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Review Article

Transfusion-Transmitted Malaria in Iran: A Narrative Review Article

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Received 13 Sep 2015
Accepted 20 Apr 2016

Keywords:
Transfusion-transmitted malaria,
Blood transfusion,
Donors,
Screening,
Iran

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Abstract

Background: Malaria is the most important transfusion-transmitted infection (TTI) in worldwide after viral hepatitis and human immunodeficiency virus (HIV) infection. The main objective of the present study was to review and evaluate the transmission of malaria via blood transfusion in Iran.

Methods: A literature search was done without time limitation in the electronic databases as follows: PubMed, Scopus, Google Scholar, Web of Science, Science Direct, scientific information database (SID), Magiran, IranMedex and Irandoc. The searches were limited to the published papers to English and Persian languages.

Results: Six papers were eligible. From 1963 to 1983, 344 cases of Transfusion-transmitted malaria (TTM) had been reported from different provinces of Iran. The most prevalent species of involved *Plasmodium* in investigated cases of TTM was *Plasmodium malariae* (79.24%). The screening results of 1,135 blood donors for malaria were negative by microscopic examination of peripheral blood smears and rapid diagnostic test (RDT) methods.

Conclusion: Lack of TTM report from Iran in the last three decades indicates that the screening of blood donors through interviewing (donor selection) may be effective in the prevention of the occurrence of transfusion-transmitted malaria.

Introduction

Malaria is one of the most important protozoan parasitic infections of humans in the world mainly transmitted by the bite of infected female *Anopheles* mosquitoes. Nearly half of the world's population (3.3 billion people) are at risk of being infected with malaria and 198 million cases of malaria were reported from 97 countries with 584,000 deaths in 2013 (1).

The first case of transfusion-transmitted malaria (TTM) was reported in 1911 (2). The transmission of malaria via blood transfusion is rare, but can lead to serious consequences in non-immune recipients to malaria (3-5). In malaria non-endemic and endemic areas, the frequency of TTM has been estimated to be one case per four million and more than 50 cases per million units of transfused blood, respectively (3, 6-9). Totally, more than 3,000 cases of TTM were reported globally (3, 6, 10).

The most prevalent species associated with TTM are *Plasmodium falciparum*, *P. malariae* and *P. vivax*. Considering the malaria infected blood donors are semi-immune, the parasites load is low and no clinical symptoms is observed, as well as *Plasmodium* species can survive for years in those donors. As the result of the asymptomatic persistence of parasites, the transmission of *P. malariae* has been documented as long as 44 years, *P. vivax* for five years and a period of eight years for *P. falciparum* after the last exposure (3, 11). The malaria parasites can live for about 20 days at temperature between 2 °C and 6 °C, the used condition for banking red blood cells (RBCs) or erythrocytes (10, 12-14). Although whole blood and RBCs concentrates are the most common source of TTM, cases from blood components containing infected RBCs such as platelets, leukocytes and fresh frozen plasma (FFP), as well as frozen RBCs have been reported (15-20).

The screening of blood donors for malaria is performed in malaria non-endemic and endemic countries by various strategies including donor selection (donor history) and laboratory tests (parasitological, immunodiagnostic and molecular methods) (4). Donor selection or screening of blood donors through interviewing is the first and in many countries the only step in the prevention of transfusion-transmitted infections (TTIs) such as malaria (21). The laboratory tests available for malaria screening include the light microscopic examination of peripheral blood smears, quantitative buffy coat (QBC), and antigen and antibody detection by immunodiagnostic methods and polymerase chain reaction (PCR) types. All of these tests have limitations in sensitivity, specificity, cost, speed, reliability and complexity (14, 22). Although the world health organization (WHO) recommends that all donated blood should be screened for malaria (23, 24), there is no reliable approved laboratory test yet available for malaria screening in blood donors (14). However, the optimum strategy for minimizing the risk of TTM in non-endemic and endemic areas is a combination of proper donor selection together with donation blood screening by using a laboratory test, which should be simple, sensitive, fast and cost effectiveness (4, 11, 25).

In Iran, located in the Eastern Mediterranean Region, malaria is one of the most important public health problems that its transmission mainly occurs in the southeast of country. This part of Iran consists of three provinces as malaria endemic areas with low endemicity, including Sistan and Baluchestan, Hormozgan and Kerman (Fig. 1) (1, 26). In 2013, based on the latest report of the WHO, 1,373 malaria cases were reported from Iran, of which 82% were microscopically diagnosed as *P. vivax* and the remaining 18% as *P. falciparum* (1).

The objective of this study was to review and evaluate the transmission of malaria via blood transfusion in Iran and to remind the necessity of blood donors screening in malaria endemic areas of Iran by appropriate laboratory test.

