The perception of pain in children with haemophilia, and its impact on their lives: a case-control study

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Introduction and Objective

Haemophilia is characterized by frequent haemartroses and bleeding that cause pain and functional impairment. There are only a few reports evaluating the pain in children. The aim of this study was to assess the perception of pain in a group of haemophiliac children compared with a group of healthy subjects of the same age, and to assess how the pain affected the lives of these young patients

Materials and Methods

Hemophiliac children were included in this study. During planned examinations they were asked to define their pain on that day and to complete a questionnaire about their lifestyle. Pain was assessed by the Wong-Baker Faces Pain Rating Scale (3-8 years) or by the Numerical Pain Rating Scale (9-16 years). The same questions were put to the control group.

Results

18 patients and 27 healthy subjects were evaluated. 94.4% of patients had haemophilia A, 83.4% of which severe. 66.7% were on prophylaxis. 4 patients presented inhibitors, 75% of them were treated with immune-tolerance induction. At the examination 55.6% of patients had pain, in 7/10 caused by haemartroses. Five patients in the youngest group reported a mean value of pain intensity of 4.6, lower than the mean (6.6) in older group. In the control group seven children reported pain (25.9%), 5/7 were in the youngest group. In all cases the pain was caused by trauma. In the youngest control group the mean value of pain was higher than in the haemophiliacs (8.7), while in the other one it was similar to cases (7.4). 72.2% of patients practiced sports, of which 75% were swimmers. Due to pain 30% of patients had lost school days (mean 7 days), while 67% of them had to give up physical activity (mean 21 days).

Conclusions

The perception of pain is different among the younger and older hemophiliac children , lower in the former. The younger healthy subjects tended to attribute a double value to pain intensity, compared to the hemophiliacs of the same age. Pain causes a loss both in school days and in physical activity, worsening the quality of life of these patients.

Acknowledgments

Thanks to our young patients and their parents, and to the children of the “Elementary School “ of Forni di Sopra – Forni di Sotto (UD- Italy), to their parents and their teachers

Reference

Text

1. *Rambod M, Forsyth K, Sharif F, Khair K. Assessement and management of pain in children and adolescents with bleeding disorders: a cross-sectional study from three haemophilia. Haemophilia, 2016 Jan;22(1):65-71.*
2. *Dogan MC, Yazicioglu I, Antmen B. Anxiety and pain during dental treatment among children with haemophilia. Eur J Paediatr Dent. 2013 Dec;14(4):284-8*
3. *Holstein K, Klamroth R, Richards M, Carvalho M, Pérez-Garrido R, Gringeri A; European Haemophilia Therapy Standardization Board. Pain management in patients with haemophilia: a European survey. Haemophilia, 2012 Sep;18(5):743-52.*
4. *Riley RR, Witkop M, Hellman E, Akins S. Assessment and management of pain in haemophilia patients. Haemophilia, 2011 Nov;17(6):839-45.*
5. *Sherry DD. Avoiding the impact of muscoloskeletal pain on quality of life in children with hemophilia. Orthop Nurs, 2008 Mar-Apr;27(2):103-8*

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Cost-effectiveness of efmoroctocog-alpha in the treatment of severe haemophilia A patients: a single Centre experience

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Introduction

Primary prophylaxis started early at the dosage of 25-40 IU/kg three times/week is considered the gold standard for the treatment of patients with severe hemophilia, improving their quality of life (QoL) and reducing bleeds. In the last years a new extended half life (EHL) concentrate has been marketed, allowing a reduction of infusions and a concomitant improvement of compliance to treatment, but its cost is often considered high compared to traditional products.

Objectives

The aim of this study was to compare the differences between a prophylaxis with efmoroctocog-alpha and octocog-alpha in terms of bleeding reduction, concentrate consumption, number of infusions and costs in a group of patients with severe hemophilia A (HA)

Methods

All patients with severe HA, referred to the Hemophilia Center of Padua, previously receiving octocog-alpha (2nd generation), and subsequently switched to efmoroctocog-alpha were considered in our study. Statistical analysis were performed considering one year of treatment for any type of treatment.

