

Management of Acute Bleeding in Severe Haemophilia Using Homeopathic Medicines: a Multicentric Case Series

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Received date: Apr 14, 2015; Accepted date: Aug 17, 2015; Published date: Aug 24, 2015

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Abstract

Background & Introduction: Homeopathic medicines are extensively used in India and are recognized by the Government for regular management of different ailments. Though factor concentrates are being supplied increasingly at government hospital yet the distribution is erratic and patchy across the country. Present study builds our previous experience and explores the utility of homeopathic medicines along with non-factor managements in arresting the acute bleeding episodes in severe haemophilia patients who has very little access to factor concentrates.

Materials and Methods: Severe haemophilia patients (PWH) having acute bleeding episodes of various types with very little access to factor concentrates who continued to bleed or remained symptomatic at least for 6 hr after all measures (RICE, EACA/ Tranexamic acid locally or systemically, in small number of patients single dose of factor concentrates/ FEIBA or novoseven. Local pressure etc) failed to arrest the bleeding or the symptoms were included in this analysis in this multicentric report. All the patients maintained a bleeding diary.

The study was conducted at three centres at Mumbai. Nashik and Surat between December 2007 to march 2014 involving 494 patients between 9 days to 51years of age. Evaluation of bleeding and the degree of relief by homeopathic medicines was done by experts in modern medicine in a blind fashion. Homeopathic Medicines were given by trained homeopaths with experience in treating haemophilia for at least 5 years. For objective selection of medicine computer based repertorisation was initially done using RADAR software and from the list of appropriate medicines the homeopathic practitioner selected his own medicine for the occasion.

Efficacy of the intervention was assessed by i) Stoppage of bleeding within 6 hr of treatment ii) No drop in haemoglobin of more than 1 Gm/dl over 24 hr iii) No need for blood transfusion and/ or factor infusion after homeopathic intervention iv) Relief of pain and swelling and other features of inflammation in cases of haemarthrosis. All coagulation related investigation of the patients were done at the haemostasis laboratory of National institute of Immunohaematology at Mumbai, which is an International Haemophilia Training Centre (IHTC).

Initial correlation of selection of similar class of homeopathic medicines between three homeopathic physicians at three centres was tested by requesting them to select homeopathic medicines in hypothetical cases and analysing them by Fleiss kappa statistic. Chi square (X²) test was done to see the statistical significance of management compared to those cases where at least one dose of factor concentrate was given.

Results: Four hundred and ninety four severely affected PWH from Nashik (292), Mumbai (182) and Surat (20) presented with 636 episodes of bleeding. Five hundred and seventy eight bleeding episodes (91%) were successfully managed with homeopathic medicines only. In 21 episodes (3.1%) homeopathic medicines failed but responded to additional factor concentrates. 37 patients who received factor concentrates without any apparent benefit in the given time responded to homeopathic medicines. Out of 31 patients who bled with inhibitor (2.4–6.7 BU/ ml) but 23 of these patient responded (65%) to homeopathic medicines. The inter prescriber correlation on the class of medicine prescribed by three homeopathic physicians was substantial (Fleiss kappa of 0.67). Pain relief in these patients were also substantial (87/105 i.e., 83% patient with acute haemarthrosis). Single patient of severe factor XIII deficient who continuously bled from umbilical stump responded to abrotanum 30.

Conclusion: Homeopathic medicine prescribed by homeopaths experienced in managing haemophilia patients can significantly reduce bleeding and improve symptoms in a large majority of severely affected haemophilia patients along with non-factor supportive therapy and can be an alternative way of treating these patients where factor concentrates are not optimally available.

