	4	11.04±2.45 (range: 8-14)	-QoL -Max O2 Consumption -Physical activity - Jointstatus	-HaemoQoL questionnaire -VO_2pico -ASK assessment -HJHS score	-Children with severe hemophilia A without joint damage, have a similar QoL to that of healthy subjects. - The greater the age, the better the perception of QoL -Correlation between the QoL of parents and children
M. Morfini et al.2007	Observacional study	128	17	42.6 (range: 14-61)	-Pain -Physical state -Radiological joint deterioration -QoL	-VAS scale -Gilbert score -Pettersson score -EQ-5D score	-Patients with hemophilia and inhibitor have worse QoL than patients without antibodies.
Poon et al.2012	Observacional study	329	24	33.5±12.6 (range: 2-64)	-QoL -Limitation and joint pain -Range of movement	-SF-12 questionnaire -PedsQL40 questionnaire -Goniometry - Likert scale (pain, movement)	-In patients with severe hemophilia, there are more pain and physical limitations, and worse QoL. -Children and adults with moderate and mild hemophilia, with a similar QoL to healthy controls -Worse QoL according to the severity of haemophilia
Lindvall et al.2012	Observacional study	105	60	42.8±16.1 (range: 18-84)	-QoL -Pain	-SF-36 questionnaire -VAS scale	-The greater the age, worse QoL. - Better QoL in patients undergoing orthopedic surgery - In patients with severe hemophilia, the better the QoL after a period of five years
Khair et al.2012	Estudioobservacional	84	NS	11.52±3.4 (range: 6-18)	-QoL -Rendimiento físico -Physicalactivity	-HaemoQoL questionnaire -KINDL scale -HEP-Q score	-There are better QoL in children who play sports.

447 Type: type of article; N: number of patients in the study; Duration: duration of the study (weeks).

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449 Figure 1. Flow diagram of the search