

Hemophilia Treatment in Developing Countries: Products and Protocols

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ABSTRACT

The most important aspect of management of hemophilia is to provide adequate replacement of safe clotting factor concentrates to prevent or treat bleeding episodes. There has been considerable progress in many countries in the developing world with regard to this aspect of care. However, very little data are available in the literature on the types of products being used for factor replacement and the doses being administered for control or treatment of bleeding in different countries. These data are important to document because only then can data from different centers be compared. This article provides data from seven countries: Korea, Malaysia, Thailand, Venezuela, Argentina, Iran, and India. It shows that there is wide variability not only in the types of products used (plasma to recombinant factor concentrates) but also in the doses administered (minimal to very high) for similar indications. Prospective documentation of data on musculoskeletal outcome at these centers and correlation with dose of factor replacement could help identify different models of care. Comparing such data and collating the experience in different countries could be useful for optimizing care and establishing cost-effective models. The combined experience in the developing world in providing hemophilia services should be used to define standards of care that are practical and to set achievable goals.

KEYWORDS: Hemophilia, treatment, developing countries

Objectives: On completion of the article, the reader should be able to (1) appreciate the great variability that exists in the management of hemophilia in several developing countries, and (2) review the difficulties that exist in having a uniform dosage scheme for factor replacement throughout the world.

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Treatment protocols for factor replacement in hemophilia vary. Doses are often based on individual experiences and availability of products rather than data from optimal dose-finding studies. When factor con-

centrates are available in sufficient quantities, as in developed countries, prophylactic factor replacement in large doses is the preferred manner of treatment for the prevention of bleeds.¹ Although there are some

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differences, fairly uniform dosage patterns have evolved in these countries in view of similar healthcare systems supported by the government or insurance.² In developing countries, however, hemophilia care is variably supported by the healthcare system. Widely different doses are used, usually on demand, for the treatment of bleeds. Much of these practice details remain undocumented and there is very little information on treatment protocols used for the management of hemophilia in these countries.³ This article describes the current approach to use of factor concentrates in seven countries from different parts of the developing world.

KOREA

The Korean Hemophilia Foundation (KHF) has 1740 patients with hemophilia registered. With a population of approximately 48 million, this accounts for approximately 60% of the total expected in the population (six to seven per 100,000 population). Registry data show that approximately 60% of patients are younger than age 25 years and 85% are younger than age 40 years.

Factor Concentrates

Both locally produced and imported factor concentrates are used in Korea. Intermediate- and high-purity plasma-derived concentrates are made within the country. Recombinant factor concentrates are provided to all children younger than 16 years of age. In 2004, a total of approximately 80 million units were used, approximately 30% of which were recombinant. This amounts to approximately 1.6 U/capita use of factor concentrates. Almost 60% of total factor concentrates used in the country are in the clinic associated with KHF in Seoul.

Protocols for Factor Replacement

The official mode of replacement therapy is on demand, but given the relatively generous amounts of factor concentrates available to individual patients, some children are receiving prophylaxis. All Korean patients have a right to receive factor concentrates and can use them at home. Each patient can receive up to 10 doses per month at 20 to 25 U/kg as an outpatient. There is no limit of dosage for inpatient therapy.

Although there is lack of consensus on dosage for different situations, the usual practice is to give 20 to 25 U/kg for musculoskeletal bleeds. This is repeated until resolution of symptoms. For major surgery (e.g., joint replacement), 100% levels are maintained for 3 days followed by 20% lower targets every 3 days until day 9. Thereafter, 20 to 40% levels are maintained until the end of 6 weeks. For minor surgery, 100% levels are maintained for the first 2 days followed by 70 to 100% until day 14. Lower levels are used for arthroscopic surgery

and radioactive synoviorthesis. Physiotherapy is performed under 20 to 30% cover.

Management of Patients with Inhibitors

Immune tolerance induction has been successfully completed in 10 patients with a dose of 100 U/kg three times weekly. However, immune tolerance induction is not reimbursed.

