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Journal of Preventive Medicine and Holistic Health

Journal homepage: <https://www.ipinnovative.com/journals/JPMHH>

## Review Article

# Hemovigilance in India: Corrective Action towards Safety of Blood Transfusion

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### ARTICLE INFO

#### Article history:

Received 02-01-2021

Accepted 04-01-2021

Available online 02-02-2021

#### Keywords:

Serious Hazards of Transfusion

(SHOT)

European Hemovigilance Network

(EHN)

Pharmacovigilance Program of India

(PVPI)

Hemovigilance Program of India

(HvPI)

International Hemovigilance Network

(IHN)

### ABSTRACT

Hemovigilance is defined as the surveillance procedures covering the blood transfusion chain (from the collection of blood and its components to the follow-up of its recipients), intended to collect and assess information on unexpected or undesirable effects. The word hemovigilance is derived from the word pharmacovigilance, which encompasses activities and systems to collect information useful in supervising medicinal products, with particular reference to adverse drug reactions in human beings, and to evaluate such information scientifically. An adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function. The aim of hemovigilance is to detect and to analyze all untoward effects of blood transfusion in order to correct their cause and to prevent recurrence, and to improve the safety of blood transfusion. Although several reports have been published on adverse events, including transfusion-associated deaths, the relative risk based on the number of actual cases divided by the number of units of blood products issued or transfused, is relatively low. Scope of different hemovigilance systems varies due to differences in spectrum of reporting. Ideally, the hemovigilance system should cover processes throughout the entire transfusion chain, from blood donation, processing, and transfusion to patients for the monitoring, reporting, and investigation of adverse events and reactions and near misses related to blood transfusion.

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## 1. Introduction

The revolutionary work on hemovigilance started in France in 1991, with the setup of monitoring systems by Blood Transfusion Committees followed by the starting of the Centre National d'Hémovigilance in 1992. Since 1993, multiple definitions of hemovigilance have been formulated differing from one country to another. In some countries, only focus was laid on the transfusion act, while in other countries hemovigilance started from the very first part of the blood collection process. Further, some systems focused on the follow-up of only immediate adverse events, others on long-term adverse events, and others on both. Because of the complex interactions in the transfusion

chain, the scope of hemovigilance is all levels of potential transfusion hazards, i.e. from the selection of potential donors to the transfusion to the recipient. To reach this goal: the core of hemovigilance, as a system of public health surveillance, is a prospective surveillance and alert system. On European level, hemovigilance started around 1995. The European Council published its Resolution of June 2, 1995 and a Communication on "Blood Safety and Self-Sufficiency in the Community" with the aim to improve public confidence in the safety of the blood supply. In the same year and for the first time on ISBT Congresses, at the ISBT 5th Regional (4th European) Congress in Venice, Italy, a hemovigilance symposium "Hemovigilance procedures in Transfusion Medicine" was organized. The conclusion of this symposium was that hemovigilance should be considered as part of the quality

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assurance process in transfusion medicine. In 1996, the European Commission organized at an informal meeting of Ministers of the European Commission in Adare, Ireland, a Colloquium on Blood, which resulted in the document "Blood Safety and Self-Sufficiency: an Agenda for the European Community". Six areas of action were defined and one of them was hemovigilance. In the United Kingdom, the Serious Hazards of Transfusion (SHOT) scheme was launched, which receives and collates reports of death or complications of transfusion of blood or components on a voluntary confidential basis. In SHOT's first annual report the findings indicated that blood itself is extremely safe, but it draw attention to the need to direct resources towards the development of novel systems to ensure that it is correctly administered. At different countries discussions were organized on the structure of hemovigilance systems (voluntary or compulsory), the required (type of) data, the data on blood donors, the data on the usage of blood components or also on plasma derivatives, and on the security of systems. Further the set up-of an information alert system and a website as a tool of communication was discussed intensely.<sup>1-6</sup>

## 2. Methodology

The method involved the review of research articles, review articles and other materials from the internet source. Various journals, articles, reports were thoroughly searched for analysis of Hemovigilance scenario in different countries. The information obtained helped to understand the status of Hemovigilance compared to other countries.