Patient ID	Age	Previously Prophylaxis	No. of infusions/yr	IU/kg for prophylaxis/yr	New Prophylaxis	No. of infusions/yr	IU/kg for prophylaxis/yr	Δ (%) (Infusions)	Δ (%) (IU/kg)
E-01	15	29 IU/Kg three times week	156	4,524	35 IU/Kg every third day	122	4,270	-21.8	-5.6
E-02	12	30 IU/Kg every other day	183	6,405	40 IU/Kg every third day	122	4,880	-33.3	-23.8
E-03	13	37 IU/Kg three times week	156	5,772	50 IU/Kg two times week	104	5,280	-33.3	-8.5
E-04	15	33 IU/Kg two times week	104	3,432	50 IU/Kg every fifth day	73	3,650	-29.8	+6.4
E-05	22	28 IU/Kg three times week	156	4,368	26 IU/Kg two times week	104	2,704	-33.3	-38.1

Table 1 Difference between prophylaxis with octocog-alpha and efmoroctocog-alpha (grey) for each patient.

Results

Five previously treated patients (PTPs), 12-22 years-old were switched to efmorococog-alpha. All five PTPs in the last year of treatment with octocog-alpha had bleeds, with a mean annualized bleeding rate (ABR) of 4 (range 2-8). During the first year of prophylaxis with efmoroctocog-alpha only one patient had an ABR=2, while the other ones reported an ABR=0. Overall, the mean annual reduction of concentrate consumption and number infusion after the switch were respectively 13.9% and 30.3% (Table 1). A decrease on drug consumption also allowed an economic saving.

Conclusions

In our study the switch to efmoroctocg-alpha was proved to be more effective compared to prophylaxis with octocog-alpha. ABR and number of infusions were reduced, while compliance to treatment was improved. The cost of annual prophylaxis with efmorococog-alpha also resulted less expensive the former treatment.

References:

1. Efmoroctocog Alfa: A Review in Haemophilia A. Frampton JE. Drugs 2016.
2. Cost-utility analysis of life-long prophylaxis with recombinant factor VIIIFc vs recombinant factor VIII for the management of severe hemophilia A in Sweden. Henry N et al. J Med Econ. 2017.
3. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. Shapiro AD et al. J Thromb Haemost 2014.
4. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. Young G et al. J Thromb Haemost 2015.
5. Haemophilia patients' unmet needs and their expectations of the new extended half-life factor concentrates. von Mackensen S et al. Haemophilia 2017 Jul.

HIGH RISK OF INTRACRANIAL HAEMORRHAGE IN ADULT MILD HAEMOPHILIAC PATIENTS: DATA FROM THE EMO.REC REGISTRY

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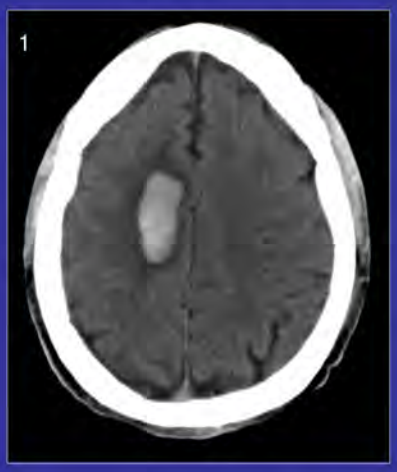
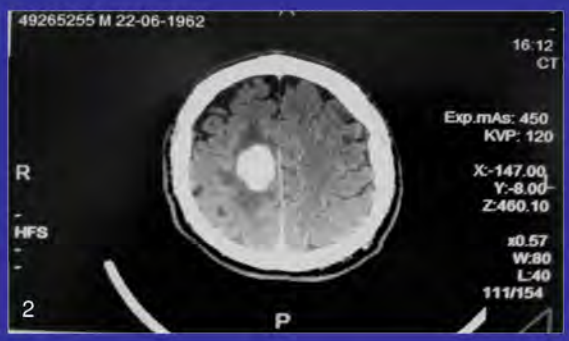
Introduction and Aim:

