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An Exploratory Study of Autonomic Function Investigations in Hemophiliacs on Homoeopathy Medications Using Impedance Plethysmography

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Abstract

Background. Status of autonomic homoeostasis in hemostasic disturbances due to hemophilia needs to be studied. *Objectives.* To compare autonomic nervous system markers measured by heart rate variability (HRV) and blood flow variability (BFV) in hemophiliacs and healthy age-matched control population using medical analyzer system. *Design.* Cross-sectional study. *Settings.* Motiwala Homoeopathy Medical College, and Hemophilia Clinics, Nashik. *Subjects.* Eighty subjects. *Interventions.* Nil. *Outcome Measures.* Autonomic function markers for HRV and BFV. *Results.* Among 80 subjects, BFV time domain measure, root mean square of successive NN (normal-to-normal) interval differences (RMSSD), was significantly higher among hemophiliacs than nonhemophiliacs. Frequency domain analysis parameter, low frequency for both HRV and BFV was significantly higher among hemophiliacs as compared with nonhemophiliacs. *Conclusions.* Hemophiliacs were shown to have higher autonomic activity as compared with healthy controls. Homoeopathic medicines used as an adjunct was associated with decrease in parasympathetic modulations.

Keywords

hemophilia, homeopathic, autonomic control

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Hemophilia is a known a genetic disorder affecting hemostatis. It results from deficiency of clotting factor VIII (hemophilia A) or factor IX (hemophilia B). People with hemophilia (PWH) suffer various kinds of bleeding manifestations during their lifetime, 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 eexample, genitourinary tract or gastrointestinal bleed, acute joint bleed, and so on (major joints, eg, knee, elbow, and ankle are most often affected joints). In developing country like India, where 80% of population reside in rural areas and more than 80% of PWH belong to lower socioeconomic strata having per capita income between INR 15,000 and INR 40 000/year. The exorbitant cost of the standard hemophilia management, the distance need to travel by PWH in order to visit primary health centres, and improper management of haemophilia by the rural physicians led the scope to use alternative medicines in such constrained situations. With the use of homoeopathic medicines attempts are being made to limit this treatment gap.

The Government of India facilitated the spread and development of homoeopathy by recognizing and integrating it into health care delivery. The Government of India recognizes ayurveda, yoga and naturopathy, *unani*, siddha, and homeopathy (AYUSH) system of medicine in the same way as it recognizes modern medicine.[1] The Ministry of AYUSH was formed with effect from November 9, 2014 by elevation of the Department of AYUSH. The Department of Ayurveda, Yoga and

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Naturopathy, Unani, Siddha and Homoeopathy, abbreviated as AYUSH, is a governmental body in India with the purpose of developing education and research in ayurveda (Indian traditional medicine), yoga, naturopathy, *unani*, siddha, and homeopathy, Sowa-Rigpa (traditional Tibetan medicine), and other indigenous medicine systems. With the new national policy, the Government of India aims to promote India as a center of excellence for the AYUSH systems and harness their potential for improving primary and preventive health care. The policy aims at making the AYUSH systems the preferred choice of treatment in primary care and will set specific targets for regulation and research as well as set standards for AYUSH medicines and treatments. A very conscious aim of the strategy is to fill the gap in the supply of doctors by training AYUSH practitioners to handle primary care needs. As part of a wider strategy promoting AYUSH, India is seeking to collaborate with the World Health Organization (WHO) and the United States in research and development of AYUSH. One specific objective will be to establish WHO benchmarks for the practice of the AYUSH systems.[2]

Increased usage of complementary and alternative medicine was found among hemophiliacs due to financial and other logistical reasons. A patient can choose which system of medicine he or she wants to be treated with. Sometimes, they opt for a combination of more than one system. Hence there is no moral or ethical barrier in giving homeopathic medicines to PWH once they have understood aits management by the given system of medicine and availability of other systems of medicine as well as "factor concentrates" available to them.[3] Significant factors associated with usage of this 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.[4] In a recent study, authors evaluated a large number of severe and moderately severe PWH for the efficacy of homeopathic medicines in stopping acute bleeding and related symptoms in PWH. It was observed that homeopathic medicine prescribed by homeopaths experienced in managing hemophilia patients can significantly reduce bleeding and improve symptoms in a large majority of severely affected hemophilia patients along with nonfactor supportive therapy and can be an alternative way of treating these patients where factor concentrates are not optimally available.[5]