## 3. Progress of Hemovigilance in Developed Countries

### 3.1. Advances in US and Europe

The implementation of a national US hemovigilance system remains incomplete, despite the transfusion of over 17 million units of blood products annually. Currently, US hemovigilance consists of mandatory reporting of blood transfusion and blood collection fatalities and voluntary reporting of transfusion-associated adverse events (TAAEs) to the US Food and Drug Administration (FDA), and voluntary reporting of TAAEs to the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) Hemovigilance Module (HM). Several other robust research and private-sector programs have contributed to a better understanding of transfusion and blood collection safety over the years, including the National Heart, Lung, and Blood-funded REDS (Recipient Epidemiology and Donor Evaluation Study) studies, the AABB Center for Patient Safety, and donor vigilance programs through Vitalant (formerly Blood Systems), and the American Red Cross. In the other hand, the objectives for a European Hemovigilance Network (EHN) are aiming to increase blood safety at a European level.

The aim of EHN is to develop and maintain in Europe a common structure with regards to safety of blood and blood products aimed on hemovigilance of blood transfusion and transfusion medicine. The first inventory showed that legislation in the field of hemovigilance was not equal and that not in all countries regulation concerning hemovigilance exists by law. In Austria, France, Germany, Netherlands, Sweden and Switzerland, notification of AEs to the authorities is mandatory. In Denmark, only notification of viral infection by blood is required. Notification on a voluntary basis is implemented in Belgium, Greece, Ireland, Luxembourg, Russia, Sweden, and the United Kingdom.<sup>7</sup>

### 3.2. Advances in India

In India, there was a lack of standardized and effective hemovigilance system. This was mainly due to the reporting of adverse transfusion event was not mandatory. Also, under-reporting by the medical staff was observed. However, with gradual increase in awareness over the last few years on hemovigilance and blood safety, many institutes and centers across India have recently published significant data on adverse transfusion events. Thus, considering the significance of the situation, a national hemovigilance program was launched as an integral part of the Pharmacovigilance Program of India (PVPI) at a national level on December 10, 2012. As per the Ministry of Health and Family Welfare, Government of India, there are 2760 authorized blood banks in India which emphasize the need of a centralized hemovigilance system in India.<sup>8</sup>

## 4. National Hemovigilance Program of India

Indian Pharmacopoeia Commission in collaboration with National Institute of Biologicals, Noida, Uttar Pradesh launched Hemovigilance Program of India (HvPI) on December 10, 2012 across the country as an integral part of PVPI, under Ministry of Health and Family welfare, Government of India. It is a centralized, well-structured program for monitoring adverse reactions associated with transfusion of blood and administration of blood products. This program was implemented with a dedicated budgetary provision of INR 29.36 crore for a Five Year Roadmap Plan (2012-2017) and divided into three phases (initiation phase for financial year 2012-13, expansion and consolidation phase for financial year 2013-15 and expansion and maintenance phase for financial year 2015-17) for establishment of hemovigilance program. The main aim of this program was to track adverse reactions and episodes related to blood transfusion and blood product administration and to help determine the trend and recommend best practices and interventions required to improve patient care and safety. A software Haemo-Vigil was developed to collect and analyze the data related to

hemovigilance all over India. For HvPI, National Institute of Biologicals is acting as the co-ordinating centre. The ultimate goal of this HvPI was to be a part of the International Hemovigilance Network (IHN) and the same was achieved in December 2014. Currently IHN is having 33 countries as its member including India and provides a global forum for sharing best practices and benchmarking of hemovigilance data.<sup>9,10</sup>

### 5. Objective of Reporting Adverse Reactions in National Hemovigilance Program

1. Monitor blood transfusion reactions
2. Create awareness among health-care professionals
3. Generate evidence-based recommendations
4. Advise the Central Drugs Standard Control Organization (CDSCO) for safety-related regulatory decisions
5. Communicate findings to all key stakeholders
6. Create national and international contacts