Both activated prothrombin complex concentrate (APCC) such as factor VIII inhibitor bypassing activity (FEIBA) and activated recombinant factor VIIa (rFVIIa) are available for treatment of bleeds.

Adjuvant Therapy

Both intravenous and intranasal preparations of desmopressin acetate (DDAVP), are available. Tranexamic acid is used for mucosal bleeds and menorrhagia. Fibrin sealant is also available and is used for surgical hemostasis but is not reimbursed.

Reimbursement of Cost

All Koreans are covered by a national medical insurance scheme that covers 80% of the cost. The remaining 20% is covered by the government. People with assets valued at more than U.S. \$500,000 have to pay for their medical costs up to U.S. \$3000.

MALAYSIA

The national registry had 941 patients with hemophilia by 2004. This is approximately 60% of the expected number in the population of approximately 24 million.

Factor Concentrate

All patients are treated entirely with factor concentrate. Eighty percent of concentrates are imported and 20% are obtained through contract fractionation using Malaysian plasma. The average annual use per patient is approximately 16,000 U for FVIII deficiency and 42,000 U for those with FIX deficiency.

Protocol for Factor Replacement

A national guideline is available. Generally, patients receive on-demand therapy. Patients with recurrent intracranial or target joint bleeds receive secondary prophylaxis for 3 to 6 months or longer. Muscular skeletal bleeds are managed with doses of 20 to 30 U/kg. For major bleeds such as iliopsoas bleed, patients are given 30 to 40 U/kg initially and the subsequent doses and duration of treatment are adjusted according to clinical response. For major surgery, 100% factor level is the goal

during surgery and the dose is reduced to 50% after surgery. Factor replacement is given until the wound is healed or when sutures are removed.

Management of Patients with Inhibitors

Patients with inhibitors are managed with activated and nonactivated prothrombin complex concentrates as well as with rFVIIa. Immune tolerance therapy is offered occasionally at 25 U/kg three times a week for up to 6 months.

Adjuvant Therapy

DDAVP is available and used in patients with mild deficiency. Tranexamic acid and epsilon-aminocaproic acid (EACA) are used to control mucosal bleeds and during dental surgeries.

Reimbursement of Cost

Factor concentrates are available free of charge at all hospitals within the Ministry of Health, where nearly all patients are treated.

THAILAND

With a population of 62 million, the expected number of patients with hemophilia is approximately 4000. Of these, 1325 (approximately 30%) were registered in 2004.

Because national data were not available, most of the data mentioned below pertain to the major treatment centers located at the University Hospitals.

Factor Replacement Products

Fresh frozen plasma (FFP) and cryoprecipitate continue to be widely used in Thailand for factor replacement, accounting for 55 to 60% of total factor usage. The remainder is made up of intermediate- to high-purity factor concentrates. The average annual quantity used by patients with FVIII deficiency is approximately 3600 U; for those with FIX deficiency, the average annual quantity used is approximately 3000 U.

Protocols for Factor Replacement

In general, treatment is provided on-demand at the treatment center. Some patients receive home therapy. No primary prophylaxis is practiced but secondary prophylaxis for 1 to 3 months is given to patients after corrective joint surgery or intracranial bleeds. Single-day prophylaxis is also available for children for special events.

Musculoskeletal bleeds are usually treated with a dosage of 10 to 30 U/kg. For hemarthrosis, the initial dose is 20 to 30 U/kg followed by 10 to 15 U/kg for 3 to 7 days depending on the response. For major bleeds (intracranial, iliopsoas), an 80 to 100% level is initially maintained followed by 40 to 50% levels for 5 to 7 days or longer. Adjusted-dose continuous infusion is used for surgery and major bleeds. Children receive an initial dose of 4 U/kg/h that is then adjusted by daily factor assays. Factor levels are targeted at 100% during surgery followed by 60 to 80% in the first 3 days, 40 to 50% during the next 3 days, and 30 to 40% during the next 2 weeks or until suture removal.

