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By h h

Review Article

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

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7

8 **Abstract**

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

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

16 **Method.** This review has been developed a bibliographic search in different
17 databases: PubMed, PEDro, the Virtual Library of health and Isi Web, and in
18 different journals: *Haemophilia*, *Physical Therapy* and *Manual Therapy*.

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

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

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

30

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

32

33 Introduction

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

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

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

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

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

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

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

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

66 (9)

67 The World Health Organization (WHO) defines physiotherapy as the "art and
68 science of physical treatment of re-education exercise, heat, cold, light, massage
69 and electricity" (10). Physiotherapy, like other health professions, has been
70 developed in different fields finding a wide range of specialist areas such as
71 neurological physiotherapy, orthopaedic, rheumatology, paediatric or geriatric (11).
72 The primary role of physiotherapy in hemophilia is haemarthrosis the prevention of
73 and physical sequelae the restoration of functionality after acute bleeding
74 episodes, and maintenance of range of motion, muscle strength and periarticular
75 proprioception in cases of deterioration advanced joint (12).

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

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

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

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

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

104 **Material and Method**

105 *Design of the study*

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

108 *Documentary sources*

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

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

115 *Search strategy.*

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

122 *Criteria for selection of articles*

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

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

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

136 *Qualitative analysis of the level of scientific evidence*

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

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

142

143 **Results**

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

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

28

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

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

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

159

160 Discussion

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

166 1. Characteristics of the selected article

167 - Type of study

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

170 - Sample

171 The number of patients who started the study was 28: 12 were assigned to the
172 experimental group (EG) and 15 to the control group (CG). Patients were recruited
173 from two hospitals in Hamburg and were assigned to each group according to their
174 availability. The mean age of the 28 patients at baseline was 40.68 years (SD:
175 12.7, range 22-64), with no significant differences between groups (GE: 42.54
176 years, GC: 39.07 years).

177 The majority of patients (78.5%) had a medical diagnosis of hemophilia A and
178 64.2% had a viral infection as a result of pharmacological therapy. Just the 28.5%
179 of patients were on prophylaxis at baseline, while none of them had antibodies to
180 FVIII / FIX (inhibitors).

181 92.8% of subjects were administered pharmacological treatment in their own home
182 (self-treatment) and just over half of them (53.5%) already had a target joint.

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

186 - Intervention

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

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

197 - Measuring Instruments

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

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

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

210 - Results

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

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

218 2. Qualitative analysis of the level of scientific evidence

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

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

227 3. Quantitative analysis of the selected article

228 - Variables of treatment and of the patients

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

233 - Methodological Variables

234 The sample size of the experimental group at baseline was 13 patients, and at the
235 end of treatment of 9 patients with hemophilia. In the control group, of the 15
236 patients recruited 12 were assessed in the evaluation after the study period of 12
237 months. The differential mortality after treatment period was 25% (7/28), being
238 30.7% in the experimental group and 20% in the control group.

239 4. Assessment of descriptive studies

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

245 hemophilia were enrolled with a great variability of sample size. 4 articles (18, 24,
246 28, 29) used between 20 and 96 subjects, in 3 (1, 26, 27) the sample was over 100
247 patients, and in only 1 article (25) the sample size was less 13.

248 The analyzed studies evaluated patients with different age ranges. More than half
249 of the articles choose a range of young ages, between childhood and adolescence
250 (4 yrs - 26 yrs), six articles recruited patients with a wider range of age (2 yrs - 65
251 yrs), and only one study does the analysis in patients of all kinds of ages with a
252 range from 7 months to 81 years.

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

258 *5. Limitations of the study*

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

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

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

268 *6. Relevance of the study for clinical practice.*

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

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

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

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

282 7. Future lines of research

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

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

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

299 Finally, it would be appropriate to apply physiotherapy techniques that have proven
300 effective regarding physical variables most affected in patients with hemophilia.

301 The treatment of pain and deficit of the range of movement, muscle strength and
302 proprioception in patients with hemophilia has been studied in several studies,
303 using techniques of electrotherapy (33), hydrotherapy (34) or strength exercises
304 against resistance (35). It would be interesting in future studies to assess the
305 relationship of these techniques to the perception of QoL of patients, thereby to

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

308

309 Conclusions

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

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

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

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

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427 26.

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

429

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.