### 6. Transfusion Reactions under HvPI

There are several types of transfusion reactions, which can be subdivided into different groups according to the time of occurrence, pathogenesis and/or symptomatology. According to the time of occurrence, it is subdivided as acute (< 24 hours after transfusion) and delayed (> 24 hours after transfusion) reactions. As per their pathogenesis, adverse reactions can be further divided as infectious and non-infectious adverse reactions. Major non-infectious acute reactions include Acute Hemolytic Transfusion Reactions (AHTR), Febrile Non-Hemolytic Transfusion Reactions (FNHTR), allergic reactions including anaphylactic reactions, Transfusion Associated Acute Lung Injury (TRALI), Transfusion Associated Circulatory Overload (TACO), hypotensive reactions and hyperkalemia. Non-infectious delayed transfusion reactions are Delayed Hemolytic Transfusion Reactions (DHTR), Delayed Serological Transfusion Reactions (DSTR), Post-Transfusion Purpura (PTP), Transfusion-Associated Graft Versus Host Disease (TAGVHD) and hemosiderosis. The major acute infectious adverse reactions are due to bacterial contamination of the blood component, and delayed infectious reactions may be due to viral (e.g., hepatitis B/C, HIV) or parasitic (e.g., malaria) transmission. Regarding documenting and reporting of transfusion reactions, a reporting format, Transfusion Reaction Reporting Form (TRRF) has been prepared by HvPI, which mentions all information regarding the patient, transfusion reaction details, blood component or blood product details, list of relevant and necessary investigations needed to be done, nature of adverse reaction and imputability assessment. This TRRF is freely available in the website of HvPI. The safety regulatory guidelines will be formulated and

modified from time to time by CDSCO based on the inputs from TRRF, which will be implemented by health care professionals and blood banks for the benefit of patients. All the medical colleges in India have been encouraged to enroll under HvPI and upload the transfusion related adverse events through the haemo-vigil software after filling up the transfusion reaction reporting form. As of now, 368 centers have been enrolled in this program. Medical colleges / Institutes/ Hospitals / Blood banks in India can enroll in this program. Hemovigilance reports contain no identifiable or re-identifiable data; that no patient, clinician, staff member or healthcare facility is identifiable from materials contained within the report. The data on adverse transfusion reactions and events are entered into the “haemo-vigil” software from the transfusion medicine department/blood bank/hospitals/medical colleges and transmitted to HvPI-NCC, NIB. HvPI-NCC reviews completeness of data quality, prepare SOPS, guidance documents and communicate recommendations of to IPC. IPC finally forwards recommendations of hemovigilance advisory committee to Drug Controller General of India (DCGI)-CDSCO body. It is the DCGI-CDSCO who formulates blood and blood product transfusion safety related regulatory decisions and communicate to stakeholders. There is a big role of the industry as well. It is expected that the manufacturers of equipment, reagents and disposable materials for blood centers and hospitals should establish the post marketing survey procedures for the collection and processing of data related directly and indirectly with blood transfusion. Between January 2013 and April 2016, a total of 3903 transfusion reactions were reported to the HvPI, National Coordinating Centre, NIB, Noida. These 3903 reactions had occurred in 3807 patients, thus 96 patients had more than one transfusion reaction. Out of 337 pediatric patients, 8 were neonates. The distribution among males and females was 1955 and 1852 patients, respectively. Recovery from the reaction was recorded in 3542 patients, recovery was associated with sequelae in 20 patients, and the outcome was not known in 228 patients. Mortality was reported in 17 patients; however, only in five patients, it was related to the transfusion reaction, and in the remaining 12 patients, the mortality occurred due to underlying clinical condition and the transfusion episode was coincidental.