Autonomic nervous system plays an important role in hemostasis. Surprisingly, first report of the concept that sympathetic activation has influence on hemostatic processes dates back to 100 years. Epinephrine injection was shown to have effect on clotting time in human as well as animal experiments.[6] Blood coagulation in cats was increased if scared by barking dogs. Epinephrine infusion increases factor VIII: C in plasma from a normal 100% to an average of 200%.[7,8] Study of autonomic nervous system may further help in understanding interaction among the 2 prongs of the system, namely sympathetic and parasympathetic. Physiologic variability analysis of biological variables controlled by autonomic nervous system, can study the functioning of the autonomic nervous system.[9] It has been shown recently that, homeopathy medicine produces observable changes in autonomic parameters, even in healthy subjects. Jindal et al[10-12] had recorded heart rate variability (HRV) and blood flow variability (BFV) after administration of sulfur 1 M, gelsemium 10 M, and phosphorus 30 c and observed unique changes. Similar observations were reported by Mishra et al[13] using this technique. Recently, study by Kundu et al[5] showed a significant role of homeopathy medicines as adjunct to routine allopathic care for hemophiliacs.

To our knowledge, there are no studies comparing autonomic activity using HRV and BFV markers among hemophiliacs and nonhemophiliacs. Also, autonomic activity changes if any, in hemophiliac on individualized homoeopathy medicines as an adjunct to routine allopathic care has not been studied before. In view of these factors, in order to understand in a cross-sectional study design, autonomic activity in hemophiliacs, we compared autonomic profile of hemophiliacs and healthy age-matched control population using NICOMON (Skanray Healthcare Pvt Ltd, formerly L&T Medical, Mysuru, India). Data were analyzed by using Medical Analyzer System (Electronics Division, Bhabha Atomic Research Centre, Mumbai, India).[13] Furthermore, autonomic activity was compared between hemophiliacs with and without individualized homeopathic medicines.

Material and Methods

A total of 80 subjects were included in the study. Eighteen healthy controls (mean age 11 $\pm$ 5 years) and 62 (mean age 10 $\pm$ 2 years) clinically stable but severe hemophiliac patients coming for routine homoeopathy consultation for hemophilia A were included in the study. Based on factor VIIIC assay, all patients were having factor levels 0.01 IU/mL; hence, all of them were in severe hemophilia category of hemophilia classification. Stable hemophiliacs, meaning those who have no active bleeding at least for 6 weeks before the test, were included in the study. All PWH visiting the hemophilia center were screened for the study and all of them consented for participation in the study. Homeopathy medicines are advised as an adjunct to regular allopathic consultation and treatment routinely to these patients. Clinical evaluation of the PWH was carried out by 3 blinded allopathy consultants for clinical status of hemophilia who used Wong Baker Pain Rating Scale, Joint Mobility or Disability (Modified), and Frequency of Bleeding Scale for this purpose.[14,15]

The study was carried out at the Hemophilia Care Center, and interviews were taken by homeopathy specialty investigator and 2 trained doctors. The standard format of questionnaire and specific clinical evaluation format, routinely used for assessing response to treatment and progress PWH for treatment with individualized homeopathic medicine for hemophilia care, was used in this study. The study was approved by institutional ethics committee. It was a double-blinded or double-masked study in terms of autonomic profile assessment.

After initial assessment, written informed consent was obtained and variability spectrum of heart rate and peripheral blood flow was recorded. The whole process lasted for 45 to 60 minutes. Autonomic profile of hemophiliacs and healthy age-matched control population was recorded using NICOMON (Skanray Healthcare Pvt Ltd). It

records the variability spectrum of heart rate and peripheral blood flow (details of the technology and techniques are mentioned elsewhere[13]). Data were analyzed by using Medical Analyzer System (Electronics Division, Bhabha Atomic Research Centre).[13] This system is based on the principle of Impedance Plethysmography (IPG) and records blood volume changes in any part of the body noninvasively by measuring its electrical impedance, which is inversely proportional to blood volume changes. The rate of change of impedance thus gives the rate of change of blood volume.

