



Performance Assessment of FibriTimer™ Zeta-1 for PT and APTT Testing

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ABSTRACT

The FibriTimer™ Zeta-1 (called ZETA1) is a new, semi-automated multipurpose Haemostasis system, indigenously developed featuring DUAL TECHNOLOGY. ZETA1 is designed and developed by a Bangalore MedTech Startup M/S Dfine Bio-innovations Pvt Ltd, keeping in mind the needs of smaller labs. ZETA1 has not yet been evaluated in India.

The objective of this study was to evaluate the ZETA1 performance for prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) under local laboratory conditions.

For within run the CV% for normal control PT and APTT were 2.42 and 4.25 and 5.91 and 2.65 for abnormal control, respectively ⁴ For between runs on normal control, the CV% for PT and APTT were 0.76, 0.49, 2.34, and 0.99 for Abnormal control, respectively

The correlation coefficients of INR and APTT ratio between ZETA1 and CS-1600 were 0.96 and 0.81, respectively.

Standard Error of INR and APTT Ratio were, i.e., 0.023 and 0.076, respectively.

Keywords: New Coagulometer, FibriTimer™ Zeta-1 (called ZETA1) CS 1600 automated analyzer, performance assessment, screening PT and APTT tests.

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INTRODUCTION

Hemostasis is the physiological process that stops bleeding at the site of an injury while maintaining normal blood flow elsewhere in the circulation.¹ Multipurpose hemostatic systems have emerged as a promising strategy for managing acute bleeding. By integrating multiple hemostatic mechanisms into a single product, these systems aim to provide rapid and effective hemorrhage control across a spectrum of bleeding disorders.

STUDY – 1 (USING ZETA -1 OPTICAL METHOD) 14.05.2024

Methods

Control materials were used to evaluate the precision of ZETA1 and patient samples were used for comparability *vis-a-vis* the validated Sysmex® CS- 1600 analyzer (CS-1600).

Place of Study: Manipal Hospital

Manipal Hospital is a 600 bedded tertiary level care, technologically advanced infrastructure hospital situated in

the heart of Bangalore with the best of patient care facilities, equipment, diagnostic tests and treatment available under one roof. The hospital is equipped with 144 intensive care beds amongst ICUs, ICCUs, and NICUs and 20 modular State of the Art operation theatres with modern facilities.

Results

Precision study

Means, S.D., and %CV from within-run and between-run studies are presented in Table 1

Reference range and Mean Normal determination

No statistical outliers were observed in this study. PT and APTT results from normal subjects were normally distributed. Reference ranges for PT and APTT on Z-1 optical were 11-15 Sec and 24 to 36 seconds, respectively. The mean normal for PT was 13.5 seconds and Aptt was 29 seconds.

Both the ranges and mean were within the recommendations of the manufacturer.

Table 1: Mean, standard deviation (SD), and percentage of coefficient of variation (%CV) of prothrombin time (PT) and activated partial thromboplastin time (APTT)

| | PT | | | | APTT | | | |
|------|------------------------|--------------------------|------------------------|--------------------------|------------------------|--------------------------|------------------------|--------------------------|
| | Within run | | Between run | | Within run | | Between run | |
| | Control normal level 1 | Control abnormal level 2 | Control normal level 1 | Control abnormal level 2 | Control normal level 1 | Control abnormal level 2 | Control normal level 1 | Control abnormal level 2 |
| Mean | 12.41 | 28.01 | 12.4 | 28.26 | 28.49 | 43.39 | 28.3 | 44.48 |
| SD | 0.30 | 1.66 | 0.09 | 0.66 | 1.21 | 1.15 | 0.46 | 0.44 |
| CV% | 2.42 | 5.91 | 0.76 | 2.34 | 4.25 | 2.65 | 1.64 | 0.99 |

Statistical Software Used for data analysis: StatsDirect

Comparison study

Linear regression lines and r_2 of INR and APTT ratio between Z-1 and CS-1600 are described in Figure 1. INR and APTT values covered the clinical significance ranges. The r_2 was 0.98 and 0.82, respectively. The related Bland-Altman plots are shown in Figure 2.

Discussion

It is recommended that each laboratory establish its own reference range specific to the types of analyzers and reagent.^{2,3} However, it should be emphasized that these ranges are specific to the reagent lot. Laboratories have to establish new values when they change reagent lots.