433

434

435 Table 2. Analysis of the methodological quality of Von Mackensen et al.'s study, by
436 Van Tulder scale.

437

Items	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

438

439

440

441 Table 3. Analysis of the methodological quality of Von Mackensen et al.'s study, by
442 PEDro scale.

443

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

444

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

446

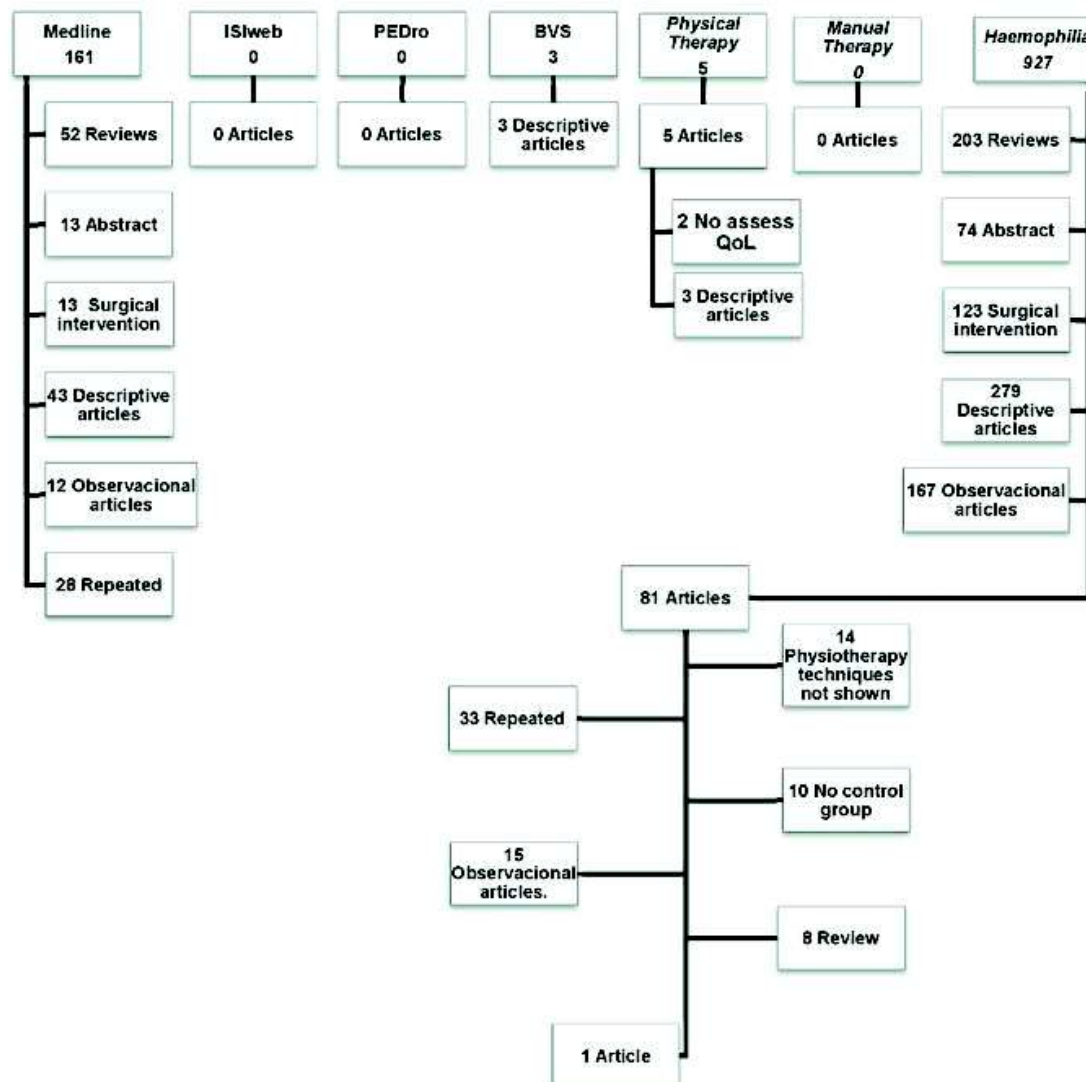
Article	Type	N	Duration	Age	Variables	Measuring instruments	Results
Solovieva 2001	Observational study	150	36	43±15 (range: 16-73)	-Bleeding frequency -Physical activity -Pain -Disability -QoL	-HAQ score -SF-36 questionnaire -VAS scale	-QoL worse depending on the age and the severity of haemophilia
Tusell et al.2002	Observational study	70	12	29.6 (range: 16-26)	-QoL -Physical activity -Radiological joint deterioration	-SF-36 questionnaire -Gilbert score -Petterson score	-Patients with hemophilia have worse QoL than healthy controls, regardless of pharmaceutical expenditure and of the treatment regimen.
Fischer et al.2005	Observational study	96		28.6±11.5 (range: 13-54)	-QoL -Radiological joint deterioration	-SF-36 questionnaire -Petterson score	-The greater the age and radiological joint deterioration, worse QoL (especially in physical function).
Van der Nel et al.2006	Observational study	13	4	11.04±2.45 (range: 8-14)	-QoL -Max O2 Consumption -Physical activity -Joint status	-HaemoQoL questionnaire -VO ₂ pico -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	Observational study	128	17	42.6 (range: 14-61)	-Pain -Physical state -Radiological joint deterioration -QoL	-VAS scale -Gilbert score -Petterson score -EQ-5D score	-Patients with hemophilia and inhibitor have worse QoL than patients without antibodies.
Poon et al.2012	Observational 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	Observational 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	Estudio observacional	84	NS	11.52±3.4 (range: 6-18)	-QoL -Rendimiento físico -Physical activity	-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).

448

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449 Figure 1. Flow diagram of the search



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