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Point-of-care test (POCT) INR: hope or illusion?

RNI Point-of-care test (POCT): esperança ou ilusão?

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Abstract

In the last decade, point-of-care tests were developed to provide rapid generation of test results. These tests have increasingly broad applications. In the area of hemostasis, the international normalized ratio, INR point-of-care test (POCT INR), is the main test of this new proposal. This test has great potential benefit in situations where the quick INR results influences clinical decision making, as in acute ischemic stroke, before surgical procedures and during cardiac surgery. The INR POCT has the potential to be used for self-monitoring of oral anticoagulation in patients under anticoagulant therapy. However, the precision and accuracy of INR POCT still need to be enhanced to increase effectiveness and efficiency of the test. Additionally, the RDC / ANVISA Number 302 makes clear that the POCT testing must be supervised by the technical manager of the Clinical Laboratory in the pre-analytical, analytical and post-analytical. In practice, the Clinical Laboratory does not participate in the implementation of POCT testing or release of the results. Clinicians have high expectation with the incorporation of INR POCT in clinical practice, despite the limitations of this method. These professionals are willing to train the patient to perform the test, but are not legally responsible for the quality of it and are not prepared for the maintenance of equipment. The definition of who is in charge for the test must be one to ensure the quality control.

Descriptors: **Thrombosis. Clinical laboratory techniques. Prothrombin time.**

Resumo

Na última década, foram desenvolvidos os testes *point-of-care* visando à geração rápida de resultados de exames. Na área da hemostasia, a razão normatizada internacional, o RNI *point-of-care test* (RNI-POCT), constitui o principal exame dessa nova proposta. Esse teste tem grande potencial de benefício em situações em que o resultado rápido da RNI influencia a tomada de decisão clínica, como no acidente vascular cerebral isquêmico agudo, antes de procedimentos cirúrgicos e durante cirurgias cardíacas, além de permitir que o próprio paciente faça a monitoração da anticoagulação oral. Entretanto, a precisão e a acurácia da RNI-POCT ainda precisam ser aprimoradas para aumentar a eficácia e a eficiência do teste. A RDC/ANVISA Nº 302 deixa claro que os testes POCT devem ser supervisionados pelo responsável técnico do Laboratório Clínico nas fases pré-analítica, analítica e pós-analítica. Na prática, o laboratório não participa da execução desses testes e liberação dos resultados, não sendo, portanto, o mais indicado para garantir a qualidade dos mesmos. Os clínicos, especialmente aqueles envolvidos com

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Abbreviations, acronyms & symbols	
CVA	Cerebrovascular Accident
CNPq	National Council for Scientific and Technological Development
FAPEMIG	Research Support Foundation of the State of Minas Gerais
ISR	International standardization reason
INR-POCT	INR point-of-care test
RR	Relative risk
RTL	Remote test laboratory
PT	Prothrombin time

a anticoagulação oral de pacientes, têm grande expectativa na incorporação da RNI-POCT na prática diária, apesar das limitações desse método. Esses profissionais mostram-se dispostos a treinar o paciente para realizar o teste, mas legalmente não são os responsáveis pela qualidade do mesmo e não estão preparados para a manutenção dos equipamentos. A definição do responsável pelo RNI-POCT precisa ser reavaliada pelos órgãos competentes, de forma a garantir que seja cumprida, e constitui etapa essencial para assegurar a qualidade do teste e, consequentemente, sua maior utilização.

Descritores: **Trombose. Técnicas de laboratório clínico. Tempo de protrombina.**

INTRODUCTION

Oral anticoagulants are used in secondary prevention of thromboembolic events in patients with venous or arterial thrombosis and those with heart disease that may predispose to thrombus formation. The indications for long term use of oral anticoagulants have been increasing as medical conditions that predispose to thromboembolic events are detected [1]. Silva et al. [2] found that prophylactic oral anticoagulation was safe and significantly reduced the incidence of venous thrombosis after implantation of electronic cardiac devices in high-risk patients (RR: 0.57, 95% CI: 0.33 to 0.98). In addition to ensuring the treatment efficiency, regular monitoring of oral anticoagulation should ensure the prevention of hemorrhagic phenomena [3].