Keywords: Severe haemophilia; Acute bleeding; Similia principle; Repertorisation software; Developing country; Effectiveness of homeopathic medicines; Haematuria; Epistaxis; Melaena; Haemoptysis; Haematemesis; Acute haemarthrosis

Introduction

Haemophilia is a genetic bleeding disorder resulting from deficiency of clotting factor VIII (Haemophilia A) or Factor IX (Haemophilia B). PWH suffer various kinds of bleeding manifestations during his life time which may range from superficial cut to severe life threatening intracranial bleed. These bleeding episodes include superficial cut, epistaxis, gum bleed due to loss of deciduous teeth, deeper mucosal bleed for e.g., Genitourinary tract or gastrointestinal bleed, acute joint bleed etc. (major joints e.g., knee, elbow ankle are most often affected joints) [1].

In developing country like India where 80% of population reside in rural areas and more than 80% of PWH belong to lower socio-economic strata having per capita income between 15,000-40,000/year. The exorbitant cost of the standard haemophilia management, the distance need to travel by PWH in order to visit primary health centres, and improper management of haemophilia by the rural physician's led the scope to use alternative medicines in such constrained situations. With the use of homeopathic medicines attempts were made to limit this treatment gap [2,3].

Increased usage of complementary and alternative medicine was found among the haemophiliacs due to financial and other logistical reasons. Significant factors associated with usage of these therapy were economic status, comorbidity status and educational status of the family. Individualized homeopathic medicines are proved to reduce the consumption of factor concentrate by reducing the frequency of bleeding episodes. In the present study we evaluated a large number of severe and moderately severe PWH for its efficacy in stopping acute bleeding and related symptoms in PWH using homeopathic medicines. The present study is a prospective observational study with homeopathic medicines as an intervention in PWH with acute bleeding episodes.

Materials and Methods

Patients

494 Consecutive patients diagnosed as severe haemophilia from Nashik, Mumbai or Surat Chapter were recruited for the study.

Inclusion criteria

494 patients from Nashik (292), Mumbai (182) and Surat (20) Chapters, diagnosed moderate or severe Haemophilia A or B between December 2007 to March 2014 were included in the study. All these patients were diagnosed at National Institute of Immunohaematology (one of the International Haemophilia Training Centre in India) using standard techniques. These patients were negative for standard viral markers and liver function tests. Prothrombin time in all these patients

were normal. These patients were aged between 9 days to 51 years. All the patients maintained a diary for bleeding. 32 out of these 494 patients had varying degree of inhibitors (2.4-6.7 BU/ml) which was present for at least one year after its detection (1-2.5 years). One of the patient who was 9 days old had severe factor XIII deficiency and presented with continuous umbilical bleeding since birth and needed blood transfusion twice (30 ml each time). 76 patients of 497 had haemophilia B and rest had haemophilia A. All inhibitors were against factor VIII only.

Exclusion criteria

None

IRB

The study was cleared by Institutional Review Board and parent of all patients provided consent for treatment and all the photographs presented in this paper were taken after their consent.

Intervention

The patients were treated at a clinic or hospital with paracetamol 500 mg to 1 gm/4 hourly for pain along with RICE therapy in cases of joint bleed. If the pain was unbearable the patient was given Etoricoxib (60 mg) if more than 6 years of age and 90 mg if more than 18 years of age along with Omeprazole 20 mg in those cases where there no gastrointestinal bleed. Antifibrinolytic drugs example tranexamic acid mouth wash was used at 25 mg/ 5 ml concentration as a mouth wash for mouth bleeding. For haematuria fluid therapy along with alkalinisation of united bed rest was given. For gastrointestinal bleeds systemic tranexamic acid at a dose of 15-20 mg /kg every 6 hr by IV injection was initiated and red cell transfusion was given when needed. Factor concentrates and anti-inhibitor therapy whenever was available was administered. In the event of bleeding not stopping within 6 hr and patients discomfort i.e., pain restlessness etc. increasing during the period and no more factors concentrate available for the patient the he is referred to homeopaths for further engagement.

Before the study was started and every 6 months subsequently all these seven homeopaths took an examination of six bleeding cases with different histories and presentation and independently selected homeopathic medicines appropriate for the condition. The correlation on the prescription of these drugs as a particular class was tested by using Fleiss statistic.