To summarize, FNHTRs constituted the most frequently reported transfusion reaction (40.84%). Mild allergic reactions which were reported in “other reaction” category comprised 27.26% of the reactions. Anaphylactic/hypersensitivity reactions were 12.68% and hemolytic transfusion reactions were 4.31% (164 out of 3903). Out of these 164 hemolytic transfusion reactions, 22 (0.56%) were due to ABO mismatch, 58 (1.49%) were due to non-ABO alloantibodies, and 84 (2.15%) were due to nonimmune causes. There was incomplete information

on cause/error which led to the ABO mismatch. In 9 out of 22 cases where information was available, 6 cases had a bedside sampling/administration error. Allo-antibodies were identified and reported in three patients only. In the rest, immune-hematology workup was not available for review in the TRRF. The nonimmune hemolytic transfusion reactions were mainly due to ward/bedside storage and handling errors as per the available information. The remaining categories of transfusion reactions reported were TAD (2.38%), TACO (0.67%), PTP (0.64%), TTBI (0.46%), TRALI (0.26%), TT malaria (0.03%), and TAGvHD (0.03%). In the category of “other reactions,” majority were mild allergic reactions (27.26%) and mild FNHTRs (5.02%), and the rest were either not specific or symptoms not possible to classify into a specific reaction. Mortality was reported in 17 patients; in ten patients, it was clearly due to the underlying critical condition of the patient and transfusion was not causally related. Two deaths were associated with hemolytic transfusion reactions, one each with TT bacterial infection, TACO, TRALI, TAD, and severe FNHTR. As of 2015, a total of 24 continuing medical educations (CMEs) on HvPI have been organized all across the country for proper dissemination of the information. During the year 2012 to 2013, CMEs on hemovigilance were organized mainly for the personnel involved in blood banks and transfusion medicines departments. However, it was felt that, since the clinicians and nurses are important link to success of this program, dissemination information about the importance and need of the program may boost up the reporting to HvPI. The first CME on hemovigilance for clinicians was organized on 26th April 2014 at Government Medical College, Chandigarh. Thereafter, in every CME on hemovigilance organized by NIB, clinicians and nurses were actively involved as participants, panelists and speakers.<sup>11–14</sup>

