

Point of Care Testing and Transfusion Safety in Resource Limited Settings: A Review

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Abstract

Worldwide, one of the fastest growing aspects of clinical laboratory testing is point of care testing (POCT). Decentralized patient care and access to testing in under-served areas are key elements in the evolving expansion of POCT. Several available POCT devices can potentially contribute to safer transfusion practices in resource-limited settings. Only "rapid diagnostic tests" and some simple hemoglobinometers are normally encountered in the peripheral hospitals of low income countries. Strengths, weaknesses and barriers of large scale utilization of POCT in transfusion medicine are discussed.

Keywords: Transfusion safety; Hemoglobinometers; Anaemia; Developing countries

Introduction

There is a growing interest in new or rediscovered laboratory technologies that can be utilized without the presence of specialized personnel, at the bedside and/or in extreme field conditions, with limited or no infrastructure and without specialized maintenance services. Point of care testing (POCT) allows for rapid and accurate laboratory testing at the bedside where immediate and effective clinical decisions need to be made. This can be performed at community level, in operating rooms or in complex emergency settings. These diagnostic devices are increasingly recognized as appropriate in low and middle income countries, where human, financial and logistic resources are scarce, and where there are major constraints in supply and maintenance services [1,2]. ASSURED the acronym that has been proposed to summarize the main criteria that define POCT devices stands for: affordable, sensitive, specific, user friendly, rapid and robust, equipment free and delivered [3]. The spectrum of available technologies varies from low-tech to high tech, and their effective introduction depends on the specific target product profiles [4], i.e. their intended settings. Examples of POCT devices that are increasingly utilized in high income countries include dry chemistry analyzers, rapid immunological tests, coagulometers and hematology analyzers. Other devices, like CD4 counters and Nucleic Acid Amplification Tests -NAAT-, are more specifically conceived for infectious diseases control programs in developing countries [5].

In the hospital setting blood transfusion is an essential treatment that is available worldwide; however the more current, sophisticated and high throughput technologies utilized in transfusion medicine in high income countries are hardly suitable for blood banks in resource-constrained health services. In these contexts few blood units are collected and transfused daily and often only in emergencies, therefore

instruments and devices that allow single or small batch testing and rapid turnaround time are required. Global improvement in transfusion safety depends on technologies that can be safely operated in disadvantaged situations.

Study Design and Methods

We examine the contribution of POCT in the four main areas of transfusion medicine: hematology, hemostasis, infectious diseases screening and pre-transfusion testing. We address strengths and weaknesses of POCT transfusion medicine, as well as factors that may influence their widespread implementation in resource-limited settings. PubMed was searched from January 1st, 1990, to February 28th 2014, with the terms "point-of-care" and "transfusion", "point-of-care" and "hematology" and "rapid tests" and "transfusion" for all available articles. We selected reports, reviews and, epidemiological studies published in English and we also reviewed references from selected publications. The titles and abstracts of each article were screened for relevance with regard to the limited-resource setting, the identified articles were retrieved for assessment of the full text.

Results

507 articles were initially identified utilizing the search criteria. Further selection based on their relevance in the context of resource-limited settings reduced the number to 84 papers which were reviewed and organized according to the four areas of interest in transfusion medicine.

Hematology

Rapid and reliable hemoglobin level testing is the cornerstone for appropriate blood transfusion and therefore represents the first step in the transfusion process. The Global Neglected Tropical Diseases (NTD) program launched the requirements for a method to measure

hemoglobin concentrations that should be accurate enough to detect the anticipated changes in haemoglobin levels induced by interventions for NTDs, should not require mains electricity, can be performed with minimal training and supervision and uses whole blood so that no dilution steps are required [6].

There are several options of POCT in hematology some of which have been marketed for decades. A review was recently published [7] which details the options available for POCT in hematology. Essentially they are divided in single parameter, i.e. hemoglobinometers, and multi-parameters analyzers.

Traditional and more recent “visual” hemoglobinometers, such as Shali, Lovibond and the Hemoglobin Color Scale, are simple devices which are however too subjective and inaccurate to correctly identify severely anemic patients that may require RBC transfusion [8-10]. A new POC visual method that can also be interpreted via smartphone has been recently tested and has given some promising results [11].