Intracranial haemorrhage (ICH) is the most serious event in patients with haemophilia (PWH) which leads to disability and in some cases death. ICH is more frequent in patients with severe haemophilia, aged <2 or >50 years while only few data are available for mild PWH. The aim of our study was to assess the incidence of ICH in a population of adult mild PWH, the risk factors for ICH, and the outcome

Methods:

All PWH with ICH were retrospectively (from 2009 to 2012) and prospectively (from 2013 to 2017) collected at 13 Italian Haemophilia Centres. The adult mild patients were subsequently evaluated and compared with the moderate/severe ones.





Figures 1-2. Two examples of Intracranial Haemorrhages (ICH)

Results:

35 patients with ICH (Figures 1-2) were recorded, 23 were adults, of whom 47.8% were affected by mild haemophilia. Mean age was 47 years, lower than non-mild patients (61 years). In 91% of the cases ICH were spontaneous, higher than in the other ones (75%). One patient had a low-titre inhibitor, same data recorded in the other group. 9 out of 11 mild patients suffered from hypertension (81.8%), while only 33.3% of non-mild subjects had this co-morbidity ($p<0.05$). Smoke and alcohol intake were similar between two groups. All mild patients were treated with coagulation factors concentrates only on-demand at the time of ICH event, while 25% of the moderate/severe patients were on prophylaxis. 27.3% of the mild patients died, 66.7% in the other groups ($p=0.09$). 50% of the survivors had a permanent disability. Prophylaxis after acute treatment was continued life-long (9%) or for 2-6 months (45.5%) in mild subjects. Data confirmed in the moderate/severe group where only 25% of the patients continued the prophylaxis after the acute treatment, and 50% of the survivors had disabilities.

Conclusions:

Incidence of ICH in adult mild PWH is high and similar to moderate/severe ones. The hypertension was proved to be the major risk factor for ICH in mild subjects, data not confirmed in the other group ($p<0.05$). 87% of the adult patients were on-demand treatment, 100% in case of the mild subject cases, which indicate the important role of the prophylaxis in preventing ICH.

References:

1. Intracranial haemorrhage in children and adolescents with haemophilia A or B – the impact of prophylactic treatment. Andersson NG et al. BJH 2017.
2. Intracranial haemorrhage in the Italian population ofhaemophilia patients with and without inhibitors. Zanon E et al. Haemophilia 2008.
3. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. Witmar C et al. BJH 2011.
4. Intracranial haemorrhage in haemophilia A and B. Lijung RC. BJH 2008.
5. Intracranial haemorrhage in French haemophilia patients (1991-2001): clinical presentation, management and prognosis factors for death. Stieltjes N et al. Haemophilia 2005.

Immune tolerance induction with moroctocog-alpha (Refacto/ Refacto AF) in a population of haemophilia A patients and high-titre inhibitors: data from the REF.IT Registry

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Introduction and Aim:

The development of alloantibodies to factor VIII is the most serious complication in haemophilia A (HA) patients. The primary objective in a patient with a high-titre inhibitor is the eradication. Immune tolerance induction (ITI) is the only therapeutic option to achieve this. The primary aim of our study was to assess the efficacy of moroctocog-alpha as ITI regimen in a population HA patients with high-titre inhibitor.

Methods:

The REF.IT Registry is a retrospective-prospective study that collected data on all patients with HA and high-titre inhibitor treated with moroctocog-alpha as ITI regimen at 12 Italian Hemophilia Centres. The study started on November 2013, and enrolled all eligible subjects from the previous ten years for the retrospective phase and up to the end of October 2017 for the prospective one.