## 7. Hemovigilance for Recipients and Donors

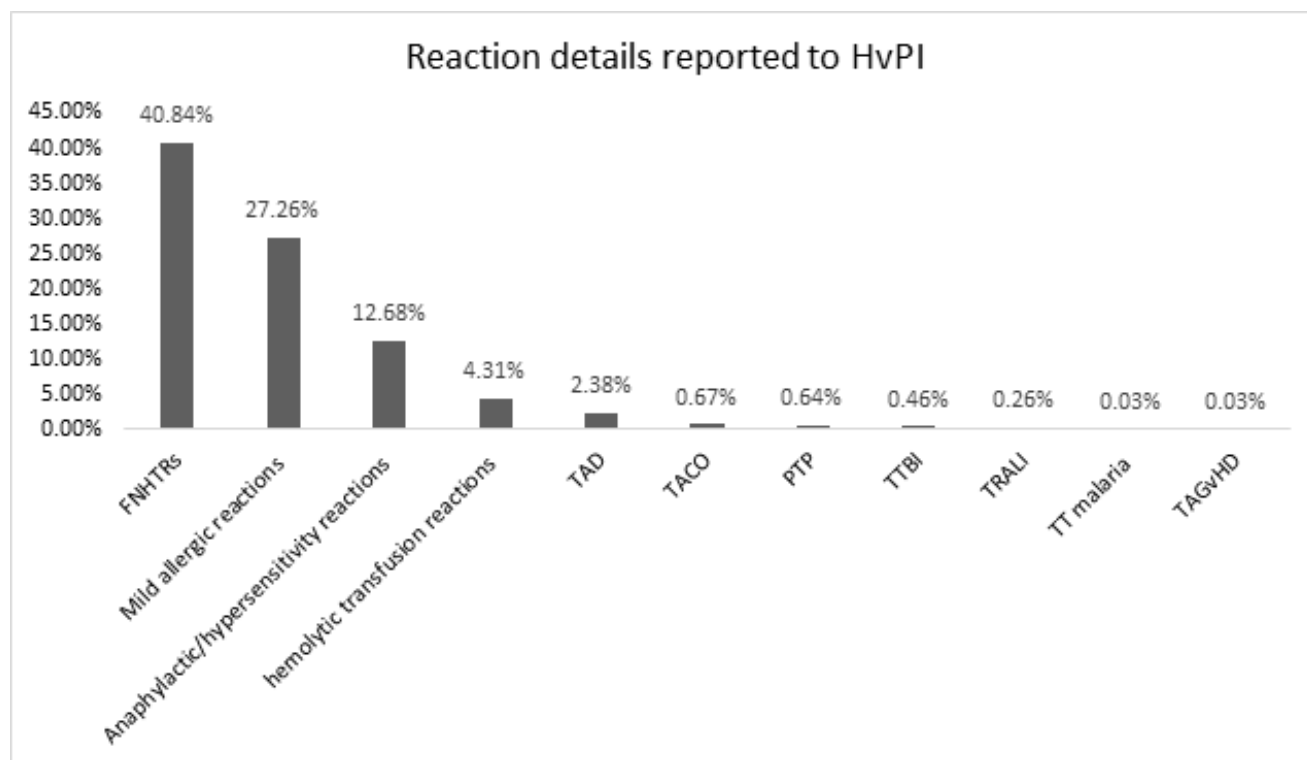
An internationally accepted scale is used to grade the ‘severity’ of an adverse reaction in recipient. The likelihood for adverse reaction or imputability can be attributed to the blood component transfused and it is also important to determine whether blood component has been involved or not. Blood donor hemovigilance is also equally important as far as adverse reaction or event during whole blood or component donation is concerned. Adverse reaction in donor is complicated as the etiology is different from those in the recipient. These adverse reactions may be due to donation, selection, and management of donors, which may directly affect the donor or impact the quality of the product, which ultimately influence the recipient. The recipient’s transfusion reactions/events were under the Hemovigilance Program of India. According to the guidelines of the HvPI, vigilance in donors, i.e., revealing adverse reactions related to a donation of blood was intended to be started

by 2017. Although with the accomplishment of the HvPI it was chosen to undertake donor vigilance program. Consequently, a National Blood Donor Vigilance Program (NBDVP) was initiated on June 14, 2015 on the World Blood Donor Day at Science City Kolkata, West Bengal, India. The increase in voluntary non-remunerated donations in South-East Asia was mainly contributed by India, with a reported collection of 8.5 million donations from voluntary non- remunerated blood donors, an 85% increase from the reported 4.6 million in 2008 according to World Health Organization (WHO), Global Database on Blood Safety (GDBS) 2016. Low and middle-income countries still lack enough voluntary non- remunerated blood donors, with low blood donation rates accompanied by high rates of discard. Ten countries declare for 65% of blood collections worldwide, and India is in the third position only after the United States and China. WHO targets 100% of voluntary donations by the year 2010 and India is expected to be on the top of the table.<sup>15</sup>

## 8. Studies and Practices of Hemovigilance in Hospitals of India

Information on incidence of various transfusion reactions could help in early recognition as well as management and could also help to institute adequate measures to make blood transfusion as safe as possible. In a cross-sectional, observational study conducted over a period of 22 months from September 2014 to June 2016 in the Department of Transfusion Medicine, JIPMER, all patients admitted to the wards of various specialty departments who were transfused with blood components and reported to have transfusion reaction during or after transfusion of blood components were included. A total of 90,758 components were issued during the study period, and 137 transfusion reactions were reported which accounted for 0.15% of total transfusions. Febrile non-hemolytic transfusion reaction (46.7%) was the most common reaction followed by allergic reaction (31.3%). Among different blood components, packed red blood cells (82%) were most commonly associated with transfusion reactions. It was concluded that transfusion reactions unless serious are grossly underreported either due to lack of attributing the adverse event to transfusion or because the milder reactions are usually managed and unreported as the staff are too often used to having them, especially in chronically transfused patients.

