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PROPHYLAXIS THERAPY IN HAEMOPHILIA A: CURRENT SITUATION IN SPAIN

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TITLE: PROPHYLAXIS THERAPY IN HAEMOPHILIA A: CURRENT SITUATION IN SPAIN

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SUMMARY

The Spanish Epidemiological Study in Haemophilia carried out in 2006 enrolled 2400 patients (2081 -86.7%- with haemophilia A (HA) and 319 -13.3%- with haemophilia B (HB)); 465 of them (19.4%) were on prophylaxis. These rates were higher in patients with severe haemophilia (45.4%) and severe paediatric cases (72.5%). Based on the information recorded in this study we analysed the current situation of prophylaxis therapy administered to patients with HA in Spain, as well as their orthopaedic status. Prophylaxis was used in 399 (19.2%) patients with HA; such prophylaxis was primary (PP) in 20.3% and secondary (SP) in 75.9% of cases. Among severe HA patients, 313 (45.9%) were on prophylaxis (22.3% on PP and 74.7% on SP). Taking into account the patients' age, 34.7% of severe HA adults were on prophylaxis (6% PP and 92.1% SP) whereas 71.5% of severe HA paediatric patients (40.5% PP and 55.4% SP) received this kind of treatment.

Established haemophilic arthropathy (EHA) was detected in 142 from 313 severe HA patients (45.3%) on prophylaxis, but only in 2.9% of patients under PP versus 59% of patients receiving SP. There was no EHA in adult severe HA patient on PP, whereas 70.4% on SP had joint damage ($p < 0.00001$). Among paediatric severe HA patients, EHA was detected in 3.3% under PP and 37.8% under SP ($p < 0.00001$). In conclusion, our data suggests that an early initiation of prophylaxis avoids EHA in the long term in patients with severe HA. We should emphasize the early onset of prophylaxis regimens.

INTRODUCTION

A comprehensive epidemiological study aimed to update available information on clinical features of haemophilia patients registered in 51 haemophilia treatment centres throughout the country was carried out in Spain in 2006; from these reports relevant

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3 clinical and therapeutic information from 2400 patients (2081 -86.7%- with haemophilia
4 A and 319 -13.3%- with haemophilia B) was recorded. Illness was severe in 32.3% of
5 patients, moderate in 16.4%, and mild in 51.3%. Adult patients (14 years of age or over)
6 represented 77.2% of cases [1].

7
8 We found that 465/2400 (19.4%) were on regular prophylaxis. If we consider patients
9 with severe haemophilia, 45.4% of them were on prophylaxis. Nevertheless, if we
10 consider only paediatric severe patients, 72.5% were on regular prophylaxis treatment.

11
12 Data collected during such study were the basis on which the Spanish Haemophilia
13 Registry was built in 2008; this database comprised information on 2905 haemophilia
14 patients (2518 with haemophilia A and 387 with haemophilia B) from 53 haemophilia
15 treatment centres [2].

16
17 On the basis of the information from the Spanish Epidemiological Study [1] we aimed
18 to achieve a deeper knowledge of various issues involved in clinical practice like the
19 real current situation of primary and secondary prophylactic treatment provided to both
20 paediatric and adult haemophilia A (HA) patients in our country, as well as their current
21 orthopaedic status according to the Pettersson score [3] and the implementation of
22 central venous access devices (CVAD) insertion often required for an adequate
23 compliance of therapeutic schedules involving frequent intravenous infusions [4].
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37 MATERIALS AND METHODS

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40 Data used for our evaluation were obtained from the database made up for the Spanish
41 Haemophilia Epidemiological Study, involving 2081 HA patients registered and
42 managed in 51 haemophilia treatment centres [1].

