

Clinical Utility of the ProTime® Microcoagulation System

A Summary of Clinical Reports

The original ProTime, in commercial distribution since 1996, is a five-channel device in which the patient specimen is tested in triplicate and two simultaneous controls (Level 1 and Level 2) are run with each assay. This system was subsequently modified to the low blood volume ProTime3, which is a three-channel device containing a single patient test and two internal controls. Both systems are used worldwide for both professional and patient self-testing use.

A number of clinical documentation's of the use of these ProTime systems in both the professional and self-testing environment have been published. Relevant papers are summarized below.

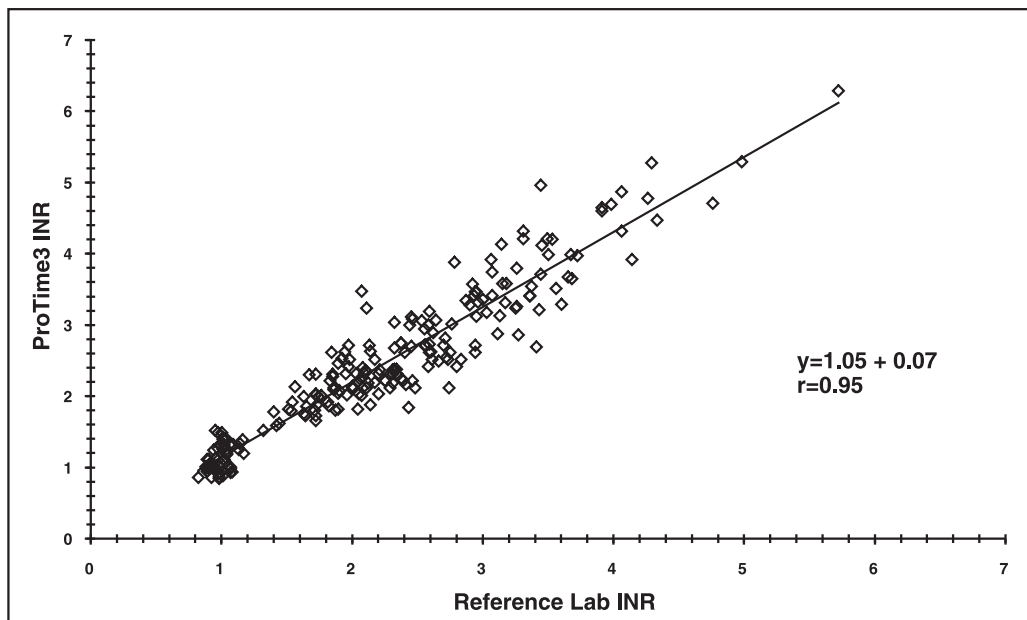
Since first commercialization, several abstracts and publications have featured the ProTime system. In 2001 the "Oral Anticoagulation Monitoring Study Group", consisting of five of the premier clinical opinion leaders in the field of anticoagulation management, published two companion papers in the American Journal of Clinical Pathology^{1,2}. These papers documented an extensive trial of the clinical accuracy of the ProTime (standard volume) system, showing its equivalence to the reference laboratory for quantifying the INR in the hands of professional operators¹ and patients^{1,2}, as measured using accepted clinical methods of linear regression analysis, mean versus difference plots, and clinical agreement. Equivalent results were determined whether tested by professional operators, i.e., healthcare workers or patient self-testers. Most importantly these trials, comprising collectively of more than 700 independent prothrombin time assays, showed the equivalence of the ProTime and the local laboratory in quantifying the patients' INR in comparison to the reference laboratory, which had been calibrated to the WHO standard INR method. In these trials, the percentage of agreement between the two systems compared to the reference lab was shown to be equivalent using accepted clinical indicators of agreement; namely within 0.4 INR and within 0.7 INR:

Agreement to Reference Lab	ProTime	Local Lab
Within 0.4 INR	77.3%	75.4%
Within 0.7 INR	93.6%	93.4%