The prothrombin time test (PT) is sensitive to reductions in coagulation factors II, VII and X. The INR calibration model (international normalization ratio), adopted in 1982, has since been used in a standardized way to report the results of PT, measured with the thromboplastin used in each laboratory [4]. According to Rosendaal [5], control of oral anticoagulation should be performed by specialized clinics to minimize risks and improve the practice. Chiquette et al. [6] compared to conventional care anticoagulation control, the regular attendance at a clinic and a follow-up period at specialized clinics for anticoagulation control. Rates of occurrence of smaller events were found in specialized clinics, both for thromboembolic accidents and for bleeding episodes.

Campos et al. [7] proposed that the objectives of a specific follow-up clinic for oral anticoagulation would be achieved when patients remained most of the time with their INR within the desired ranges, or the percentage of tests with the desired INR increasing.

In the last decade, the point of care test were developed, known as near patient or bedside testing, aimed at the rapid generation of test results, to enable effective clinical decision making in a short time. These tests have increasingly broad applications. In the area of hemostasis, the PT expressed in INR, INR point of care test (INR-POCT), is the main consideration of this new proposal [8,9].

Recently, several automated or semi-automated portable coagulometer have been developed to determine the INR samples collected by venous or digital puncture. The procedure consists of applying a drop of in a disposable cartridge containing thromboplastin which then is introduced into the coagulometer that detects clot formation.

PRINCIPLES OF DETERMINATION OF INR-POCT

Different principles have been used to detect clot formation in the portable coagulometer:

1. Monitoring thrombin generation by a substrate cleavage

A drop of blood is added to the reaction chamber of the equipment and the process of coagulation is triggered by the contact of the sample factor VII with calcium thromboplastin. The sequential activation of factor X, factor V in the presence of calcium ions results in conversion of prothrombin into thrombin. Thrombin acts on the formed HD-phenylalanyl-pipecolyl-arginine-p-amino-p-methoxydiphenylamine (Phe - pipecolic acid - Arginine -

NH - C6H4 - NH - C6H4 - OCH3) and cleave the amide bond on the carboxyl terminal region of the arginine residue. This region is structurally similar to that present in the molecule of fibrinogen, which is cleaved by thrombin to generate fibrin monomers. The thrombin-substrate reaction generates the electrochemically inert tripeptide (Phe - Pipecolina - arginine) and the electroactive compound (NH3 @ + - C6H4 - NH - C6H4 - OCH3), which is detected by amperage. This time represents the thrombin generation period [10].

2. Monitoring capillary blood flow

A drop of blood is added to a single use cartridge which is inserted in a portable coagulometer. By capillarity, blood flows into the reaction chamber, which contains thromboplastin obtained from rabbit brain. Factor VII activation is present in the blood sample, triggering the coagulation cascade. When fibrinogen is broken into fibrin monomers, there is a reduction of blood flow velocity, which is optically monitored by a laser and displayed in seconds. This value is in seconds, then converted to INR [11].

3. Motion detection of metal particles in a magnetic field and light reflection

The test strip contains thromboplastin and particles of iron oxide. The blood drop applied to the coagulometer, by capillarity, goes to the area of reaction at 37 ° C. The coagulation process is initiated by the contact of the sample factor VII with calcium thromboplastin. This machine has two magnets located below the test strip, a permanent magnet, which promotes the horizontal alignment of the iron particles, and an electromagnet, which promotes the vertical alignment of them originating a regular pulse magnetic field. A photodetector above the test strip records the change caused by this pattern of pulsation in the reflected light. Once initiates the formation of the fibrin clot, the movement of the iron particles decreases, and consequently reduces the light reflection. The coagulometer accurately detects the beginning of the reduction in light reflection, which coincides with the beginning of the formation of fibrin. An algorithm programmed into the chip device converts the start of the reduction of light reflection to INR [5].

The principle of coagulometer detection of clot formation has an impact on the outcome of the obtained INR, so that the equipment employing the capillary blood flow tend to provide lower INR values of samples with increased viscosity, particularly when hematocrit is more than 55% [5].