The pulsatile blood flow during ventricular systole is reflected as well-formed peaks in IPG, and the instantaneous heart rate is derived from the time elapsed between 2 consecutive peaks. The blood flow index (blood flow in milliliters per 1000 cm^3 of body tissue per cardiac cycle) is obtained from the amplitude of the peak and gross electrical impedance of the body segment.[16]

For measuring autonomic tone, 4 band electrodes were placed on dominant arm. Outer 2 electrodes (I1, I2) are called as current carrier electrodes and inner 2 electrodes (V1, V2) are called as voltage-sensing electrodes. After initial stabilization of signal, recording was started and a 5-minute record of instantaneous heart rate and blood flow values thus obtained. Then it was analyzed off-line, where it is interpolated to obtain periodic values of these parameters as a prerequisite before fast Fourier transformation. The task force specified many different HRV metrics for both short-term records (5 minutes) and long-term records (24 hours). Taking the reliability and accuracy of HRV measurements into account,[17] SDNN (standard deviation of normal-to-normal RR intervals), and RMSSD (root mean square of successive normal-to-normal interval differences) as the time domain measurements were chosen in this study. For frequency domain analysis, fast Fourier transform was done, the HRV and BFV signal were decomposed into its individual spectral components and their intensities.[10,17,18] The subsequent Fourier transform depicts the contribution of various rhythms that cause variability in the physiologic parameters and represented by very-low-frequency (VLF 0.01-0.04 Hz), low-frequency (LF 0.04-0.15 Hz), and high-frequency (HF 0.15-0.40 Hz) peaks. Changes in the LF band spectral power (0.04-0.15 Hz frequency range) reflect a combination of sympathetic and parasympathetic autonomic nervous system outflow variations, while changes in the HF band spectral power (0.15-0.40 Hz range) reflect vagal modulation of cardiac activity. The physiological explanation of the VLF component (0.0033-0.04 Hz) is much less defined and the existence of a specific physiological process attributable to these heart period changes might even be questioned.[19] The study was not reported to clinical trial registry of India and we are in process of reporting it retrospectively. Data were analyzed using statistical software package SPPS, using Levene's test for equality of variances and *t* test for equality of means, 2-tailed with level of significance $\leq .05$. The study flow sequence was as follows:

1. Protocol compliance obtained and screening of subjects
2. Clinical assessment
3. Autonomic function measurement
4. Offline data analysis of population data

Results

A total of 80 subjects participated in the study. Of these, 62 were hemophiliacs and 18 were nonhemophiliac healthy controls with average age 10.0 ± 2.4 and 11.1 ± 5.4 years, respectively. Among these 62 hemophiliacs, 13 were not on individualized homeopathic medicines, 49 were on individualized homoeopathic medicines. Among these 49 patients, 34 were on homeopathic medicines and feeling better symptomatically, and 12 were on homeopathic medicines and were not feeling better symptomatically. The data of 3 patients was not recorded properly due to technical limitations, so were not analyzed and were excluded. The investigator who analyzed data was blinded to identity of subjects as patient or healthy control. Data were analyzed using SPSS statistical software package. Table 1 shows comparison of all hemophiliacs (n = 62) and healthy controls (n = 18) for HRV and BFV variables where statistical significance was observed ($P < .05$). It was observed that time domain analysis parameter, RMSSD for blood flow variability analysis showed statistically significant difference between control group and all hemophiliacs, with increased RMSSD in hemophiliacs. For frequency domain analysis, statistically significant difference was seen for LF (Area2) of HRV, and LF (Amplitude2) of BFV, with higher values in hemophiliacs. The remaining variables for HRV and BFV did not reach statistical significance. Table 2 shows that for subgroup analysis, HF (FC3) component of BFV analysis was significantly different for hemophiliacs not on homoeopathic medications when compared with other subgroups. HF component (FC3) was also significantly different when compared between all hemophiliacs on homeopathic medication and those without homeopathic medication.

Table 1. Comparison of All Hemophiliacs, H (n = 62) and Healthy Controls, C (n = 18) for Heart Rate Variability (HRV) and Blood Flow Variability (BFV) Variables.[a]

Variable	Group	Mean	SD	*P* (*t* Test for Equality of Means)
RMSSD BFV	Control (n=18)	0.2550	0.08557	.007
	Hemophiliacs (n=62)	0.3202	0.09299	
Area2 (LF) HRV	C	25.1984	12.36413	.001
	H	39.0000	17.63019	
Amp2 (LF) BFV	C	19.5000	11.96299	.021
	H	25.7333	10.75109	

Abbreviations: SD, standard deviation; RMSSD, root mean square of standard deviations of beat-to-beat intervals; LF, low-frequency components; Amp2, Amplitude2.
[a]Level of significance, $P < .05$.