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44 The degree of severity of haemophilia was sorted according to previously published
45 standard criteria related to FVIII plasma levels as severe (<0.01 U dL⁻¹), moderate
46 (≥ 0.01 U dL⁻¹ to < 0.05 U dL⁻¹) and mild (≥ 0.05 U dL⁻¹ to 0.4 U dL⁻¹) [5]. Patients ≥ 14
47 years of age were rated as adults and those < 14 as paediatric.
48

49
50 Definition of the type of prophylactic treatment was made following the
51 recommendations of the PEDNET group (European Paediatric Network for
52 Haemophilia Treatment) [6] as:

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54 - **A primary prophylaxis (APP):** Regular continuous (minimum 46 weeks a year)
55 treatment started after the first joint bleed recorded and before the age of 2 years.
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3 - **B primary prophylaxis (BPP)**: Regular continuous (minimum 46 weeks a year)
4 treatment started before the age of 2 years without any evidence of a previous joint
5 bleed.
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8 - **A secondary prophylaxis (ASP)**: Regular continuous (long term) treatment started
9 after 2 or more joint bleeds recorded or at an age >2.
10
11

12 - **B secondary prophylaxis (BSP)**: Intermittent regular (short term) treatment provided
13 in order to cover frequent haemarthroses.
14

15 Assessment of joint status was made by visualisation of X-rays of elbows, knees and
16 ankles according to the Pettersson score [3]; scores of ≥ 3 for any particular joint were
17 consistent with established haemophilic arthropathy (EHA).
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19 Information related to CVAD was focused on particular aspects like catheter duration
20 and incidence of the two most frequent complications associated to their use: infection
21 and thrombosis.
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26 *Statistical analysis*

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28 A descriptive analysis was done, using absolute and relative frequencies for qualitative
29 variables and centralization and dispersion measures for quantitative variables.
30

31 Pearson's Chi-square test (or Fisher's exact test for 2x2 tables, or reason of
32 verisimilitude mxn tables, if necessary) were used to find the relation between
33 qualitative variables. The T Student test or one-factor ANOVA were used for the
34 comparison of continuous variables, if parametric criteria were fulfilled. The statistical
35 significance value has been established at $p < 0.05$.
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42 **RESULTS**

43 Information from 2081 HA patients registered in the Spanish Epidemiological Study
44 was analysed; 682 (32.8%) of them were patients with severe haemophilia, whereas 290
45 (13.9%) and 1109 (53.3%) were moderate and mild cases respectively. Patients
46 classified as adults accounted for 77.2% (1607) of the whole series and children 474
47 (22.8%).
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53 **Prophylaxis in haemophilia A patient population**

54 Evaluation of this group of 2081 HA patients showed that 399 (19.2%) of them were on
55 prophylaxis: primary in 81 cases (20.3 %), secondary in 303 (75.9%) and undetermined
56 in 15 (3.7%). Details are shown in Table 1.
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In the analysis by groups of age and type of treatment we founded the following results (see Table 2):

- Only a minor proportion of adult HA patients (215; 13.4%) were on prophylactic therapy: primary in 13 (6.1%) and secondary in 196 (92.2%).
- The rate of paediatric patients on prophylaxis was far higher, as expected (184; 38.8%); rates of primary (PP) and secondary prophylaxis (SP) for this age group were 26.9% (68 cases) and 58.1% (107 cases) respectively.

Prophylaxis in severe haemophilia A patient population

Almost half of the 682 severe HA patients (45.9%; 313) were on prophylactic treatment, either PP (70 cases; 22.3%) or SP (234 cases; 74.7%) (Tables 1 & 2). Among paediatric patients diagnosed with severe HA (n=207), prophylaxis was administered to 71.5% (148 cases): 40.5% (60 cases) for PP and 55.4% (82 cases) for SP. Adult severe HA patients (475 subjects, 433 on treatment) were far less frequently on prophylaxis (34.7%; 165 cases); the vast majority of them followed a SP treatment scheme (92.1%; 152 cases) and only 6.0% (10 cases) a PP one (Tables 1 & 3).

Figure 1 reflects the rate of prophylaxis used in the whole Haemophilia A population and in the severe HA patients by age groups.