TK & AS assisted by AN at Nashik Centre, AS at Surat Centre and PS at Mumbai centre selected homeopathic medicine using similia principle with their long experience in managing haemophilia with homeopathic medicines. Their selection was assisted through repertorisation[5] where a short list of 4-6 homeopathic medicines are selected on the basis of most compatible medicine using a software programme called RADAR[6]. This software takes clinical details of the patients which include in addition to site of bleed, amount of bleed color. Associated clot at the site, pain and other symptoms along with mental symptoms of the patients i.e., anxious, indifferent restless,

peevish etc. This data is then searched by the software out of more than 2500 reference works in homeopathic medicines from world literature and short lists 4-6 medicines. From this short listed medicine a homeopath then selects the medicine based on his/ her experience.

Hammamelis Q (mother tincture) (Witch Hazel) was used as universal local haemostat. Briefly during acute bleeding episode the patients were advised to use the medicine soaked on a gauze piece and apply locally (1 drop of medicine in 30 ml of clean water). The medicine is also given spoonful (5 ml) orally every 30 minutes till the main homeopathic medicine started acting. For pain all the homeopaths used *Arnica 30*, *Ledum pal 30* or *Rhus tox 30* (All homeopathic Medicines and Placebo unless stated was given as 4-6, no 30 sugar of milk globules moistened with 2 drops of given medicine or ethyl alcohol in the case of placebo). When active medicines were not needed placebo was continued 4-6 dose 6 hourly no more than 4-6 doses of active homeopathic medicines given every 30 minutes to 4 hr depending on the emergency of the situation were required to control the condition. If 4-6 doses did not control the condition i.e., bleeding and pain it was considered failure of homeopathic Medicines.

Placebo was continued with improvement in general condition of the patient. The selection of acute medicine was based on acute totality. In cases where medicine was changed Gibson-Miller remedy relationship was followed [5]. The potency and repetition of medicine was decided by individual susceptibility [7]. In cases where bleeding did not stop within two hours of administration of homeopathic medicine, factor infusion was recommended. In some cases where bleeding continued for more than two hr but the clinical condition of patient did not deteriorate or where patient opted for homeopathic medicines were continued with homeopathic medication. The cases where despite of factor infusion, no satisfactory relief of complaints observed, individualized homeopathic medicines were prescribed.

All the medicines were purchased from the same company i.e., (Dr. Willmar Schwabe India Pvt.Ltd, N Delhi) by one of us (TK) and then distributed to other centres for usage during the whole period of study to maintain the uniformity of potency and quality of medicines among three centres.

Infusion of factor concentrates

When factor concentrates were infused the amount was infused to raise the factor between 30%-50%. Only one dose of factor could be administered in 31 patients. One dose of Novoseven (60 ug/kg) or FEIBA (50 iu/kg) was available for patients with inhibitor (32 patients, Inhibitor level between 2.4-6.7 BU/ml).

Assessment of the progress

The patient was evaluated independently by physicians trained in modern medicine (KG, SK and RK). Bleeding was visually confirmed where possible and in concealed bleeds, pain swelling local inflammation and vital signs, measurement of the swelling and ultrasound examination was the guide. USG was taken in all the patients where applicable. The evaluations were made every 2 hourly till the patients bleeding stopped, haemoglobin/PC stabilised or pain and signs of inflammation was relieved. Standard biochemical,

haematological, grouping, cross matching and coagulation work up was done as per the clinical requirement and situation.

Statistical analysis

Fleiss statistic [9] was used to see the inner homeopathic prescriber's variation in selecting the medicine in cases of bleeding with different clinical presentations. Chi square test was used to compare the effects of Homeopathic medicine compared to factor concentrates. All laboratory investigation on haemostasis was done as per Dacie [10].

Permission to publish the photographs were obtained from the parents of the patients.

All coagulation assays except emergency screening coagulation tests were done at National Institute of Immunohematology, Mumbai. AP was responsible for statistical analysis of the data.