Discussion

In the present study, we report among time domain measures, that LF component of both the HRV and BFV analysis were higher in hemophiliacs as compared with healthy controls. Since frequency of LF component represent combination of sympathetic and parasympathetic activity, its increase depicts stress response activation of autonomic nervous system. Previous studies show dose-dependent effect of epinephrine on factor VIII:C3. In addition, epinephrine infusion consistently

Table 2. Subgroup Analysis: Hemophiliacs Not on Homoeopathic Medications (HC) When Compared With Other Subgroups, Namely Hemophiliacs on Homoeopathic Medicines Feeling Symptomatically Better, Hemophiliacs on Homoeopathic Medicines Not Feeling Better Symptomatically.[a]

Variable	Group	Mean	SD	*P* (*t* Test for Equality of Means)
FC3 (HF) BFV	HC (13)	0.3429	0.03417	.004
	All hemophiliacs on medicines (46)	0.2680	0.08280	
FC3 (HF) BFV	Hemophiliac control not on homoeopathy medicines (HC) (n = 13)	0.3429	0.03417	.004
	Hemophiliacs on medicines feeling better symptomatically (n = 34)	0.2675	0.08650	
FC3 (HF) BFV	HC (13)	0.3429	0.03417	.002
	Hemophiliacs on medicine not feeling better symptomatically (12)	0.2656	0.07216	

Abbreviations: SD, standard deviation; BFV, blood flow variability; HF, high frequency; FC3, Frequency Component 3.
[a]Level of significance, $P < .05$.

induced an increase in plasma von Willebrand factor antigen levels to a mean peak response of 166%. The studies also suggest that platelets become activated by adrenergic infusion in vivo as evidenced by an increase in different markers (eg, platelet size, aggregation, and releasing factors),[20] which supports our findings of appropriate autonomic activation for hemostasis. So, this increase in LF component may be suggestive of autonomic activation in hemophiliacs as a response to stress. Interestingly, time domain parameter RMSSD for BFV, which is considered as marker of parasympathetic activity, was found to be higher in hemophiliacs as compared with nonhemophiliacs, which may be reflecting peripheral vascular compensation for reduced vagal activity. Subgroup analysis, comparing patient receiving homeopathic medicines with those not receiving, showed significant changes HF FC3 component of BFV analysis, which depicted decrease in parasympathetic activity. This decrease in parasympathetic activity in hemophiliac patients taking homeopathic medicine may suggest possible effect of homeopathic medicines on BFV by reducing vagal input to heart, allowing sympathetic system to respond to stress and hemostasis.[3-5]

Limitations of the Study

Sample size of healthy controls could have been more to represent healthy population's autonomic activity in better way but due to practical issue with feasibility we could not match it. Though our study focused on autonomic parameters, its correlation with biochemical parameters would have been helped further understanding of the same. Repeated physiological variability measurement on different occasion in same subject would have been better in assessing reliability of measurements and exploring further the mechanisms of symptom relief in hemophiliacs on individualized homoeopathic medicines. We will be definitely exploring on these lines in our future research on this aspect.

Conclusion

Hemophiliacs were shown to have higher sympathetic and parasympathetic activity as compared with healthy controls. Homeopathic medicines use as an adjunct was associated with decrease in parasympathetic modulations in hemophiliacs. The HRV and BFV markers by this technique can be used to asses status of autonomic activity profile of hemophiliacs, which may further help in management of these patients using routine allopathy care as well as adjunctive individualized homeopathic medicines. Individualized homeopathic medicines may affect symptom alleviation by altering autonomic responses of the patients suffering from hemophilia. Further follow-up studies will be needed to study autonomic profile of hemophiliacs to assess the effect of homeopathic medicines on autonomic activity of hemophiliacs.

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Author Contributions

TKK was involved with ideation and execution of study, homeopathy expertise, and manuscript review. PPP was involved with ideation for possible autonomic component, technique expertise, data collection and analysis, and manuscript preparation. GDJ performed higher data analysis and provided technique expertise. FFM performed higher data analysis, provided homeopathy expertise, and reviewed the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Institutional ethical committee approval.

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