Joint status

Assessment of joint status was possible for 1228 of all patients enrolled in the epidemiological study and evidence of EHA was proved for 555 (45.2%) of them.

Among the 313 severe HA patients receiving prophylaxis, EHA was detected in 142 of them (45.4%), but only in 2.9% of patients under PP versus 59% of patients receiving SP (p<0.001) (Table 4).

For all 433 treated severe HA adult patients recorded, EHA was found in 74.4% (322/433) of them and rates of chronic joint damage were significantly higher for patients receiving on demand treatment (79.4%) than for patients receiving prophylaxis with regular factor VIII infusions (66.1%), p=0.002. There was no EHA in adult severe HA patient on PP, whereas 70.4% on SP had joint damage (p<0.00001) (Table 4).

This evaluation was also made in 148 paediatric severe HA patients on prophylaxis. Pettersson scores consistent with EHA were found in 33 (22.3%) of them, but only in 3.3% (2/60) of paediatric severe HA patients on APP or BPP; however signs of chronic joint damage were found in 37.8% (31/82) of children on ASP or BSP (p<0.00001).

Type of factor VIII concentrate used for prophylaxis

Recombinant factor VIII concentrates were administered for prophylaxis to 71.4% (285/399) of HA patients, and plasma derived products were used in 28.6% of cases (114/399) at the time of data collection. Rates of recombinant concentrate use were higher among the patients on PP (87.7%) than among those on SP (66.7%).

Frequency of infusions and bleeds

During the study period mean number of factor VIII concentrate infusions for the 399 HA patients were 3 (SD: 0.76). The mean annual number of bleeds was 1.3 for subjects belonging to the APP subset (range 0-18, SD: 3.14), 1.2 for those on BPP (range 0-8, SD: 1.88), 3.1 for ASP (range 0-78, SD: 8.14) and 4.3 for BSP (range 0-17, SD: 4.85). Mean number of annual bleeding episodes for HA patients on prophylaxis was 2.9 (range 0-78, SD: 6.53).

Infusion routes of factor VIII concentrates

Factor concentrate was mostly administered through peripheral veins to HA individuals on regular prophylaxis (87.2%). Only in 9.5% of patients a CVAD was required and in 1.7% of cases both types of venous access were used. Important differences were found in CVAD insertion frequencies between patients on PP (23.4%) and SP (7.3%).

Complications associated to the use of CVAD were reported in 29 of 41 (70.7%) of catheters inserted. Infection was the most common of these complications (11 patients; 37.9%) with a rate of 0.73 patient days throughout 2006. No cases of thrombosis were reported. CVAD malfunctioning was recorded in 4 patients (13.8%) and some type of minor undetermined complication in almost half of cases (14; 48.3%).

DISCUSSION

Our current study aimed to get a real and deep knowledge of the implementation of prophylactic therapy in patients with HA in Spain and to compare this information with that reported in other countries in order to find out any potential differences in clinical practice in this setting which might be susceptible to be improved. However such comparisons are often difficult to make due to heterogeneity in the criteria used for patient definition and classification in the series reported. These differences may largely depend on age cut-offs used, definitions of prophylaxis, dosage intervals prescribed, FVIII:C plasma levels considered for the diagnosis of severity of haemophilia and also type of evaluations used: cross-sectional, retrospective, prospective, etc.

Regarding the rates of HA patients by degree of severity, our series shows a proportion of severe cases of 32.8%, which is similar to that reported in the Canadian (Biss et al; 30.6%), Swedish (Larsson et al; 30%) and Dutch (Plug et al; 39%) studies [7-9]. These figures are significantly higher in other published series of patients from the USA (Butler et al; 53%) [10], Poland (Windyga et al; 59.7%) [11] and most recently Japan (Ono et al- 69.5%-; Taki et al -73.4 %-) [12, 13].