Results

636 bleeding episodes were encountered over the period between December 2007 and March 2014. These includes epistaxis(206), bleeding from the gums (216), haematuria(36) and miscellaneous bleeds (178) which includes Haemoptysis, Haematemesis, Melena, Conjunctival bleed, bleeding from the injured site, local haematoma and haemarthrosis and haematuria.

Hammamelis mother tincture found effective in concealed as well as in open bleeding. For open bleeding as in gum bleed or bleeding from cuts or wounds *Hammamelis* mother tincture was applied as 10-15 drops depending upon the site of affection dissolved in 30 ml of water. The bleeding gum was packed 15-20 minutes with gauze piece with the mixture of *Hammamelis* mother tincture and water.

Figure 1: Range of homeopathic medicines used in this study. Abrotanum 30 was used in a single baby with severe factor XIII deficiency and continuous umbilical cord bleeding.

Homeopathic medicines were prescribed as per the symptom similarity and were repeated in three to five doses in lower triturations. *Merc Sol*, *Calc carb*, *Sepia*, *Sulphur*, *Silicea*, *Veratrum album*, *Tuberculinum*, *Medorrhinum*, *Lachesis*, *Lycopodium*, *Phosphorus*, *Pulsatilla*, etc., were the medicines used in these acute bleeding episodes (Figure 1). These medicines were prescribed in 30°C or 200°C potency. After active medicine dummy sugar globules rolled in ethyl alcohol (placebo) continued twice daily dosage for a few days. The minimum time required to manage the open bleed i.e., gum bleed or bleeding from the cuts was recorded as 4 minutes 33 seconds and the mean time was recorded as 90 minutes for haemarthrosis/ intramuscular bleed mean time recorded as 11.3 hr and minimum time recorded was 8 hr. Haemostasis was achieved as early as within 30 minutes in case of epistaxis and mean time recorded as 45 minutes whereas in case of haematuria and melena the minimum time required was 120 minutes and mean time required was 240 minutes (Table 1). Pain relief in haemarthrosis was also reasonably rapid at 2 hr.

Type of bleeding	Min time required	Maximum time required	Mean time required
Epistaxis	30 minutes	180 minutes	45 ± 7.5 min

Bleeding from teeth	4 min 33 sec	120 minutes	90 ± 23 min
Haematuria/ melena	120 minutes	360 minutes	240 ± 38 min
Miscellaneous(conjunctival bleed, bleed from injured site etc.)*	6 hr	36 hr	16.5 ± 7.5 hr
Pain relief in Haemarthrosis	2 hr	6.5 hr	3.2 ± 1/3 hr

Table 1: Management of acute bleeding. *Haemarthrosis (105),Haematoma (19),Bleeding due to injury including epistaxis and oral bleeds(27).Melena (12), haematemesis (11), Cord Bleed(1), Haemoptysis(3).

Out of 636 bleeding episodes 578 (90.88%) episodes were managed with homeopathic medication whereas 21 (3.30%) episodes required factor infusion ($P < 0.0001$; χ^2 with Yates correction and 1 degree freedom=84.257). These were the bleeding episodes where bleeding did not subside or no other sign of improvement like reduction in the intensity of pain or mental disturbance was observed within next 24 hr. All episodes of epistaxis and haematuria were successfully managed with the homeopathic medicines. In 37(5.8%) episodes early resumption of bleeding follow concentrate infusion were the reasons to undergo homeopathic medication. (Table2). 13/23 patients needed 2-3 units of red cell transfusion. In rest of these patients there was no drop of haemoglobin of more than 1 gm/dl. Hb level at presentation varied between 10.3-12.7 gm/dl (10.8 ± 1.6 gm/dl) except in patients

with haematemesis and melena where haemoglobin dropped to 7.6 gm/dl (6.3-7.9 gm/dl) before transfusion was started. There were 32 patients with varying degree of Inhibitors (2.4–6.7 BU/ml) but in only 9 patients the by pass agents controlled the bleed whereas in the remaining 23 patients responded to homeopathic medicines ($P < 0.0001$; χ^2 with Yates correction and 1 degree freedom=25.536). The patient with umbilical cord bleed had severe factor XIII deficiency and responded quickly to *Abrotanum 30*.