Fig. 1: Geographical situation of malaria endemic areas of Iran namely Sistan and Baluchestan, Hormozgan and Kerman provinces in the southeast of this country, bordering Afghanistan, Pakistan, the Oman Sea and the Persian Gulf (27)

Materials and Methods

Search strategy and databases

The present research was performed without time limitation using such terms as follows: "Malaria", "Blood transfusion", "Transfusion-transmitted malaria", "Induced malaria", "Blood donors", "Screening" and "Iran" alone or in combination, both in English and Persian (Farsi) languages. The used electronic databases for searching included as follows: PubMed, Scopus, Google Scholar, Web of Science, Science Direct, scientific information database (SID), Magiran, IranMedex and Irandoc. The searches were limited to the published papers to English and Persian languages.

Data extraction and collection

We comprehensively searched all above-mentioned databases. The collected bibliographic references were carefully screened to eliminate the duplicates and non-related studies. Overall, six papers were selected. As the number of carried out studies was low in Iran, all six found papers were reviewed. The following data were extracted from the papers: first author, calendar period, year of publication, geographical region (province/city) of study, sample size, laboratory screening method and malaria prevalence. Finally, the extracted data were recorded in a checklist that was prepared for this purpose.

Results

After search in all nine databases, six papers were eligible. Two papers were in English.

The incidence of TTM had been reported from different provinces of Iran in two papers. In the annual reports of the malaria eradication organization (MEO) and the Employees Health Department of the National Iranian Oil Company 111 cases of TTM had been recorded from 10 provinces during the 10 years from 1963 to 1972 (Fig. 2). The species of plasmodia involved in 56 investigated cases of TTM from 1970 to 1972 were *P. malariae* (73%, 41/56) and *P. vivax* (27%, 15/56) by the light microscopic examination of peripheral blood smears.

From 1973 to 1983, 233 cases of TTM had been recorded in the general office of malaria eradication (GOME) of the Ministry of Health and the School of Public Health and Institute of Public Health Research of Tehran University from 19 provinces during the 11 years (Fig. 2). In 50 diagnosed cases using the light microscopic examination of Giemsa-stained thick and thin blood smears, the plasmodia species were *P. malariae* (86%, 43/50) and *P. vivax* (14%, 7/50).

So far, the *P. falciparum* has not been reported as the cause of TTM from Iran and the *P. malariae* is the most prevalent reported species (79.24%, 84/106).

Five studies had been done on 1,135 blood donors from malaria non-endemic and endemic areas of Iran including Gilan (n = 177), Tehran (n = 404), Sistan and Baluchestan (n = 504) and Hormozgan (n = 50) provinces. All studies were cross-sectional and had been conducted in 1973-75, 2002, 2009 and 2010, respectively. In these studies, blood donors had been screened for malaria using light microscopic examination of Giemsa-stained thick and thin blood smears, antigen detection by rapid diagnostic test (RDT) or Dipstick, antibody detection with indirect immunofluorescence assay (IFA) or enzyme linked immunosorbent assay (ELISA) and PCR methods.

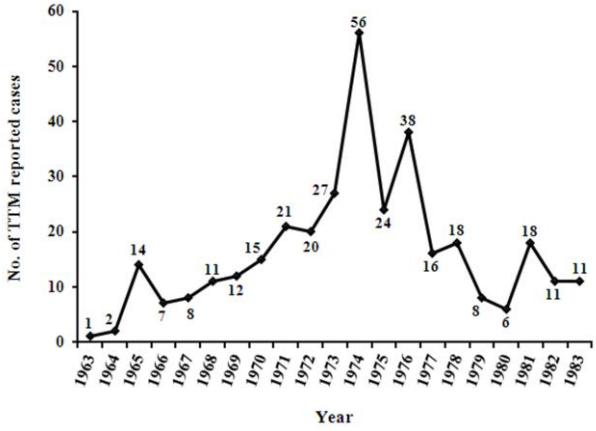

Fig. 2: Trend of transfusion-transmitted malaria (TTM) reported cases from different provinces of Iran during the 21 years from 1963 to 1983 (28, 29)

The malaria screening results of blood donors were negative by microscopic examination of peripheral blood smears and RDT methods, as well as PCR but 1% (2/50) belonging to Bandar Abbas City that were positive with real-time PCR. In four studies that the blood donors screening for malaria had been performed using IFA and ELISA methods, the tests results were positive in 13.98% (91/651) and 4.69% (18/384), respectively (Table 1).

Discussion

The need for blood and blood components is universal and are mainly used in the management of patients who suffer from cancer, blood disorders, trauma and emergencies. Although blood transfusion is a lifesaving procedure, it may also cause adverse reactions and the transmission of blood-borne pathogens (34). Many infectious diseases can be transmitted via blood and blood components such as human immunodeficiency virus (HIV), viral hepatitis, syphilis, brucellosis, visceral leishmaniasis (VL), malaria, toxoplasmosis, measles, American trypanosomiasis (Chagas disease) and babesiosis(10, 35).

