Performance characteristics and comparison of Abbott and artus real-time system for hepatitis B virus DNA quantification

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Abstract

Virological monitoring of hepatitis B virus (HBV) DNA is critical to the management of HBV infection. With several HBV DNA quantification assays available, it is important to use the most efficient testing system for virological monitoring. In this study we evaluated the performance characteristics and comparability of three HBV DNA quantification systems: Abbott HBV real-time PCR, artus HBV real-time PCR with QIAamp DNA blood (artus-DB) and artus HBV real-time PCR with QIAamp DSP virus (artus-DSP) purification kit. The lower limits of detection of these systems were established against the WHO international standards for HBV DNA and were found to be 1.43, 82 and 9 IU/mL respectively. The intra-assay and interassay coefficient of variation of plasma samples (1 to 6 Log$_{10}$ IU/mL) ranged between 0.05 to 8.34% and 0.16 to 3.48% for Abbott, 1.53 to 26.85% and 0.50 to 12.89% for artus-DB and 0.29 to 7.42% and 0.94 to 3.01% for artus-DSP respectively. Ninety HBV clinical samples were used for comparison of assays and paired quantitative results showed strong correlation by linear regression analysis (artus-DB with Abbott, r=0.95, Abbott with artus-DSP, r=0.97 and artus-DSP with artus-DB, r=0.94). Bland-Altman analysis showed a good level of agreement for Abbott and artus-DSP with a mean difference of 0.10 Log$_{10}$ IU/mL and limits of agreement of -0.91 to 1.11 Log$_{10}$ IU/mL. No genotype-specific bias was seen in all three systems for HBV genotypes A, C and D that are predominant in this region. This finding illustrates that Abbott real-time HBV and artus-DSP systems show comparable performance than the artus-DB system, meeting the current guidelines for assays to be used in the management of hepatitis B.
Introduction

According to global estimates about 2 billion people are infected with hepatitis B virus (HBV) and around 350 million live with chronic infection (14). HBV DNA kinetics studies has helped clinical researchers in framing guidelines and definitions for the assessment of treatment responses and resistance to HBV drugs. Virological monitoring of HBV DNA is therefore a best predictor in the management of hepatitis B (6, 8, 11). As more HBV DNA quantitative assays become available, it is important to use an accurate HBV virological tool in monitoring of patients infected with HBV.

Nucleic acid testing has made a major impact on viral diagnostics and real-time PCR has become the standard diagnostic technology for many viruses. With the high sensitivity and broad dynamic range, real-time PCR has gradually replaced other signal amplification and target amplification technologies for HBV DNA detection (10). A standardized approach for use of HBV DNA assays in clinical practice has been recommended for efficient management of HBV (9). In order to ensure comparability between the assays, HBV DNA levels should be universally reported in IU/mL that has been calibrated with the World Health Organization (WHO) International Standard for HBV DNA (9). In therapeutic monitoring of HBV, a more sensitive assay with a lower limit of detection (LLD) of 10 IU/mL is recommended for early detection of viral rebound (5, 11). In addition, the assay employed should equally quantify all HBV genotypes (11). As there are assay to assay variations in quantification of HBV DNA, the use of same assay for a given patient is important in clinical practice to precisely monitor the antiviral efficacy of any given drug (5, 11).

There are currently 4 nucleot(s)ide analogues available for treatment of HBV. The success of antiviral treatment is measured by the complete loss of HBV DNA, HBeAg and HBsAg with or without the presence of anti-HBe and anti-HBs antibodies (6). The major challenge against
these oral drugs is the emergence of antiviral resistance. Currently, all the oral-drugs for HBV target the HBV reverse-transcriptase domain (rt) of polymerase gene that entirely overlaps the HBV surface gene. Mutations occurring in rt may thus impact nucleotide substitutions in surface region (12). Therefore, assays developed for HBV targeting surface region should be capable of detecting all the major mutations against the antiviral drugs.