TK, AS (surat) and PS consistently together had a Fleiss statistic between. 0.57-0.68 showing strong correlation and they took the lead role in medicine selection.

Type of bleeding	Min time required	Maximum time required	Mean time required
Epistaxis	30 minutes	180 minutes	45 ± 7.5 min
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Pain relief in Haemarthrosis	2 hr	6.5 hr	3.2 ± 1/3 hr

Table 2: Management of acute bleeding. *Haemarthrosis (105),Haematoma (19),Bleeding due to injury including epistaxis and oral bleeds(27), Melena (12), haematemesis (11), Cord Bleed(1), Haemoptysis(3).

Illustrative cases

Case 1

A 4 ½ years old severe hemophiliac presented with the bleeding from upper incisor with history of fall of the tooth. Bleeding was continuing since past nine hr and patient reported on 15 December 2012 at 4:46 pm (Figure 2a). Hammamelis Q was applied by the patient who stopped the bleeding for two hr but it resumed again. The child was active and playful despite continuous bleeding. There were no signs of fear on face or by gestures even on seeing the blood flowing from the mouth. The child was continuously biting the injured site in spite of bleeding. On examination it was observed as bright red fluid bleeding. The acute totality was constructed and Phosphorus 30 single dose was given at 5:06 pm and bleeding stopped within 4 minutes 32 seconds by the formation of clot (Figure 2b). But the clot formed was quiet large in size which could resume bleeding in case of its fall due to gravitational force. The child was still active and restless. He was attempting to run out despite of having large clot hanging from the gum. The case was re-analyzed and prescribed Tuberculinum 200 single dose, at 6:06 pm. Within next seven minutes the clot fell down without any further bleeding. The child was made to wait for next 45

minutes to see any resumed bleeding which did not start again. Being Sunday next day they informed telephonically of child's well-being and no further bleeding and followed up on 17 December 2012 and was found to be well (Figure 2c).

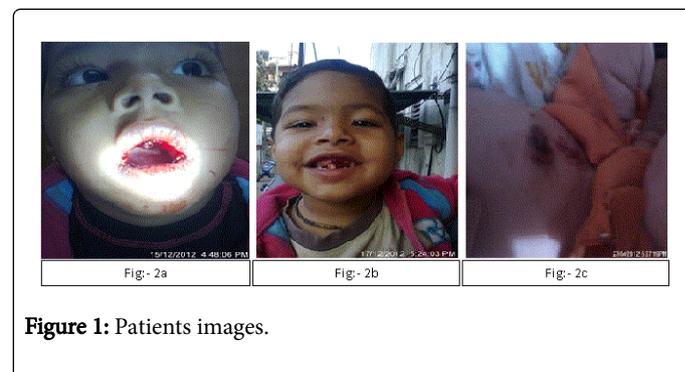


Figure 1: Patients images.

Case 2

A 9 days old male baby was referred by pediatrician having deficiency of Factor XIII on 27 April 2012. The child was presented with the bleeding from the umbilicus which started one day later of separation of umbilical cord from the placenta. The child was delivered normally and has the family history of haemophilia (deficiency Of Factor XIII) with mental retardation. The bleeding was observed as dark red in color (Figure 3a). Child appeared pale with marasmus of lower part of body, irritable and cross, with coldness of the skin.

In such case no behavioral symptoms could be elicited except irritability, but again it was a vague term without any specification. So The Dictionary of Practical Materia Medica By Dr. Robert [7] and the Materia medica by Dr Boericke [8] was referred where he advocated the use of Abrotanum in condition of oozing of blood and moisture from the navel of newborn. Abrotanum 30 three doses were prescribed to be given at 12 hr of intervals. The patient reported after 3 days with the clotting of blood and no more oozing of the blood (Figure 3b).