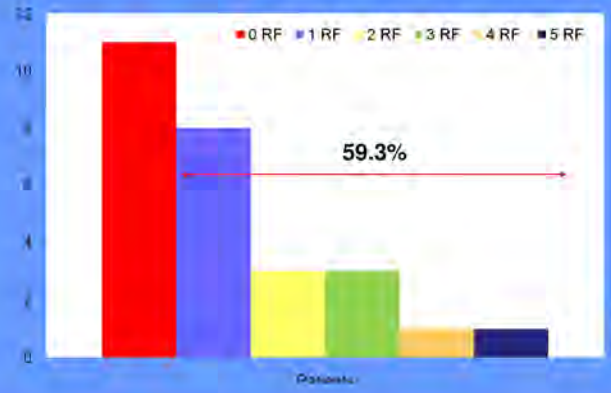

Figure 1 Patients with one or more risk factors (RF) for poor ITI-prognosis

Results:

Statistical analyses were performed on 27 patients. At the ITI onset 85.2% were children (<12 years). All patients were high responders, 88.9% had severe HA. 16/27 patients (59.3%) had one or more risk factors for poor ITI-prognosis (e.g. ITI rescue; age ≥7 years; historical inhibitor peak ≥ 200 BU; etc.). Figure 1. Of these, 56.3% achieved a complete or partial response. ITI failed in 11 patients, 63.6% of them with poor prognosis risk factors. In the remaining patients without poor prognosis risk factors a success was achieved in the 64% of cases. Inhibitors appeared after a median of 17 exposure days. Mean historical peak was 76.4 BU. The primary ITIs started on average 16.6 months after the diagnosis, with a mean inhibitor titre of 11.8 BU. 56.6% of the children achieved a partial or complete response after a mean of 15 months of treatment, while the same result was obtained by 75% of the adults after 22 months from ITI onset. 59.3% of patients were treated with high-dose moroctocog-alpha (200UI/kg/day), of these, 62.5% had at least one risk factor for poor ITI-prognosis.

Conclusions:

In our study partial or complete success of ITI was achieved in the 59.3% of total patients. Treatment with moroctocog-alpha resulted effective also in a population of high responder patients with poor prognosis risk factors.

References:

1) Immune tolerance induction(ITI) in haemophilia A – patients with inhibitors – the choice of concentrate affecting success. Kreuz W et al. Haematologica 2001; 2) Immune tolerance induction in haemophilia A patients with inhibitors by treatment with recombinant factor VIII: a retrospective non-interventional study. Rivard GE et al. Haemophilia 2013; 3) The principal results of the International Immune Tolerance Study: a randomized dose comparison. Hay CR et al. Blood 2012; 4) Induction of immune tolerance inhaemophilia A inhibitor patients by the *'Bonn Protocol'*: predictive parameter for therapy duration and outcome. Oldenburg J et al. Vox sanguinis 1999; 5) Immune tolerance induction in patients with severe hemophilia A with inhibitors. Ryu JE et al. Blood Res 2015.

OPTIMIZING THE TREATMENT: THE PRECISION MEDICINE USING MYPKFIT IN A POPULATION OF PATIENTS WITH MODERATE OR SEVERE HEMOPHILIA A

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INTRODUCTION and OBJECTIVES

The precision medicine usually represents the personalized treatment in oncology, based on biological characteristics of tumor and on patient's features. Same approach may be applied in haemophilia considering the molecular and clinical characteristics of disease, combined with the features of each patient as bleeding phenotype, lifestyle and pharmacokinetics (PK). An assessment of all these peculiarities allows to establish the best treatment for any single patient. The aim of this study was to remark the advantages of the precision medicine in a setting of patients with hemophilia A (HA) in terms of infusion frequency, outcomes, and concentrate consumption.

METHODS

The evaluation was performed in all patients with severe or moderate HA, referred to Haemophilia Centre of Padua and previously receiving octocog-alpha. Tailored approach was established using a computing program (MyPKfit) to determine the PK. Compliance to treatment was based on personal diary of infusions of each patient. The outcomes were assessed based on acceptance of new regimen of treatment and bleeding for each patient.