For agreement analysis by Bland-Altman plot, the standard error of PT-INR and APTT – Ratio on Zeta – 1 was low (Figures 3 and 4). The highest bias in INR on Z-1 was 0.33 and for Aptt Ratio was 0.34, which may not be clinically significant. While such discrepancies in clotting times are normal with two different brands of instruments/reagents combination, the detection principle and analytical process could also have been the contributing factors. Clotting time in the Sysmex CS automation series is calculated from the middle of the coagulation curve while clotting time in the Z-1 is reported when the instrument detects the left point (T1) of the bell curve and right point (T2) of the bell curve with 70% of the maximum slope and the average of this T1 and T2 values are calculated indicating the coagulation time.

Specimens with normal clotting time usually generate a strong fibrin whirl, which can decrease the transmitted light earlier. However, a specimen with prolonged clotting time may have a weaker fibrin whirl. As a result, a longer time may be needed to develop a strong fibrin for the analyzer to detect. This effect may also cause discrepancies between Z-1 and CS-1600 at high levels of clotting time. In addition, Z-1 is a semi-automated analyzer in which the accuracy and precision of testing are dependent on the operator. Inter-operator variation and the competency of the operator can affect the accuracy of test results. However, this would not explain discrepant results in this study because a well-trained investigator performed all assays and the precision of all parameters was within acceptable limits.

Simple linear regression (Zeta -1 INR Vs Lab INR)

Equation: $E = 1.077688 D - 0.059523$
 Standard Error of slope = 0.023346
 Correlation coefficient (r) = 0.991201 ($r_2 = 0.982479$)
 95% CI for r (Fisher's z transformed) = 0.983305 to 0.995371
 Two sided P < 0.0001
 Power (for 5% significance) > 99.99%
 Correlation coefficient is significantly different from zero

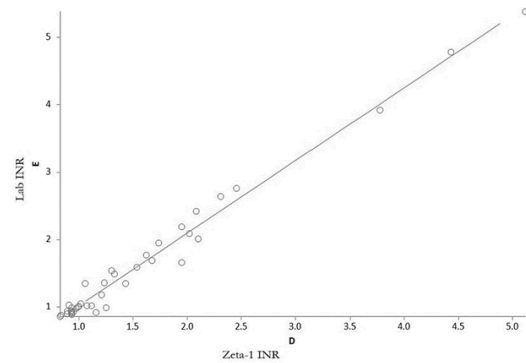


Figure 1: Regression curve

Bland - Altman Plots of Differences (Zeta -1 INR vs Lab INR)

Standard deviation = 0.157078
 Standard error = 0.024836
 95% CI = -0.110777 to -0.010305
 One sided P = 0.0097
 Power (for 5% significance) = 65.98%
 95% Limits of agreement = -0.368409 to 0.247327

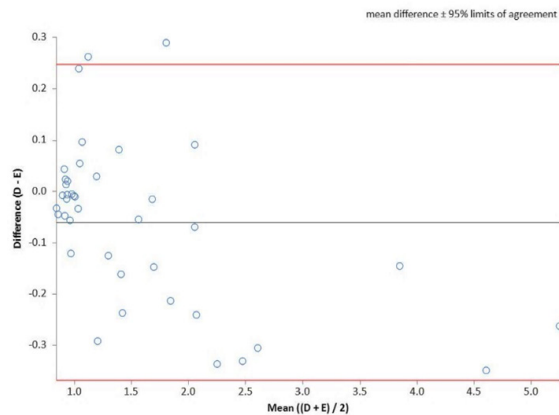


Figure 2: Regression curve - APTT ratio

Simple linear regression(Zeta -1 Aptt Ratio Vs Lab Aptt Ratio)

Standard Error of slope = 0.076329
 Correlation coefficient (r) = 0.907179 (t₂ = 0.822974)
 95% CI for r (Fisher's z transformed) = 0.82747 to 0.951049
 Two sided P < 0.0001, Power (for 5% significance) > 99.99%
 Correlation coefficient is significantly different from zero

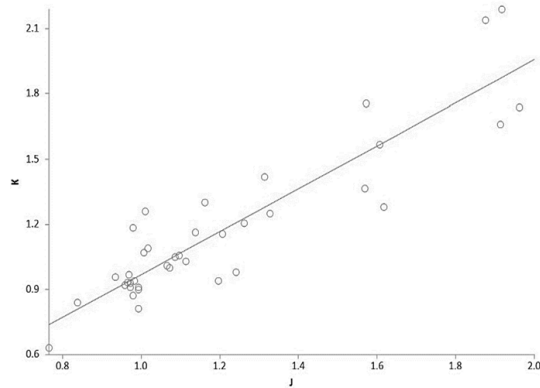


Figure 3: Simple linear regression

Bland - Altman Plots of Differences: (Zeta -1 Aptt Ratio vs Lab Aptt Ratio)