Management of Patients with Inhibitors

Management of patients with inhibitors is difficult. PCC, APCC (FEIBA), and rFVIIa are used depending on availability. Immune tolerance induction is occasionally attempted with locally prepared cryoprecipitate.⁴

Adjuvant Therapy

DDAVP is available only in intravenous form and is used for patients with mild disease. Tranexamic acid is used for dental procedures and mucosal bleeds. Fibrin sealant (manufactured at the National Blood Center of the Thai Red Cross Society), made with heat-treated cryoprecipitate and commercially available human thrombin, is also used for dental procedures and for surgical hemostasis before wound closure.

Reimbursement of Cost

The costs of factor replacement for the employees of the government and their children up to 20 years of age are reimbursed. Recent reforms allow a budget for treatment of patients in hospital where FFP, cryoprecipitate, and cryosupernate are predominantly used with minimal amounts of factor concentrates.

VENEZUELA

The national registry in Venezuela has 1444 patients (1101 with hemophilia A and 343 with hemophilia B). With a total population of approximately 24 million, this would be > 95% of the total number expected. This is attributed to the fact that during the last 5 years, there has been a concerted effort in the country to actively survey and characterize any person with a potential bleeding disorder.

Factor Concentrates

Venezuela has gradually moved away from the use of cryoprecipitate.⁵ A variety of intermediate- and

high-purity factor concentrates are used. These are centrally purchased and provided to the treatment centers. Those patients who are covered by social security can receive a mean dose approximately 30,000 U/yr (approximately 40% of patients), whereas those covered by the National Health Service (approximately 60% of patients) receive approximately 20,000 U/yr. A total of approximately 22 million U has been used annually to produce a per capita use of 0.92 U.

Protocols for Factor Replacement

Factor replacement is generally provided on demand. Both bolus and continuous-infusion strategies are used. No primary prophylaxis is performed. Secondary prophylaxis of short duration is provided for those with target joints or after central nervous system (CNS) bleeds.

Musculoskeletal bleeds are treated with 40 to 50 U/kg doses (three doses at 0, 24, and 72 hours). Early treatment of hemarthroses is done with 30 U/kg. For major surgery, 70 to 100% levels are maintained during the procedure followed by initiation of bolus or continuous infusion 4 hours after surgery for 5 to 7 days or until suture removal.

Management of Patients with Inhibitors

Limited quantities of PCC, APCC, and rFVIIa are available for the treatment of these patients. Immune tolerance induction is not attempted.

Adjuvant Drugs

DDAVP is used for patients with mild disease after a trial response is assessed. Tranexamic acid is used for dental procedures and mucosal bleeding. Fibrin sealant is used for surgical procedures.

Reimbursement of Cost

The cost of treatment with factor concentrates for hemophilia is covered by the National Health Service and Social Security. The Hemophilia Foundation of Venezuela provides DDAVP, tranexamic acid, PCC, APCC, and rFVIIa (occasionally) for those in need. The payment for these is optional.

ARGENTINA

For a population of approximately 37 million people, the national registry has 1793 patients. This would account for approximately 80% of the expected number in the country per usual estimates of the prevalence of hemophilia.

Factor Concentrates

Only high-purity plasma-derived and recombinant factor concentrates are centrally procured for replacement therapy. About 50% of the registered patients receive an average of more than 30,000 U/year. The remaining patients receive lower quantities.

Protocols for Factor Replacement

Argentina is perhaps the first developing country to have sanctioned primary prophylaxis for all children with hemophilia who have healthcare coverage. Currently, procedures are being established to procure prophylaxis also for children, even those without such coverage. Prophylaxis is administered at the following doses: 30 to 50 U/dose, three times a week for hemophilia A and twice a week for hemophilia B. On-demand treatment is provided for the rest at 20 to 50 U/dose every 12 to 24 hours until resolution of symptoms. For minor surgery, factor levels of 100% are provided during the procedure, followed by 50 to 70% levels postoperatively for 3 to 5 days. For major surgery, similar levels are provided during surgery, followed by 70 to 100% levels for 7 to 10 days.