The INR-POCT advantages

The main advantage of INR-POCT is the determination of the fast result, which can have great impact on medical management. An example is the determination of INR POCT-prior to administration of thrombolytic therapy in patients with acute ischemic cerebrovascular accident (CVA). The efficacy of thrombolysis in acute cerebrovascular accidents strongly depends on the interval between the onset of symptoms and administration of thrombolytic therapy [12]. Rizos et al. [13] observed significant and clinically relevant time to onset of thrombolytic therapy, 28 ± 12 minutes with the use of INR-POCT.

The use of INR-POCT also allows the reduction of problems related to venipuncture, particularly in patients with difficult venous access and in children, the difficulty of puncture can cause errors in results of blood coagulation [14]. Moreover, it represents greater convenience for patients, especially those who live in remote locations having to go to the laboratory to measure the INR [7,8].

Another great advantage of INR-POCT is the limitation of the indication of fresh frozen plasma in cardiac surgery, because the INR monitoring throughout surgery clinical team would provide the correct information related to the need for replacement of coagulation factors [9.15,16].

A systematic review of the Cochrane Database, which included 18 studies involving patients with oral anticoagulation monitored by INR-POCT, showed improvement in the control of anticoagulant therapy, and reduction of thromboembolic events and mortality. This study also included the evaluation of the adjustment of the dose of warfarin made by the patient (according to the result of the INR-POCT) and adjusting the dose of warfarin made by the clinician (prior knowledge of INR-POCT value). There was no difference in incidence of new thromboembolic events and bleeding, which showed that patients were able to correctly adjust the anticoagulant dose. However, the authors warned that not all patients are capable of performing the monitoring of anticoagulant therapy [10].

PROBLEMS ASSOCIATED WITH INR-POCT

The major problem related to INR-POCT is the accuracy in relation to the reference method, the conventional prothrombin time. When a POCT device is validated, the criteria commonly used to assess the concordance between the two methods are INR-POCT values and the reference method in the same clinical category (in other words, both values within, above or below the therapeutic range), or an 0.4 INR difference between the methods, or even 85% of paired results in the therapeutic range should have a difference of ± 0.5 INR between the methods. According to the International Standards Organization criteria when the INR is lower than 2.0, it is desirable that more than 90% of the results have a difference of ± 0.5 INR, when the INR is greater than 2.0, the results matched should differ by no more than 30% [17]. Such criteria may

not be suitable for patients receiving vitamin K inhibitor, since the results with a ± 0.2 INR difference of the therapeutic range require medication dosege change. Thus, even if a INR-POCT has adequate accuracy, according to the criteria set, this accuracy can be insufficient in patients receiving vitamin K inhibitor, once the small differences between the methods can result in an inappropriate dosage change and risk of adverse events such as thromboembolism or bleeding [18-21].

Furthermore, even for those tests that follow this standardization, the results vary among manufacturers. The most commonly used guidelines for the management of patients using vitamin K inhibitor, the American College of Chest Physicians suggest that health professionals who choose to use INR-POCTin their patients should be careful to evaluate this test periodically comparing the results with the reference method, once or twice per year for each patient in order to evaluate the discrepancy in relation to the reference method [22].

It is known that the accuracy of INR-POCT is lower for INR values above 3.5 and it even decreases to values above 4.5. The International Sensitivity Index Calibration System approves INR-POCT results only when the values are lower than 4.5 [10]. Thus, this test is not suitable for patients with valve metal, for which the therapeutic range of INR is between 2.5 and 3.5 [23].

Another difficulty associated with the use of INR-POCT is the cost of the exam (it is still much higher than the reference method), to obtain sufficient volume of blood through digital puncture (coagulation analyzers available on the market require 3-50 mL of blood). Tests which require more blood may induce compression to increase the puncture site bleeding, which is not desirable, since it changes the test results [10]. In addition to these limitations, some patients have difficulty in collecting the blood drop and snap the cartridge into the coagulometer, particularly for individuals with arthritis or tremors [8]. Therefore, it is necessary to repeat test, which further increases its cost.