More sophisticated and reliable point-of-care photometric hemoglobinometers have been utilized for decades for POCT in different settings. The haemoglobin method that has been most widely used in NTD programmes is the HemoCue system. The HemoCue system® (HemoCue, Angelholm, Sweden) provides a reliable, rapid one-step haemoglobin determination with a sensitivity of 80–96.6% compared to standard laboratory methods [12,13]. The method utilizes dedicated microcuvettes suitable for direct hemoglobin determination from undiluted venous or capillary blood. The main advantages are that it uses battery power, is easy of use, accurate, provides rapid results, and is portable [14]. As well as being accurate the HemoCue method is robust and has an in-built quality checking tool [15]. New versions of these portable photometric analyzers, the HemoCue Hb 301 system and The DiaSpect Hemoglobin T system (DiaSpect Medical, GmbH, Sailauf, Germany) offer the additional advantage of utilizing “reagent free” microcuvettes that can be stored in high temperatures and in high humidity conditions, situations that are not uncommon in developing countries [16]. The main disadvantages of these portable hemoglobinometers are represented by their cost and scarce availability at the local level [17]. Another method, the Haemoglobin Colour Scale (HCS) has been designed for field situations in resource-poor countries and is considered to be better than clinical diagnosis in detecting anaemia in children and pregnant women [18,19]. The main disadvantages are the need for a specific type of chromatography paper as well as good natural light. The method is not able to detect incremental changes in haemoglobin less than 1 g/dl. The Lovibond comparator method is an alternative technique for measuring haemoglobin that does not require a dilution step, may have satisfactory precision and accuracy, but requires an exact volume of 0.03 ml of whole blood, which is difficult to achieve in field situations [20]. The Microhematocrit method is another cost-effective alternative for hemoglobin estimation. Although the method is sufficiently accurate and it utilizes fairly cheap consumables [21,22] it requires a basic laboratory infrastructure and a reliable power supply. More recently a portable hemoglobinometer that utilizes reagent strips was marketed offering another technological alternative. The TrueHb Hemometer, developed by Ambar Srivastava of the Indian Institute of Technology (IIT), is a relatively small device and represents the first case of an innovation by the biomedical engineering department of IIT-Delhi [23].

Noninvasive devices offer an appealing alternative for haemoglobin determination, however limitations in accuracy, especially in

emergency situations such as hypovolemic shock, caution against their utilization as unique transfusion decision tools [24-26].

In recent years simple, compact and affordable multiplatform hematology analyzers that utilize impedance cell counting methodology and spectrophotometric hemoglobin determination have become available [6]. “Impedance” based counters require a supply of dedicated and relatively bulky “liquid” kits as well as regular maintenance and a reliable power supply. All these characteristics make these instruments less appropriate and manageable in remote settings. The microhematocrit based automated “quantitative buffy coat”-QBC-method offers an alternative to traditional multiparameter hematology analyzers. The main advantages of this system are that it is portable and relies only on “dry” reagents. This analyzer still has a fairly limited distribution and utilization in resource-limited settings [27] notwithstanding its simplicity and remarkable performance.

Finally as far as hemoglobinometers are concerned it should be mentioned that a rapid assessment of hemoglobin concentration is usually performed before bleeding the donor. In this context the accuracy of the test result is less critical and many of the basic abovementioned methods, including the simple Hemoglobin Color Scale, can play a role in the selection of blood donors in resource-limited settings [28,29].

Hemostasis

Since blood components such as fresh frozen plasma and platelet concentrates are scarce in peripheral and resource limited settings, point-of-care devices and methods for coagulation and platelet function testing are only briefly presented in this review.

Simple bedside whole blood coagulation utilizing a dry tube is a basic and very simple method that was employed in the past to detect coagulopathy and is still utilized in cases of snake bites in Africa and elsewhere [30,31]. It has been demonstrated that a 20 minute whole blood clotting test -20WBCT- shows good correlation with fibrinogen concentration, however its clinical predictivity in the case of snake bites has been questioned [32].

In high income countries much more sophisticated devices for POC coagulation testing are available. Their main uses are the monitoring of vitamin-K antagonist oral anticoagulants, the assessment of platelet function, in particular in patients undergoing anti-platelets therapy, as well as the rapid evaluation of clotting function in bleeding patients during surgery and in emergency settings [33-37]. Out of these the viscoelastometric POCT devices are particularly useful in giving quick information on all the main phases and components of clot formation, including fibrinogen concentration, platelet activity and fibrinolysis [38]. For this reason they are utilized to guide the clinical management of acute coagulopathy that follows trauma and hemorrhages, including obstetric cases [39-41]. To our knowledge however there are no studies that document the utilization or the appropriateness of POC coagulation tests in resource-limited settings. As in the case of other more sophisticated POC devices cost and unavailability of supplies at local level are likely to represent major barriers to their utilization. As far as the management of coagulopathies is concerned, it is important to remember that in most peripheral hospitals in Sub-Saharan Africa whole blood is the only available blood product [42]. Fresh whole blood units, if available in sufficient number, are indeed an effective therapy in case of dilutional and consumption coagulopathy that follows severe acute bleeding and trauma since it rapidly restores

simultaneously red blood cells, active clotting factors and platelets [43].