Another study was conducted in the Department of Transfusion Medicine of a University Teaching Hospital of South India. This was a retrospective, observational study in which all Adverse Transfusion Reactions (ATRs) reported by the department to HvPI observed in patients admitted in various clinical departments over a period of 24 months (January 2014 to December 2015) were reviewed and analyzed. During the study, a total of 31,687 blood and blood components were issued, out of which a total



**Fig. 1:** Reaction details reported to HvPI (FNHTR: Non-Hemolytic Transfusion Reactions; TAD: Transfusion Associated Dyspnea; TACO: Transfusion Associated Circulatory Overload; PTP: Post-Transfusion Purpura; TTBI: Transfusion-transmitted bacterial infection; TRALI: Transfusion Associated Acute Lung Injury; TAGvHD: Transfusion-Associated Graft Versus Host Disease),

of 66 (0.2%) ATRs were reported. The most common type of reaction observed was febrile non-hemolytic transfusion reaction (FNHTR) 54.55% (n = 36), followed by allergic 33.33% (n = 22). The ATRs were seen mostly with packed red blood cells (78.8%).

In another cross sectional questionnaire based study, doctors of a tertiary care hospital were included to understand their knowledge and attitude towards hemovigilance. The purpose of the questionnaire was to know awareness of doctors regarding hemovigilance program of India. The study also aimed to identify the factors responsible for underreporting of transfusion reactions and to find out the possible ways to improve reporting of transfusion reactions. 38.88% and 30% of the responders were aware of the hemovigilance program and transfusion reaction reporting centres respectively. Reporting of transfusion reaction was poor 22.22% among the respondents. According to respondents creating awareness about hemovigilance by conducting continuing medical education (CMEs), and training to healthcare professionals would lead to improvement in reporting of transfusion reactions. Complacency and ignorance were the main factors which discouraged transfusion reaction reporting by doctors. Increasing awareness of hemovigilance among doctors and training on reporting

transfusion reactions would likely improve spontaneous reporting and help to strengthen the blood transfusion system.<sup>16,17</sup>

## 9. Problems Associated with Hemovigilance

The major problems arising in hemovigilance are underreporting of adverse events/effects due to fear of retribution and punishment, late reporting, use of different channels of reporting, incomplete information on incident sheets and failure to report investigation findings, difficulties in communicating with blood banks in both governmental and private sectors and in motivating hospitals to notify events and to have functional transfusion committees, fragmented blood transfusion systems, lack of understanding or awareness, lack of culture of reporting adverse events, lack of regulatory framework for hemovigilance, lack of computerized management system, lack of transparency in government agencies and absence of well-defined hemovigilance structure and protocol, lack of trained manpower, lack of training and no standardized single system common to two blood services and no development of evidence-based guidelines, lack of computerization and use of “Haemo-vigil” software makes the transfusion reactions underreported.<sup>11</sup>

## 10. Conclusion

Hemovigilance program of India is the right step towards blood transfusion safety and quality for donors, recipients and medical staffs. The information obtained from Hemovigilance helps to minimize any potential risks related to blood transfusion leading to improved practices in the chain of blood transfusion. It is the responsibility of each and every nation to build up a strong hemovigilance framework. Many doctors are still not sensitized about the importance of Hemovigilance Program and so awareness sessions via frequent CMEs are very essential to train the doctors and the medical undergraduates which will lead to the enhancement of the program.

## 11. Source of Funding

None.

## 12. Conflict of Interest

The authors declare no conflict of interest.

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**Cite this article:** Dutta A, Banerjee A, Chaudhry S. Hemovigilance in India: Corrective Action towards Safety of Blood Transfusion. *J Prev Med Holistic Health* 2020;6(2):66-71.