A separate clinical evaluation of 114 patient specimens simultaneously tested using the ProTime and the laboratory showed 89% agreement of all INR results, when categorized as within range, above range or below range:³

Clinical Agreement to Laboratory INR	Percent of Data Pairs
Both INR within therapeutic range	56.3
Both INR below therapeutic range	28.3
Both INR above therapeutic range	4.4
Total Clinical Agreement	89

The low volume ProTime3 was designed to perform equivalent to the five-channel system. The data submitted to the US Food and Drug Administration to establish this equivalence was subsequently presented at the Anticoagulation Forum (2001)⁴, the pre-eminent semi-annual gathering of the leading authorities in oral anticoagulation management. The two systems generated equivalent results. The ProTime3 showed equivalence and correlation to both the local laboratory (regression slope of 1.0, $r = 0.93$) and the reference lab as shown in the graph below (slope = 1.05, $r = 0.95$).



Clinical agreement of the ProTime (both the standard volume and low volume systems) to the lab was quantified at the clinically relevant INR differences of 0.4, 0.7 and 1.0 INR, showing clinical agreement of the two systems:

Clinical Agreement to Laboratory INR	Standard ProTime	Low Volume ProTime
Within 0.4 INR	79%	83.3%
Within 0.7 INR	94.3%	95.3%
Within 1.0 INR	97.3%	96.5%

The ProTime manufacturer conducted a detailed investigation of INR variability in 2002 in concert with the Jerry L. Pettis Memorial Veterans Administration Medical Center (Loma Linda, CA, USA) and the results of these trials were presented at the International Society of Thrombosis and Haemostasis⁵ and the American Association of Clinical Chemistry⁶. In this trial, in which blood was collected from 100 patients, the clinical agreement of the ProTime system using both the standard blood volume and the low blood volume, with both venous blood and fingerstick blood, was compared to five different laboratory INR measurement systems. The study confirmed that despite the use of the INR system of prothrombin time reporting, differences of 20% of INR could be observed among the laboratory systems.

The difference between the ProTime and the laboratory was not significantly different from that observed among the laboratory systems. Based on clinical agreement, of pairs within 0.4 and 0.7 INR, similar results were obtained between the laboratory and ProTime systems:

Comparison	Range of Agreement at 0.4 INR	Range of Agreement at 0.7 INR
Lab System to Lab System	85.4 - 97.9 %	94.8 - 99.0 %
ProTime to Lab System	74.7 - 89.9 %	87.9 - 99.0 %
<p><small>Note: Range of Agreement reflects the total study of 5 laboratory INR systems and 4 ProTime systems (fingerstick and venous)</small></p>		

Recently an independent evaluation of the ProTime (low volume) was conducted by the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (Milano, Italy)⁷, in which the ISI of the ProTime was confirmed. ISI, also known as the international sensitivity index, is a measure of the reactivity of the thromboplastin and is a critical parameter for accurate prothrombin time testing. Using the desired WHO calibration method, this study determined an ISI of 0.90, clinically insignificant from the manufacturer's stated ISI of 1.0. For the 83 specimens tested, overall agreement between the ProTime and the laboratory was found to be 89%, based upon agreement of INR results.

Summary

The selected clinical trials described above serve to illustrate the demonstration of clinical accuracy of the ProTime systems when compared to the laboratory reference. These trials are representative of a number of clinical trials which demonstrate the high degree of clinical agreement of the ProTime system and the laboratory.

References

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Frank M. LaDuca, Ph.D.

Vice President, Clinical and Regulatory Affairs



8 Olsen Avenue • Edison, NJ 08820 USA
tel: 732.548.5700 • fax: 732.248.1928

ITC Europe • Strada Rivoltana • 20090 Rodano (MI) ITALY
tel: +39.02.9532.0196 • fax: +39.02.9532.0276

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