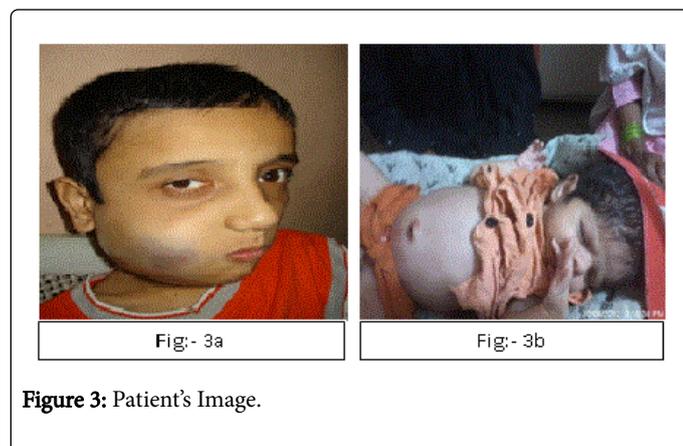


Figure 3: Patient's Image.

Case 3

A 11years old severe hemophiliac with inhibitor positive (6.7B.U /ml) presented with the intense swelling of right cheek (Figure 4a). On examination, bleeding observed under the floor of mouth with history of being slapped by mother (Figure 4a). The child was looking frightened and there was no activity. The child was looking frightened on account of swelling and inability to speak. He was taking care not to be hurt again. There was no activity on the part of the child.

Calcarea carb 30 was prescribed considering the acute totality. Three doses were repeated at 6 hr of intervals. Next days the swelling was observed to reduce and the clotted blood under the floor of mouth also observed to be reduced but still the child was unable to speak and open the mouth completely. The potency of the medicine was raised to 200C. Three doses were repeated at six hours of interval and advised to follow up next day. Next day they telephonically informed about the disappearance of clot and complete reduction of the swelling and visited 4 days later when the bleeding was completely gone (Figure 4b).

Discussion

The ideal modern management of severe haemophilia is regular replacement of deficient factor concentrates and in the case of haemophilia with significant levels of inhibitor bleeding episodes needs to be controlled with a variety of techniques including bypass therapy

and finally immunomodulation followed by prophylaxis wherever it is possible [11].

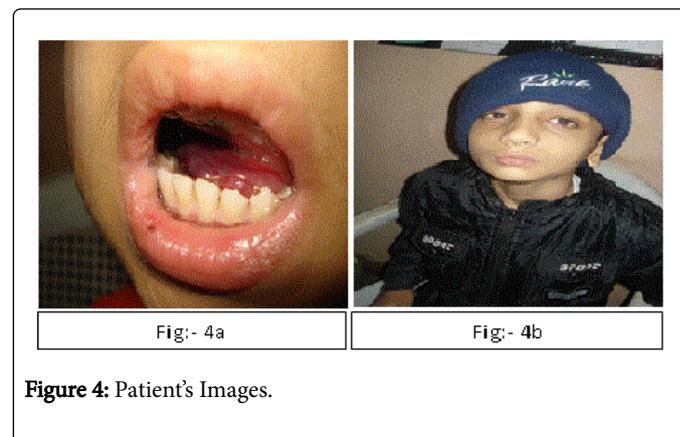


Figure 4: Patient's Images.

However all this is still a pipe dream for very poor PWH patients from developing countries [12]. Although the scenario is slowly changing in many countries yet it is going to take a lot of time before all PWH in the world can get good quality treatment. However what one can do in the interim period when patients come to the doctor with haemostatic challenge?

Antifibrinolytics like EACA and Tranexamic acid has been used in combination with lower dosages of factor concentrates or alone in any such situations [13]. In fact thromboelstographic classification of severe haemophilia has also been used to decide rationale antifibrinolytic therapy [14]. Traditional products like whole blood, fresh frozen plasma and cryoprecipitates not only prove inadequate in many situations but its potential to transmit various pathogens is something which we all want to avoid. Our finding of striking response in some patients with severe haemophilia where all other medicines including factor concentrates failed to control bleeding homeopathic medicine did so [15]. Hence a small trial was conducted to study whether homeopathic medicines substantially reduce factor concentrate requirements in a cohort of severely affected haemophilia patients [4]. This study showed 80% reduction of factor requirement in an on demand therapy schedule, this study could not be published in a main stream modern medicine journal mainly because we cannot explain in our present knowledge how homeopathic medicine works? However we must not forget that modern medicine progressed through empirical findings proving an observation then finding the cause.