Transfusion transmitted infections -“TTIs”- screening

According to global standards all blood units must be tested at least for HIV antibodies – HIV, Ab- hepatitis B antigen S -Hb Ag-, Hepatitis C antibodies -HCV Ab- and Syphilis. Other infections, such as malaria and Chagas disease, can be screened according to the epidemiological context [44]. In high income countries immunoenzymatic or chemiluminescence tests are routinely employed for TTIs screening. These sophisticated and often automated laboratory platforms require constant maintenance, regular supply of dedicated reagents and controls and must be operated by skilled laboratory personnel. All these features make their utilization and reliable functioning difficult in resource-limited and/or remote settings.

Since the late eighties Rapid Diagnostic Tests - RDTs – have been available for HIV diagnosis, and have represented a breakthrough in transfusion safety in low income countries [45-49]. Since then RDTs have been devised and marketed for the diagnosis of all major TTIs, including HbsAg and HCVAb, and a review on their utilization for transfusion safety in Africa has recently been published [50]. RDTs comply with all the “ASSURED” criteria, and therefore the term RDT is commonly used to describe the POCT devices for infectious diseases diagnosis.

RDTs are essentially based on three main principles: immunochromatography, immunofiltration or immunoconcentration and agglutination. Among these the immunochromatographic strips – lateral flow or dipstick - are the most utilized, because of their simplicity and the possibility of single step procedure. The average cost of these tests is today down to a dollar or less. Additionally many of them can utilize capillary blood in place of serum/plasma and can be stored at room temperature. One of the main limitations of RDTs is that they are operator-dependant in several aspects: preparation, interpretation and recording of results. This can explain some discrepancies in reported test accuracy and represents an additional major shortcoming in high-throughput laboratories. Sensitivity of RDTs in TTIs screening is a major concern and this is obviously a crucial aspect in blood safety. As far as analytical sensitivity of HIV RDTs is concerned, as it is in the case of testing series of progressively diluted specimens, the limits of RDTs performance are evident when compared to reference immunoenzymatic tests [51,52]. When clinical sensitivity is considered however, i.e. observations on undiluted samples from patients or from blood donors, many HIV RDTs offer an acceptable level of detection of truly positive samples [45,48]. WHO sets precise standards for acceptability of HIV RDTs: sensitivity >99%, specificity >98% associated to inter-observer variability and invalidity rate both <5%. A list of commercial kits that comply with these standards is available and regularly updated [53]. Recently a “combined” HIV P24 antigen-antibodies RDT has been marketed with the objective of increasing sensitivity during the early stages of infection. The first independent observations however show a limited diagnostic value of this combo test in the seroconversion period [54].

As far as RDTs for HbsAg and HCVAb are concerned the reported clinical sensitivity is on-average lower than HIV RDTs [45,47,55-59]. The reason for this may be the higher proportion of relatively low-titer reactive samples and the longer window period in the early phases of infection. However also for HbsAg and HCVAb there are kits that show promising results in terms of diagnostic accuracy [60-65] and a

HbsAg RDT has been recently CE marked as it achieves the requested sensitivity of at least 0.125 I.U/mL [66].

For all these reasons RDTs for the three major viral TTIs are considered an acceptable alternative for the screening of blood donations where immunoenzymatic tests are not available, i.e. in small peripheral laboratories and in emergency situations [53].

As far as syphilis is concerned Treponemal immunochromatographic RDTs are also available and can replace the more traditional agglutination non-treponemal assays.

In recent years RDTs for Malaria have gained a central role for the diagnosis of this disease, both in high and low-income countries. As blood screening tools RDTs may however fail to detect low grade parasitaemia in asymptomatic “semi-immune” adults, as “healthy” blood donors in malaria endemic countries may often be [67,68].

In general as far as the accuracy of RDTs in field conditions is concerned, it should be remembered that inappropriate storage conditions may heavily affect their performance and this can be a major problem in a tropical environment [69].

In high income countries multiplex nucleic acid amplification testing – NAAT- for HIV, HBV and HCV – is a mandatory additional screening tool. NAAT is able to reduce the infectious window period and therefore also the residual transmission of infectious diseases through blood transfusion. Technologies in molecular diagnostics have rapidly evolved in recent years but very few present operating characteristics that make them appropriate for utilization in peripheral locations of low-income countries. There are however promising NAAT platforms that simplify molecular testing by fully integrating and automating the three processes (sample preparation, amplification, and detection) required for real-time PCR-based molecular testing in a single cartridge containing all necessary elements for the reaction [70]. These instruments are simple enough to be performed reliably even by individuals without a background in nucleic acid diagnostics. Unfortunately no available POC NAAT platform yet includes, among the many testing options, kits for the combined screening of the three main blood-borne viruses. There are however promising and innovative NAAT technologies, such as the loop-mediated isothermal amplification assay (LAMP), with the potential to be sensitive, rapid and user-friendly enough to be utilized as a blood screening tool in remote settings [71].