In this study we analysed the performance characteristics and comparability of Abbott real-time HBV PCR (Abbott, Weisbaden, Germany), artus HBV RG PCR with QIAamp DNA blood (artus-DB; Qiagen GmbH, Hilden, Germany) and artus HBV RG PCR with QIAamp DSP virus (artus-DSP; Qiagen GmbH, Hilden, Germany) purification kits for quantification of HBV DNA. Performance characteristics including analytical sensitivity, precision and reproducibility were studied using HBV DNA standards and clinical samples. Additionally, clinical samples with HBV genotypes circulating in this region were compared in all three systems. The ability to detect antiviral resistant mutants in these systems was also attempted.

**Materials and Methods**

**Standards**

The second WHO international standard for HBV DNA (National Institute for Biologicals Standards and Control-NIBSC code: 97/750) of lyophilized plasma was reconstituted in 0.5 mL of nuclease free water (Ambion, Austin, TX., USA). The final concentration of $1 \times 10^6$ IU/mL was serially diluted in human plasma negative for all markers of HBV, hepatitis C and human immunodeficiency virus RNA. HBV DNA concentrations of 100, 50, 25, 10 and 1 IU/mL were used to determine the LLD of assays.
Clinical samples

HBV DNA positive blood plasma bags obtained from blood-bank of this hospital with five different concentrations (HBV DNA 1 to 6 Log_{10} IU/mL) were used in this evaluation. All samples were tested in triplicates in three runs to determine the precision and reproducibility of assays. Additionally, 90 randomly selected plasma samples were used for comparison of assays. These samples were collected from patients with chronic HBV infection attending the liver clinic of our hospital and the study was approved by the Institutional Review Board.

Abbott real-time HBV PCR

The plasma samples were processed by an automated sample preparation system-m2000sp that uses magnetic microparticle-based principle for purification of DNA. Amplification is carried-out in the Abbott m2000rt system and the HBV DNA concentration is calculated from the calibrators provided with the kit. The extraction system uses an initial sample input of 500 µl and final elution of 70 µl. This system targets HBV surface gene for real-time detection with the PCR input volume of 50 µl and the manufacturer’s stated LLD for HBV DNA is 10 IU/mL. Samples that are detected with viral load less than the LLD are showed by this system as <10 IU/mL and negative samples as not detected.

artus with QIAamp DNA Blood purification procedure (artus-DB)

The QIAamp DNA blood kit uses the silica-membrane technology for purification of DNA. The plasma sample is processed with a starting material of 200µl and eluted in 50 µl of elution buffer by spin procedure. Twenty micro litre of elute was used as a template for PCR amplification with the artus HBV RG PCR kit in the Rotor-Gene 6000 platform (Corbett Research, Mortlake, Vic., Australia). The assay targets 134 bp region of HBV core gene and the detection limit determined by the manufacturer is 20 IU/mL (95% detection limit).
artus with QIAamp DSP purification procedure (artus-DSP)

The QIAamp DSP virus procedure allows the selective binding of viral nucleic acid in silica-based membrane and is carried out on a QIAvac 24 plus vacuum manifold (Qiagen GmbH, Hilden, Germany). The viral DNA is purified from 500µl of plasma and finally eluted in 26µl of elution buffer. Reactions for amplification were performed similar to that of artus-DB. The LLD of artus HBV RG PCR using the DSP virus kit was claimed to be 3.8 IU/mL (95% detection limit).

Determination of HBV antiviral resistance mutations and genotypes

Amplification and sequencing of HBV reverse transcriptase (rt) gene was carried out for 30 samples as described earlier (7). HBV genotypes were determined by aligning study sequences with HBV genotype reference sequences. Phylogenetic analysis was performed in MEGA4 using the neighbour-joining method with a bootstrap test of 1000 replicates and maximum composite likelihood algorithm.

Serology testing

HBsAg testing was performed in EIA (Diasorin S.P.A., Saluggia, Italy) and Axsym (Abbott, Wiesbaden, Germany). HBeAg testing was performed in EIA (Diasorin S.P.A., Saluggia, Italy).