Our results show that 19.2% of HA patients are following some type of prophylaxis treatment, consistently with data published by Biss et al (20.3%) [7], but not with those reported by Plug et al (29%) [9]. Rates of prophylaxis available in Japanese series are very surprisingly heterogeneous, considering that they offer information on patients treated in the same country; thus Ono et al [12] report rates of prophylaxis of 67.2%, whereas for Taki et al [13] it is of only 11.6%.

When we focused our analysis on severe HA patients (682 altogether) we found out that almost half of them (313; 45.9%) were on some type of prophylactic treatment, a rate similar to that reported by Butler et al (44%) [10] but lower than in the Dutch (Plug et al; 67.6%) [9] or Canadian series (Biss et al; 62.3%). Comparison of our data with those in this latter study is difficult to carry out because prophylaxis as considered in this paper refers to factor VIII treatment administered at least once a week during 45 weeks a year, whereas our patients received factor VIII infusions three times a week.

As expected, a lower proportion of our moderate HA patients were on prophylaxis (22.4%). Our figures are higher than those from the study by Taki et al (17%) or Plug et al (11.9%). Perhaps physicians involved in haemophilia care should be more aware of the need of prophylactic therapy in some patients affected by moderate haemophilia.

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3 Blanchette et al [14] reported joint data from American and Canadian paediatric
4 patients; 77% of their severe HA patients in this group of age (with an age cut-off of 18)
5 were on some sort of prophylaxis treatment consistent with 72.5% from our
6 epidemiological study (using 14 as a top age for patients being considered as paediatric)
7 after exclusion of undetermined cases. Differences in age cut-offs between both groups
8 must be taken into account when comparing results from both studies. Other authors
9 like Plug et al set this cut-off at the age of 16 and report prophylaxis rates of 86% for
10 severe HA patients [9]. Great heterogeneity existing in classification of age groups can
11 be an issue when interpreting the results from different studies.
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14 The target prophylaxis rate for paediatric severe HA patients should ideally be 100%
15 but this goal is virtually impossible to achieve for various reasons: regular venipuncture
16 is difficult for children under 1 year of age, prophylaxis start can be delayed in families
17 from a low social and cultural background and also some families can be reluctant to
18 start treatment in children who still remain asymptomatic. Other reasons remain vaguely
19 determined.
20

21
22 Prophylaxis among our 475 adult severe HA patients (>14 years of age) was
23 unfortunately not so commonly used (34.7%; 165/475) as in other studies enrolling
24 similar patients like those by Biss et al (53%) [7] or Plug et al (59.3%) [9]; this latter
25 analysis includes severe haemophilia A and B patients over the age of 16.
26

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28 Among our severe HA adult patients, significant differences in the development of EHA
29 were found between those patients receiving prophylactic treatment versus patients
30 receiving on demand treatment. This data are concordant with those published by
31 Aledort et al in 1994 [15]; they found that after 6 years of observation, patients under
32 prophylaxis obtained better orthopaedic and radiological scores than patients following
33 on demand therapy even though secondary prophylaxis couldn't impede the progression
34 of the EHA.
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37 Moreover, in our study we found that primary prophylaxis resulted strongly protective
38 for the adult population.
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41 Although no differences in the degree of joint damage were noticed in the population of
42 severe paediatric patients treated on demand versus those treated with prophylaxis. This
43 results maybe due to the delay on the onset of the secondary prophylaxis in our country.
44 When we did this analysis in function of the type of prophylactic treatment
45 administered, we found that PP resulted protective for the development of EHA in the
46 paediatric population. Early onset of prophylactic treatment is definitely crucial for the
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3 prevention of EHA. Countries like Holland pioneered wide fostering of such therapeutic
4 approaches in the late sixties [9], long before it became popular in other countries like
5 Spain (where SP began to be used in the late seventies and the PP in the early nineties,
6 approximately) and this may have translated into a steady rate of arthropathy of about
7 30%, reflected in the Spanish epidemiological study [1]. In our experience the most
8 commonly affected joints were ankles followed by knees and elbows.