Pre-transfusion testing

Pre-transfusion tests, i.e. blood grouping and cross-match, are specific activities of blood bank laboratories. Traditional, simple and cheap ABO-Rh typing, utilizing commercial antisera, can be easily done at the bedside by trained health workers. Dry-reagent typing cards have been marketed for decades and offer an even more simplified typing procedure suitable for bedside blood group confirmation by ward staff [72,73]. Innovative paper based blood typing kits are also in the pipeline [74].

Together with ABO-Rh typing, however, WHO recommends the presence of at least the antiglobulin phase compatibility for a complete pre-transfusion testing [75]. Traditional antiglobulin crossmatch, in its tube version, is a relatively simple and affordable test. It requires essential laboratory equipment (low speed centrifuge, clean pipettes, water bath incubator, low power microscope, refrigerator) and reagents (sterile saline solution, antiglobulin serum). The procedure includes several critical steps and requires specific skills in

interpretation and in problem solving, especially in case of initially reactive results. According to most observations the antiglobulin test is hardly ever encountered in rural hospitals practice in low-income countries, and compatibility testing is generally limited to AB0-Rh typing, often accompanied by room temperature "major" cross-match [49,76].

Since the discovery of antiglobulin testing in the mid 20th century, a major "breakthrough" in immunohematology has been the introduction of gel microcolumn essays which allow a simplified indirect antiglobulin test, with fewer steps, and a more reliable and stable reading of results. The method however still requires specific laboratory skills, equipment and reagents and is therefore not compliant with POCT essential features.

Discussion

As described there are several point-of-care laboratory technologies that are useful for a safe transfusion practice and appropriate in resource-limited settings. However out of these only serological "rapid diagnostic tests" and some simple hemoglobinometers are available in the field. As described no point-of-care antiglobulin phase pretransfusion tests or equivalent exist or are in the pipeline. Finally, notwithstanding the availability of innovative and simplified NAAT technologies, no POCT kit is yet available in the field of molecular testing of TTIs.

Several factors and barriers that affect the adoption and scaling up of POCT have been identified. These include economic, regulatory, policy-related factors, as well as user/provider perceptions and cultural barriers [4,77].

Recent experiences in the field of POC molecular diagnostics proved however that high-tech technologies can be disseminated globally thanks to a winning combination of elements: a public-private partnership, affordable and "negotiated" prices, a global supply and assistance network, and, not least, a global validation and performance monitoring program [70,78]. In other words a strong public health commitment and the contribution of non-profit foundations and international organizations are essential for a successful introduction of new health technologies on a global scale.

If the advantages of POCT in resource-limited settings are self-evident their limitations are also straightforward and must be carefully taken into account when these devices are introduced into clinical practice. Some of the potential disadvantages of POCT are the lack of standardization in obtaining blood samples, the need for additional training and supervision in order to minimize operator subjectivity and the lack of adoption of internal/external quality assessment tools. For these reasons as far as possible rigorous quality assurance procedures, including EQA -External Quality Assessment - should be applied, both for the prevention of procedural and clerical errors as well as for tests validation [79,80]. Moreover newly introduced POC tests and RDTs need to be locally evaluated before supply is established [81]. This is particularly relevant in the field of TTI testing since the quality of local samples, the genotypes and subtypes of circulating infectious agents and other factors may influence the performance of the essay

The problem of poor-quality and counterfeit diagnostics is also an emerging problem in resources-limited settings and health authorities should strengthen their regulatory oversight to the POC tests that are frequently distributed in developing counties [82].

Conclusion

Blood Transfusions, even if limited to whole blood, are relatively sophisticated and high risk practices in under-resourced environments. The laboratory armamentarium currently available in the blood banks of high-income countries is in many ways impracticable and unaffordable in the majority of rural and remote hospitals in low-income countries.

Existing rapid tests for TTIs screening and portable hemoglobinometers are POC tests that today contribute to transfusion safety in contexts where more complex and costly devices are unavailable; however more simple, accurate and affordable systems are needed in order to achieve higher standards in all aspects of blood safety in these settings.

Several prototypes are in the pipeline especially in the field of microfluidics and nanotechnologies [83], and in future some of these may prove useful in the field of transfusion medicine. However new technologies for global health cannot be effectively developed without the involvement of the end-users in low-income countries and an active bottom-up approach [84]. Whether these innovations will actually be disseminated and effectively utilized in resource-limited settings will probably depend not only on market dynamics but also on public health policies and funding.

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