Table 1: Characteristics and results of included studies on blood donors in the present review

First author (Reference)	Calendar period	Year of publication	Province	City	No. of donors	Laboratory screening method	Malaria Prevalence (%)
Edrissian (29, 30)	1973-75	1985, 1975	Gilan and Tehran	Rasht and Tehran	531[a]	ME[b], IFA	47 (8.85) donors by IFA
Moghtadaei et al. (31)	2002	2005	Sistan and Baluchestan	Iranshahr	120	ME, IFA, PCR	44 (36.67) donors by IFA
Sanei Moghaddam et al. (32)	2009	2011	Sistan and Baluchestan	Zahedan	384	ME, RDT, ELISA, PCR	18 (4.69) donors by ELISA
Hassanpour et al. (33)	2010	2011	Hormozgan and Tehran	Bandar Abbas and Tehran	100	ME, RDT, Real-time PCR	2 (1) donors by real-time PCR[c]

ME: light microscopic examination of Giemsa-stained thick and thin blood smears, IFA: indirect immunofluorescence assay, PCR: polymerase chain reaction, RDT: rapid diagnostic test, ELISA: enzyme linked immunosorbent assay

[a] These were paid donors.

[b] This test was performed only in IFA positive donors.

[c] Two (1%) cases of 50 blood donors belonging to Bandar Abbas city

Malaria is one of the first TTIs recorded worldwide (4). With regard to the prevalence of malaria and the extensive use of blood and blood components in the world, as well as the possibility of malaria transmission through blood transfusion, the importance of TTM well is evident especially in malarious regions.

Before starting the malaria eradication program (MEP) in Iran, malaria was prevalent in most areas of the country with low to high endemicity. With the performance of the MEP and the malaria control program (MCP) since 1958 and 1980, respectively, malaria was limited to the southeast provinces namely Sistan and Baluchestan, Hormozgan and Kerman (Fig. 1) (36, 37).

The Iranian blood transfusion organization (IBTO) was established in 1974 with the purpose of supplying a sufficient and safe blood and blood components to recipients (38-40). Until that time, the blood donors mostly were paid and limited in number (28). Since the establishment and start working of the IBTO, the paid donation was forbidden and relied on family/replacement and voluntary non-remunerated blood donation (VNRBD). Since 2007, the IBTO reached to a 100% VNRBD (39, 41). In Iran, all of the donated blood is screened for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis and in some regions for human T-lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2). The malaria screening is carried out in the IBTO through interviewing with donors by a trained physician who asks questions about the history of malaria disease and traveling and living in malaria endemic areas (39, 40, 42). In Iran, based on the IBTO standard operating procedures (SOPs), volunteers who have the past history of malaria are permanently deferred from blood donation. A history of residence and travel to malarious areas leads to a deferral for three years and one year from donating, respectively.

Given the high prevalence of malaria almost in all regions of Iran before starting the MEP (36, 37) and the lack of diagnosis or report, a large number of TTM cases (30), 344 cases of reported TTM from 1963 to 1983 do not reflect the actual number of TTM (Fig. 2). Alt-

hough with the establishment and start working of the IBTO in most provinces, the paid donation was forbidden and used from blood of eligible donors instead of paid donors. During the years 1963 to 1972, the incidence of TTM had increased in Iran (Fig. 2) which could be because of more attention and more accurate survey of TTM and the report of occurred cases. However, the incidence of TTM cases had decreased from 1973 to 1983 that could be due to the establishment and start working of the IBTO and the exclusion of paid donors from blood donation, as well as the screening of blood donors through interviewing. Due to the consumption increasing of blood and blood components and more awareness and attention of physicians and health careers workers (HCW) to the diagnosis and report of TTM, the number of TTM reported cases during 1973 to 1983 was more than two times the years 1963 to 1972 (Fig. 2).

From 1983 to the end of June 2015, no case of TTM has been reported from Iran that may be for the following reasons: 1) Effectiveness of blood donors screening through interviewing (donor selection) in the IBTO; 2) Inattention to the incidence of malaria in non-endemic areas; 3) Lack of timely diagnosis and treatment of TTM cases and consequently the death or self-limited of infected individuals; 4) Severe decrease of malaria cases in the general population during the recent two decades (37, 43) and 5) Lack of reporting of the occurrence of TTM to authorities such as the ministry of health and medical education (MOHME).

In this review, the results of malaria screening in blood donors were negative using microscopic examination of peripheral blood smears and RDT methods, as well as with PCR but two cases. These results indicate that the donor selection or screening of blood donors through interviewing may be effective for minimizing the risk of TTM in non-endemic and endemic areas. However, the limitations of laboratory screening tests of malaria particularly their sensitivity should be considered in interpreting of negative results (29).

Conclusion

Lack of TTM report from Iran in the last three decades indicates that the screening of blood donors through interviewing (donor selection) may be effective in the prevention of the occurrence of transfusion-transmitted malaria. Since malaria is endemic in parts of Iran and the screening of blood donors is done only through interviewing, as well as due to the extensive use of blood and blood components, the immigration increasing from malaria endemic to non-endemic areas and traveling to malarious regions, the transmission of malaria via blood transfusion is possible.

Acknowledgements

We thank the cooperation of Prof. GhH Edrissian from the Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences (TUMS) for providing the original version of his papers. The authors declare that they have no conflict of interests.

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