Standard deviation = 0.147243
 Standard error = 0.023886
 95% CI = -0.015052 to 0.081743
 One sided P = 0.0855, Power (for 5% significance) = 26.7%
 95% Limits of agreement = -0.255245 to 0.321937

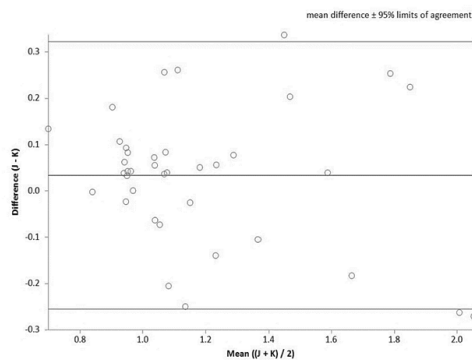


Figure 4: Bland- Altman plots of differences

Conclusion

The FibriTimer Zeta -1 is a new, semi-automated coagulation analyzer with a unique DUAL TECHNOLOGY that can perform screening coagulation assays. The default testing mode recommended by the manufacturer is optical and hence, we chose to perform the study using optical as a method. However, the mechanical testing mode looks like a useful addition serving as a secondary method for coagulation testing & further. The mechanical method can help the user test difficult samples (such as whole blood, severely lipemic, turbid, hazy, or hemolyzed samples). During our course of study, we did not feel the use of Mechanical testing except for a few random correlations, which turned out to be in agreement.

With the approval of the hospital management, the FibriTimer™ Zeta-1 was placed for a correlation and performance study for statistical evaluation and no reports were generated for clinical decision-making.

The performance of Zeta-1 (Optical) for screening tests in terms of precision and comparability to CS 1600 was acceptable. With the limited number of samples tested (40) the results of this validation study were in agreement. I suggest further validation studies with different Analysers, different reagents and more diverse sample types to generate a robust comparison and validation data.

STUDY – 2 (USING ZETA -1 MECHANICAL METHOD) DATE: 17TH MAY 2024

Department of clinical lab, Trustwell Hospitals, Bangalore, India.

Dr. Sudhindra, pathologist and lab director, Logeshkrishnan, Product Engineer. Ali, Lab Technologist. Shabbir, Lab Technologist

Methods

Control materials were used to evaluate the precision of ZETA1 and patient samples for comparability to the validated XL-1000C automated coagulation system

Place of Study: Trustwell Hospital

Trustwell Hospital is a multi-super specialty 250 bedded hospital in the heart of the city of Bangalore. The hospital comprises of highly specialized team of doctors providing comprehensive and multidisciplinary care and is an accomplished “Centre of Excellence.”

Results

Precision studies

For within run, the CV% for normal control PT and APTT were 1.6 and 2.5, respectively.

Both INR, APTT Ratio between ZETA1and XL-1000C shows good correlation with *p-value* < 0.0001for both and power of (5% significance) is >99.99%

The r² correlation values were 0.97 and 0.94 for INR and Aptt Ratio, respectively, indicating a positive and strong association. Standard error values were 0.029 and 0.042 for INR and APTT ratio, respectively,

Conclusion and Impression on Fibrimer

With the approval of the hospital administration, the FibriTimer™ Zeta-1 was placed for a correlation and precision study. The instrument has dual technology and we decided to test the performance of the instrument on its mechanical mode and correlate the results with our automated optical system. However, no reports from FibriTimer Zeta-1 were generated for clinical decision-making.

The performance of the FibriTimer Zeta1 instrument (For Mechanical testing) was found to be satisfactory for basic coagulation testing.

Zeta – 1 scored well in our correlation with our automated system and also in Precision studies.

FibriTimer Zeta–1 seems to be a good product for small labs. The company is promoting this at a competitive pricing and resonates with rural Indian budgets and testing requirements.