9
10 Patients for whom a CVAD insertion was decided were more commonly those on PP,
11 which is not surprising considering that patients in this group are more often children
12 under the age of 2 for whom recurrent intravenous infusions via peripheral veins is
13 impractical and may seriously jeopardise compliance with regular prophylaxis.

14
15 Data collected from our study disclose that about one in four of our patients on PP
16 (23.5%) had a CVAD inserted for this purpose, which is similar to rates previously
17 reported by Valentino et al [16]; other research groups however are far more active in
18 the usage of such devices in patients on PP who have one inserted in up to 82% of cases
19 according to Blanchette et al [10, 14].

20
21 Major complications of CVAD are infrequent [16]. As already mentioned above
22 catheter associated infections are the most frequent amongst these patients for whom
23 frequencies of 0.28 to 1.6 patient days for individuals without inhibitors have been
24 published up to 2003 [17]. Thus our infection rate (0.73 per 1000 patient days) lies
25 within the range just mentioned. No cases of catheter-triggered thrombosis have been
26 collected from our study, consistently with data from the paper by Ljung et al [18]
27 enrolling a similar number of patients with a CVAD. Malfunctioning frequencies in this
28 study were 18.8% during an average follow-up period of 13 months, not far from our
29 13.8% in a one-year follow-up time.

30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 **CONCLUSIONS**

49 Spanish HA patients and, more specifically severe subjects, are at the same level as
50 most developed countries regarding implementation of therapeutic strategies involving
51 prophylaxis. However information derived from our current research shows some
52 aspects of the management of patients with haemophilia in Spain which might be
53 improved. For instance the reasons leading to a lower rate of prescription of PP or SP in
54 adulthood, as well as the higher frequency of EHA in patients in this group of age must
55 be taken into account. Both issues are probably related to a historic delay in the
56 introduction of PP treatments on a routine basis in our country.
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3 Therefore, we must strongly stress the importance of adopting early PP schedules in
4 order to avoid serious bleeding episodes as well as the triggering and development of
5 degenerative joint damage. The status of EHA noticed in adult patients with
6 haemophilia along with growing age of this population will unavoidably mean a higher
7 need for orthopaedic procedures of joint replacement in the future.
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TABLES:**Table 1:** Type of treatment in HA patients in relation to the degree of severity of haemophilia and age group

| Haemophilia A | | Paediatric patients | | | | Adult patients | | | | Total patients | | | |
|------------------------------------|--------------------|----------------------|---------------------|----------------------|----------------------|----------------------|----------------------|----------------------|-----------------------|-----------------------|----------------------|----------------------|----------------------|
| | | Mild n (%) | Moderate n (%) | Severe n (%) | Total n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Total n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Total n (%) |
| Total Patients | | 207 (43.7) | 60 (12.7) | 207 (43.7) | 474 (22.8) | 902 (31.4) | 230 (14.3) | 475 (29.6) | 1607 (77.2) | 1109 (53.3) | 290 (13.9) | 682 (32.8) | 2081 (100) |
| Total Patients on Treatment | | 80 (38.6) | 54 (90) | 198 (95.7) | 332 (67.1) | 283 (31.4) | 180 (78.3) | 433 (91.2) | 896 (55.8) | 363 (32.7) | 234 (80.7) | 631 (92.5) | 1228 (59) |
| Type of Treatment | NR † | 2 (2.5) | 0 (0) | 3 (1.5) | 5 (1.5) | 6 (2.1) | 4 (2.2) | 1 (0.2) | 11 (1.2) | 8 (2.2) | 4 (1.7) | 4 (0.6) | 16 (1.3) |
| | On demand | 68 (85) | 28 (51.9) | 47 (23.7) | 143 (43.1) | 266 (94) | 137 (76.1) | 267 (61.7) | 670 (74.8) | 334 (92) | 165 (70.5) | 314 (49.8) | 813 (66.2) |
| | Prophylaxis | 10 (12.5) | 26 (48.2) | 148 (74.8) | 184 (55.4) | 11 (3.9) | 39 (21.7) | 165 (38.1) | 215 (24) | 21 (5.8) | 65 (27.8) | 313 (49.6) | 399 (32.5) |
| | Total | 80 | 54 | 198 | 332 | 283 | 180 | 433 | 896 | 363 | 234 | 631 | 1228 |