Another factor limiting the use of INR-POCT is the presence of antiphospholipid antibodies in the sample. These antibodies neutralize phospholipids included in the test to begin the cascade activation of coagulation factors, slowing down time for the formation of thrombin and thus interfere with the results provided by the devices that monitor the generation of thrombin and a subsequent substrate cleavage [24]. Other factors that may influence are the presence of hyperbilirubinemia (> 170 mmol / L) and hypertriglyceridemia (> 5 mmol / L), which interfere in the blood viscosity and therefore in the results of the equipment that determines both blood electromagnetic impedance change, such as those that monitor capillary blood flow and detect the movement of metal particles in a magnetic field and reflect the light [10,15].

The presence of heparin in the sample is another problem, since there are no reagents to counteract its action. Heparin can extend the time required for the formation of thrombin, interfering with the output of the devices that monitor the generation of thrombin and a subsequent substrate cleavage [10].

FINAL CONSIDERATIONS

In recent years, several factors have contributed to the development of equipment for POCT. The evolution of technology has allowed the production of miniature components of equipment such as sensors, transducers and detectors. This has enabled the production of portable coagulation by several companies that generally have no trouble handling. The development of software that manages information such as calibration curves, parameters of quality control, patient outcomes, and demographic data has also contributed to the efficiency of portable coagulation. Some systems allow the evaluation of operator performance in accordance with various regulatory requirements and validation of analytical data. Newer systems are associated with software that allows the transfer of patient results and quality control to a database. The recognition of the benefits of an integrated database to laboratory diagnosis is boosting the development of hardware and software enabling the electronic transfer of the POCT outcome to an information system so that doctors have quick access to them, which allows them to promptly establish the necessary therapeutic interference.

Despite the promising aspects for the development of POCT, an unanswered question is about the definition of a responsible person for implementation and quality assurance of these tests. The resolution - RDC / ANVISA No. 302 [19], transcribed below makes clear that POCT tests, called remote test laboratory (RTL), must be supervised by the technical manager of the Clinical Laboratory in the pre-analytical, analytical and post-analytical phase. In practice, the laboratory does not participate in the implementation of POCT testing and release of results, it is not, therefore, the best one to ensure their quality. Clinicians, especially those involved with oral anticoagulation of patients, have high expectations of INR POCT introduction in daily practice, despite the limitations of this method. These professionals are willing to train the patient to perform the test, but are not legally responsible for the quality of the work and are not prepared for the equipment maintenance.

Resolution - RDC / ANVISA No.. 302 of October,13t^{h} 2005 (19)

6.2.13 The implementation of the Remote Tests Laboratory - RTL (Point-of-care) and rapid tests, should be linked to a clinical laboratory, collection station or public health service or hospital outpatient.

6.2.14 The Technical Manager is responsible for the clinical laboratory by all RTL conducted within the institution, or any location, including, among others, visits to the day hospital, home and laboratory collected at the mobile unit.

6.2.15 The relationship of RTL that performs clinical laboratory should be available to the local health authority.

6.2.15.1 The clinical laboratory must provide documented procedures regarding their pre-analytical, analytical and post-analytical phases, including:

a) systematic registration and release of preliminary results;

b) procedure for potentially critical results;

c) systematic review of results and release of reports by a qualified professional.

6.2.15.2 The performance of RTL and the rapid tests is subject to the issue of decisions that determine their diagnostic limitations and other information set out in item 6.3.

6.2.15.3 The clinical laboratory must maintain records of quality controls and procedures for their implementation.

6.2.15.4 The clinical laboratory must promote and maintain records of their continued education for users of RTL equipment.

CONCLUSION

The use of INR-POCT has great potential benefit in situations where the result of rapid INR influences clinical decision making, as in acute ischemic cerebrovascular accident (CVA), surgical procedures before and during cardiac surgery. Moreover, it has the potential to be used by patients to monitor oral anticoagulation, which can help increase patient adherence to treatment, since it facilitates the understanding of the importance of controlling the INR and the risks associated with this therapy. However, the precision and accuracy of INR-POCT still need to be improved to increase effectiveness and efficiency of the test. The definition of a responsible person for quality assurance of INR-POCT, in pre-analytical, analytical and post-analytical phases, needs to be reevaluated by the competent organs, in order to ensure it is going to be fulfilled. Undoubtedly, it constitutes an essential step to ensure the quality of this test and consequently, its greater use.

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