Management of Patients with Inhibitors

Appropriate products are available for managing patients with inhibitors. Low responders are treated with large doses of the same factor concentrate (100 to 200 U/kg). Both APCC and rFVIIa are used for those with high responding titers. Minor bleeds are treated with APCC at 50 to 100 U/kg for 1 to 2 days every 12 hours or with rFVIIa 90 µg/kg every 2 to 3 hours for two to four doses. Major bleeds are similarly treated until resolution of symptoms. Minor and major surgery is undertaken in such patients with the same protocol of replacement therapy but for a longer duration (7 to 10 days). However, immune tolerance induction is not performed.

Adjuvant Drugs

DDAVP is used intravenously in mild cases. EACA is used for dental procedures and fibrin sealant is used for dental and orthopedic surgeries.

Reimbursement of Cost

The costs for patients receiving prophylaxis are covered fully by the government. For on-demand treatment, 50% costs are covered by health insurance (for those who have it) and the other 50% by the government. For those without health insurance, the Argentinean Hemophilia Foundation covers the cost along with coverage by the government.

IRAN

About 5000 patients with hemophilia are registered in the national registry of Iran. In a population of approximately 64 million, this would suggest that the prevalence of hemophilia in Iran is higher than the usually estimated number of 6 to 7/100,000 persons.

Factor Concentrates

A variety of intermediate- and high-purity factor concentrates are used. These are centrally procured and distributed through recognized treatment centers. A total of approximately 80 million U of concentrates are used, translating to a per capita consumption of approximately 1.25 U. Local fractionation facilities are being established.

Protocols for Factor Replacement

Factor replacement is essentially on-demand in treatment centers. A small number of patients in Teheran receive home therapy. Primary prophylaxis is not attempted but secondary prophylaxis is provided for those with target joints or recent CNS bleeds.

The dosage used for musculoskeletal bleeds is 15 to 25 U/kg administered every 12 to 24 hours until symptoms resolve. Factor levels are maintained at 60 to 100% for surgery and continued at 50 to 80% levels for 5 to 7 days for minor procedures and 10 to 14 days for major procedures.

Management of Patients with Inhibitors

APCC and rFVIIa are available for the treatment of these patients. APCC is used in doses of 50 to 100 U/kg/dose for treatment of bleeds every 12 hours until resolution. rFVIIa is given at 70 to 90 µg/kg per dose every 2 to 4 hours until bleeding resolves. Immune tolerance induction is occasionally attempted with 50 to 100 U/kg of the appropriate factor concentrate, three times a week.

Adjuvant Drugs

DDAVP is available and used for bleeds and minor surgical procedures in patients with mild disease. Tranexamic acid is used for treating mucosal bleeds and for dental procedures.

Reimbursement of Cost

All patients with hemophilia in Iran are covered by a national insurance plan. Procedures and diagnostic tests are reimbursed and factor concentrates are provided free of charge. The distribution, however, depends on how well the local treatment centers can use these opportunities for the patients living in those areas.

INDIA

With more than 1 billion population, the expected number of patients with hemophilia in this country would be approximately 60,000. However, given the poor treatment facilities available, life expectancy may be low and therefore at any time the actual number may be much lower than expected. In the national registry, approximately 8000 patients with hemophilia are registered, accounting for perhaps approximately 15% of the expected number.