Patient ID	Previously Prophylaxis	No. of infusions/yr	IU/kg for prophylaxis/yr	New Prophylaxis	No. of infusions/yr	IU/kg for prophylaxis/yr	Δ (%) (IU/kg)	Δ (%) (Infusions)
*PD-01	50.0 IU/kg OD	NA	NA	37.8 IU/kg every other day	183	6,917	NA	NA
PD-02	53.6 IU/kg 3 times/wk	156	8,362	37.2 IU/kg every 72 h	110	4,538	-45.7	-29.5
PD-03	36.0 IU/kg 3 times/wk	156	5,616	34.9 IU/kg 3 times/wk	156	5,444	-5.1	=
PD-04	43.5 IU/kg 3 times/wk	156	6,786	29.7 IU/kg every other day	183	5,435	-19.9	+17.3
PD-05	34.5 IU/kg 3 times/wk	156	5,382	33.0 IU/kg 3 times/wk	156	5,148	-4.4	=
PD-06	22.7 IU/kg 3 times/wk	156	3,541	20.3 IU/kg every other day	183	3,715	+4.9	+17.3
*PD-07	45.5 IU/kg OD	NA	NA	51.9 IU/kg every 72 h	110	6,332	NA	NA
PD-08	25.0 IU/kg 3 times/wk	156	3,900	21.1 IU/kg every other day	183	3,861	-1.0	+17.3
*PD-09	32.2 IU/kg 3 times/wk	156	5,023	30.4 IU/kg 3 times/wk	156	4,742	-5.6	=
PD-10	33.4 IU/kg 2 times/wk	104	3,474	19.3 IU/kg every 72 h	110	2,355	-32.8	+5.8
PD-11	22.7 IU/kg 3 times/wk	156	3,541	20.9 IU/kg every 72 h	110	2,550	-28.0	-29.5
PD-12	27.3 IU/kg 3 times/wk	156	4,259	25.9 IU/kg 3 times/wk	156	4,040	-5.1	=
PD-13	25.0 IU/kg 2 times/wk	104	2,600	26.1 IU/kg 2times/wk	104	2,714	+4.4	=
PD-14	32.8 IU/kg 3 times/wk	156	5,117	37.7 IU/kg 2times/wk	110	4,147	-19.0	-29.5
Mean		147	4,800		143	4,057	-15.5	-2.7

Table 1 Previously prophylaxis and tailored approach (grey) for each patient. * Patients with moderate HA. OD: on demand treatment

RESULTS

PK evaluations of 14 patients were carried out. A Bayesian curve and a complete PK profile were determined for each patient. Afterwards a tailored prophylaxis was assessed individually employing PK data. In case of severe HA the weekly frequency of infusions was reduced in 3 patients, while it was increased in 4 subjects. In the remaining 5 patients, the frequency remained the same. 81.8% of patients reduced the annual consumption of concentrate. All reported outcomes were either improved or unchanged. Patients previously treated on-demand were excluded by statistical analysis (Table 1).

CONCLUSIONS

A PK-based prophylaxis may lead to improve outcomes and reduce drug consumption by simply correcting the treatment regimens adopted without distorting the individual patient's therapy.

References

1. PK-driven prophylaxis versus standard prophylaxis: when a tailored treatment may be a real and achievable cost-saving approach in children with severe hemophilia A. Pasca et a. Thromb Res, 2017; 2. Guidelines for the haemophilia treatment. Ssrivastava et al. Haemophilia, 2013; 3.Tailored versus standard prophylaxis in children with hemophilia A . Santoro et al. Semin Thromb Hemost, 2013; 4.Experience of tailoring prophylaxis using factor VIII pharmacokinetic parameters estimated with myPKFiT in patients with severe haemophilia A without inhibitors. Alvarez-Roman MT et al. Haemophilia, 2017; 5.Individualized prophylaxis for optimizing haemophilia care: can we ally this to both developed and developing nations? Poon MC et al. Thromb J, 2016