The study conducted at Tata Institute of Social Sciences in Collaboration with King Edward Hospital Mumbai reported the use of Homeopathic medicines by 43.5% of PWH [3] in this country.

In the present study homeopathic medicines prescribed as per the principle of homeopathy found to arrest the bleeding without the need for factor concentrates. In cases where haemostasis was not to achieve within the desired period the use of modern conventional treatment was incorporated or vice versa. It is noteworthy to see that a large number of patients with inhibitor also secured haemostasis when by-pass therapy failed. It may be reasonably argued that in those situations where both factor concentrates as well as by pass therapy failed, the amount of the product used was not sufficient. While we all agree to that contention, in a real world situation, very few patients with inhibitor in a developing country can use the prescribed single dose of Novoseven at a dose of 270 ug/kg [16].

Our study clearly showed that haemostasis could be achieved by using homeopathic medicines as an alternative therapy.

The intelligent and timely use of both these therapy found to improve the general state of PWH. This positive interdisciplinary approach of these two different sciences needs to be welcomed in resource constrained set as in India.

The use of alternative therapy in haemophilia is not new. In Turkey one of the local herbal preparation called Ankaferd blood stopper has been extensively used as a local haemostat and its various applications has been published in more than hundred peer reviewed publications [17].

There are innumerable Homeopathic medicines from plant, animal and mineral kingdoms. These medicines were meticulously prepared by old masters [18] and they observed the reaction of these medicines in healthy volunteers which forms the empirical basis of its use in different conditions over the years.

One of the major challenges of prescribing homeopathic medicines is uniform prescription of medicine by different practitioners of the science. Recently this has been achieved by several software programmes. Other challenge of this branch of medicine is lack of plausible theory as to how these drugs act as following dilution in these drugs apparently no active drug is available. However several theories recently advanced to support the activity of homeopathic drugs [19]. Even if empirical in nature, over last two centuries overwhelming numbers of masters in this science have cured thousands of patients with different diseases using homeopathic medicines. This impressive data must surely need to be taken with some seriousness. Here we have presented a real world study where 80% of world's PWH reside and presently consume less than 20% of modern treatment resources.

Present kind of study can never be done in those countries where availability of profusion quantity of factor concentrate are available and clear evidence of their efficacy will prevent any attempt to look at alternative therapies like homeopathic medicines. However in India homeopathic medicines continues to provide substantial relief to PWH and being very cheap and affordable it serves those unfortunate 40% of the PWH population who still has no access to adequate factor concentrates as well as exerts for management of their condition.

Division of responsibilities

Dr. Tapas Kundu and Dr. Afroz Shaikh were the prescribing physician at Nashik Haemophilia Centre. Dr Priyanka Singh and Dr. Afiya Shaikh are prescribing physicians at Mumbai and Surat Haemophilia Centres respectively. Dr. Sudhir Kulkarni, the surgeon and Dr.Ranjana kulkarni, and Dr Kanjaksha Ghosh clinically evaluated effects of homeopathic medicine blindly and tried to provide factor concentrates whenever possible. Dr. Omkar Kumat collected and compiled the data and also worked as communication consultant. Ms Aruna Patil did the statistical analysis of the data. Dr. Kanjaksha Ghosh wrote the final draft of the manuscript.

Acknowledgment

The authors are thankful to interns and students serving as volunteers to collect history, create awareness and analyze the diaries

of PWH and Dr. Rita Kundu for her contribution through co-ordination of the whole project. Authors gratefully acknowledge the contribution of radiologists and laboratory medicine faculties in all the three centres for helping in the management of the cases.

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