Factor Replacement Products

Factor concentrates have been available here for the last 15 years, but availability of specific products depends on the cost and supply. Mostly intermediate-purity products are used because of their low cost. This was initiated by the Hemophilia Federation India (HFI) in 1989 and continued as none of the manufacturers or the government had taken an initiative in this direction until very recently. During the last 1 to 2 years, there has been direct marketing in the country and the central government provides 2.5 million units. Only a total of approximately 10 million units of factor concentrates are purchased every year, translating to approximately 1000 to 1500 U/kg annually per patient. This does not take into account the whole blood, plasma, and cryoprecipitate that are still used by those who do not have access to factor concentrates. Access to factor concentrates is not uniform throughout the country and depends not only on the ability to pay for it but also on local availability.

Protocols for Factor Replacement

Most patients receive infrequent on-demand factor replacement in treatment centers for major bleeds only. A few patients take on-demand treatment at home. Economic constraints have promoted the use of very low doses. The usual dose for musculoskeletal bleeds is 5 to 15 U/kg. In more serious bleeding (CNS), 30 to 50 U/kg may be used for 3 to 5 days, followed by lower doses after that, depending on response and clinical condition. For surgery, 40 to 60% levels are provided for minor procedures and 60 to 100% levels are provided for major procedures. Much lower levels are maintained after that: 30 to 40% levels for the first 3 days followed by 20 to 30% levels for next 3 days and then 10 to 20% levels till wound healing and suture removal.⁶

Management of Patients with Inhibitors

This is an extremely difficult problem in India. Only small amounts of APCC are available through the HFI. Most patients cannot afford this product and those who can, use it in small doses of 10 to 25 U/kg for one to two doses for the treatment of bleeds. Elective surgery is

not undertaken in patients with inhibitors. Immune tolerance induction cannot even be contemplated in the current situation.

Adjuvant Drugs

Intravenous DDAVP is available and is used in the few patients with mild disease who have been identified. Tranexamic acid is used extensively for the control of mucosal bleeding and for dental procedures. Fibrin sealant is not marketed in the country.

Reimbursement of Cost

Support from the central government for hemophilia is currently restricted to the provision of 2.5 million units of clotting factor concentrate annually. Different state governments are in the process of considering support. At present, the vast majority of patients have to support their own care. In this situation it is the HFI that supports the treatment of many patients through its own funds and through many of its chapters. Hemophilia care in India also relies significantly on donated factor concentrates from the World Federation of Haemophilia and other sources.

DISCUSSION

The data presented above bring out several aspects of hemophilia care in developing countries. It is obvious that in most countries large proportions of the expected number of patients remain undetected. Therefore, major efforts are needed in increasing awareness of this condition, both among the general population and in the medical community. It is also clear that ensuring an appropriate distribution and delivery system for factor concentrates is as important as procuring them, if all patients with hemophilia in the country are to benefit. In fact, this can be a more difficult goal to achieve in some countries compared with lobbying for and getting funds allocated for the purchase of adequate quantities of factor concentrates. This requires integrating hemophilia care into the national health system and training physicians in different parts of the country to provide that care.

Optimal doses for factor replacement are an issue of interest throughout the world.⁷ Ideally, data are needed on long-term outcome of patients with hemophilia treated with different doses of factor replacement therapy. A few small, single-center, short-term studies addressing these issues were performed in the late 1970s

and early 1980s but are no longer considered feasible or even ethical in developed countries where prophylactic administration of large doses of factor concentrates has become the standard of care. In the absence of such data and the unlikely prospect of such studies being conducted, perhaps the next best option is to collect longitudinal data on different patient populations treated with different doses. Such data would show outcomes at those doses and provide much-needed information that could help define different models of care and the outcomes that could be expected.⁸ A multicenter international study is currently underway in nine developing countries to address this issue.

Finally, it is important for clinicians in countries with limited resources to appreciate that current dosages used in developed countries have a large margin of comfort.⁹ Although there is no doubt on their efficacy, this may not be the most cost-effective way to treat hemophilia. It is in everyone's interest to attempt to find the dose that would be safe for achieving hemostasis without overtreating patients. The resources saved could be used to further so many other aspects of hemophilia care that need attention throughout the world.

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