† NR: Not recorded in the case report form the type of treatment followed by the patient (on demand or prophylaxis)

Table 2: Type of prophylaxis in HA patients in relation to the degree of severity of haemophilia and age group

| Type of prophylaxis | Severity | | | Age group | | Total n (%) |
|---------------------|-----------------|-------------------|------------------|---------------------|------------------|-------------------|
| | Mild n (%) | Moderate n (%) | Severe n (%) | Paediatric n (%) | Adult n (%) | |
| Undetermined | 3 (14.3) | 3 (4.6) | 9 (2.9) | 9 (4.9) | 6 (2.8) | 15 (3.8) |
| APP * | 0 | 4 (6.2) | 32 (10.2) | 28 (15.2) | 8 (3.7) | 36 (9) |
| BPP # | 4 (19.1) | 3 (4.6) | 38 (12.1) | 40 (21.7) | 5 (2.3) | 45 (11.3) |
| ASP †† | 6 (28.6) | 35 (53.9) | 165 (52.7) | 88 (47.8) | 118(54.9) | 206 (51.6) |
| BSP †† | 8 (38.1) | 20 (30.8) | 69 (22) | 19 (10.3) | 78 (36.3) | 97 (24.3) |
| TOTAL | 21 (100) | 65 (100) | 313 (100) | 184 (100) | 215 (100) | 399 (100) |

(*) **APP**: A Primary Prophylaxis

(#) **BPP**: B Primary Prophylaxis

(††) **ASP**: A Secondary Prophylaxis

(††) **BSP**: B Secondary Prophylaxis

Table 3: Type of prophylactic treatment in HA patients of different age groups

| Type of prophylaxis | Paediatric patients (<14 years) | | | | Adult patients (≥ 14 years) | | | |
|---------------------|---------------------------------|-------------------|------------------|------------------|-----------------------------|-------------------|------------------|-------------------|
| | Mild n (%) | Moderate n (%) | Severe n (%) | Total n (%) | Mild n (%) | Moderate n (%) | Severe n (%) | Total n (%) |
| Undetermined | 2 (20) | 1 (3.9) | 6 (4.1) | 9 (4.9) | 1 (9.1) | 2 (5.1) | 3 (1.8) | 6 (2.8) |
| APP * | 0 | 2 (7.7) | 26 (17.6) | 28 (15.2) | 0 | 2 (5.1) | 6 (3.6) | 8 (3.7) |
| BPP # | 3 (30) | 3 (11.5) | 34 (23) | 40 (21.7) | 1 (9.1) | 0 | 4 (2.4) | 5 (2.3) |
| ASP †† | 3 (30) | 14 (53.9) | 71 (48) | 88 (47.8) | 3 (27.3) | 21 (53.9) | 94 (57) | 118 (54.9) |
| BSP †† | 2 (20) | 6 (23.1) | 11 (7.4) | 19 (10.3) | 6 (54.6) | 14 (35.9) | 58 (35.2) | 78 (36.3) |
| TOTAL | 10 (100) | 26 (100) | 148 (100) | 184 (100) | 11 (100) | 39 (100) | 165 (100) | 215 (100) |