Equation: Lab INR = 0.94185 Zeta - 1 INR + 0.036162
 Standard error of slope = 0.029023
 95% CI for population value of slope = 0.881812 to 1.001888
 Correlation coefficient (r) = 0.989256 ($r_2 = 0.978628$)
 Two sided $p < 0.0001$
 Power (for 5% significance) > 99.99%
 Correlation coefficient is significantly different from zero

For differences between Zeta - 1 INR and Lab INR:
 Mean of differences = 0.0372 (n = 25)
 Standard deviation = 0.076391
 Standard error = 0.015278 95%
 CI = 0.005667 to 0.068733
 95% Limits of agreement = -0.112524 to 0.186924

APTT Ratio + 0.140929
 Standard error of slope = 0.042453
 95% CI for population value of slope = 0.798805 to 0.974447
 Correlation coefficient (r) = 0.974633 ($r_2 = 0.94991$)
 Two sided $p < 0.0001$

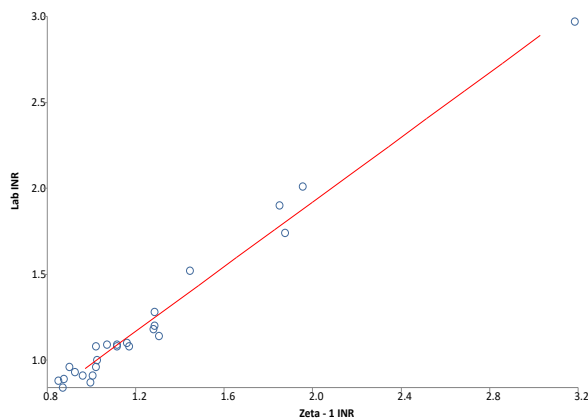


Figure 5: Simple linear regression

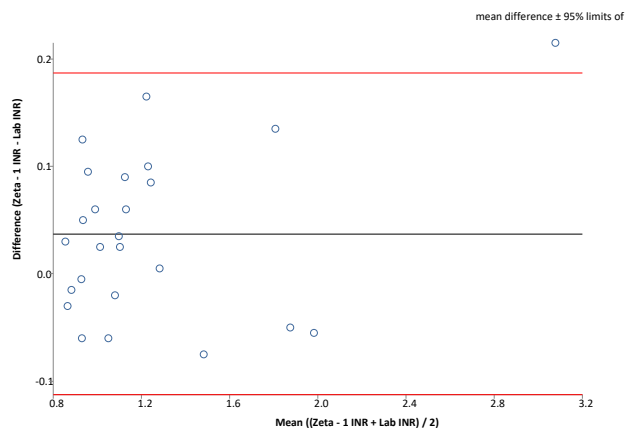


Figure 6: Bland-Altman Plot of Differences

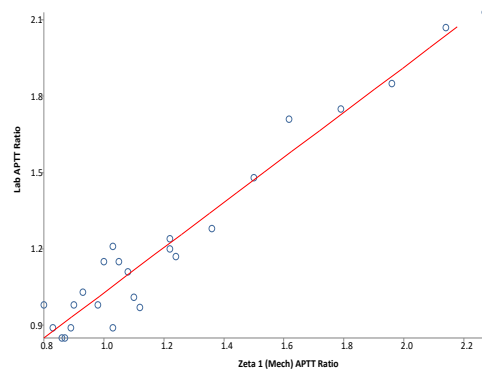


Figure 7: Simple linear regression

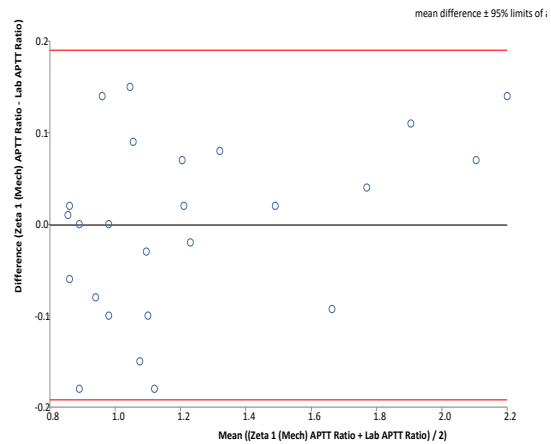


Figure 8: Bland-altman plot of differences

Power (for 5% significance) > 99.99%
 Correlation coefficient is significantly different from zero

For differences between Zeta 1 (Mech) APTT Ratio and Lab APTT Ratio.

Mean of differences = -0.00131 (n = 25)
 Standard deviation = 0.097502
 Standard error = 0.0195
 95% CI = -0.041557 to 0.038937

Two sample analysis of agreement

95% Limits of agreement = -0.192412 to 0.189791

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