(* **APP**: A Primary Prophylaxis

(# **BPP**: B Primary Prophylaxis

(†† **ASP**: A Secondary Prophylaxis

(†† **BSP**: B Secondary Prophylaxis

Table 4: Established Haemophilic Arthropathy in relation to age and type of prophylaxis

| Haemophilia A | | Established Haemophilic Arthropathy (EHA) | | |
|----------------------------|-----------------------|---|-----------------------|-----------------------|
| | | Paediatric severe patients | Adult severe patients | Total severe patients |
| | | N (%) | N (%) | N (%) |
| Treated patients | | 44/198 (22.2) | 322/433 (74.4) | 366/631 (58%) |
| Type of treatment | NR † | 0/3 (0) | 1/1 (100) | 1/4 (25) |
| | On demand | 11/47 (23.4) | 212/267 (79.4) | 223/314 (71) |
| | On prophylaxis | 33/148 (22.3) | 109/165 (66.1) | 142/313 (45.4) |
| Type of prophylaxis | NR † | 0/6 (0) | 2/3 (66.7) | 2/9 (22.2) |
| | APP * | 0/26 (0) | 0/6 (0) | 0/32 (0) |
| | BPP # | 2/34 (5.9) | 0/4 (0) | 2/38 (5.3) |
| | ASP ‡ | 27/71 (38) | 65/94 (69.2) | 92/165 (55.8) |
| | BSP ‡ | 4/11 (36.4) | 42/58 (72.4) | 46/69 (66.6) |

† NR: Not recorded in the case report form the type of treatment followed by the patient (on demand or prophylaxis)

(*) APP: A Primary Prophylaxis

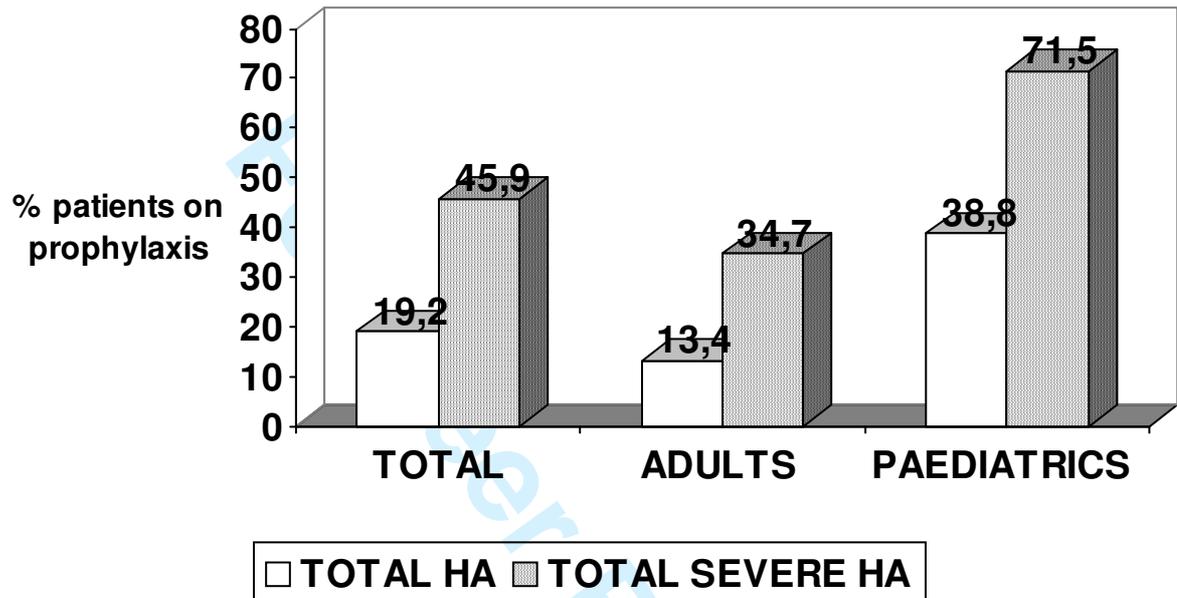
(#) BPP: B Primary Prophylaxis

(‡) ASP: A Secondary Prophylaxis

(‡) BSP: B Secondary Prophylaxis

FIGURES

Figure 1: Frequency of prophylaxis used in the entire Haemophilia A population and in the severe HA patients.



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