All clinical samples and HBV DNA standards were stored in aliquots at -60°C till testing.

Statistical analysis

Pearson's correlation coefficient and linear regression analysis were performed to measure the overall correlation between the assays. The Bland-Altman plots were used for the analysis of agreement between the assays. These analyses were performed using STATA 10.0.
(STATACORP, College Station, TX, US). Probit analysis was used to determine the LLD of assays using SPSS 16.0 for windows (SPSS, Chicago, IL, USA).

Results

Analytical sensitivity (lower limit of detection)

To determine the LLD the WHO standard of HBV DNA (NIBSC) at dilutions 100, 50, 25, 10 and 1 IU/mL were tested in quadruplicates in five runs to obtain 20 data points for each dilution. Probit analysis showed the LLD of Abbott, artus-DB and artus-DSP to be 1.43 (CI not determined), 82 (95% CI 56 to 179 IU/mL) and 9 IU/mL (95% CI 5 to 31 IU/mL) respectively (Table 1). HBV DNA standards at dilutions 100, 50 and 25 IU/mL (2, 1.69897 and 1.39794 Log$_{10}$ IU/mL) for which quantitative values were available were plotted against the obtained mean Log$_{10}$ HBV DNA values for individual assays. The expected and measured concentrations significantly correlated for Abbott (r=0.90) and artus-DSP (r=0.92) respectively. The mean difference for HBV DNA standards 100, 50 and 25 IU/mL were 18.5, 14.75 and 9.5 IU/mL for Abbott and 33.8, 12.35 and 5.3 IU/mL for artus-DSP respectively. The correlation of artus-DB for these standard dilutions was poor (r=0.54) with a mean difference of -65.25, -39.68 and -18.78 IU/mL respectively. (Fig.1)

Precision and reproducibility

Precision and reproducibility of the assays was evaluated by intra-assay and interassay variations using five different concentrations of blood plasma bag samples (1 to 6 Log$_{10}$ HBV DNA IU/mL). Each sample was run in triplicates for three days. The intra-assay coefficient of variation (CV) ranged 0.05 to 8.34%, 1.53 to 26.85% and 0.29 to 7.42% for Abbott, artus-DB and artus-DSP respectively. The interassay CV ranged from 0.16 to 3.48%, 0.50 to 12.89% and 0.94 to 3.01% for the three systems respectively. (Table 2)
Clinical performance characteristics

Among 90 clinical samples tested, 64 samples were detected by artus-DB system with HBV DNA viral load ranging between 2 and $4 \times 10^8$ IU/mL (median 745 IU/mL). The Abbott system detected 82 samples with HBV DNA level of <10 IU/mL to $4 \times 10^8$ IU/mL (median 1256 IU/mL). Likewise, 77 samples were detected by artus-DSP with 1 to $1 \times 10^8$ IU/mL of HBV DNA (median 1095 IU/mL). Out of 56 (62.2%) samples that are quantitated in all three systems the mean difference in quantification was 0.46 Log$_{10}$ IU/mL (artus-DB – Abbott), 0.06 Log$_{10}$ IU/mL (Abbott - artus-DSP) and 0.40 Log$_{10}$ IU/mL (artus-DSP – artus-DB) respectively.

Linear regression analysis

Linear regression analysis between assays was carried out for the paired quantitative results (Fig. 2). Comparison of artus-DB with Abbott, Abbott with artus-DSP and artus-DSP with artus-DB showed strong correlation between the assays ($r=0.95$, 0.97 and 0.94; $P<0.0001$).

Level of agreement

A Bland and Altman plot was used to determine the agreement between assays. Using this method, the differences between the HBV DNA Log$_{10}$ IU/mL values by two assays were plotted against the averages of two techniques. The mean difference between artus-DB and Abbott system was -0.48 Log$_{10}$ IU/mL (CI -0.66 to -0.29) with limits of agreement of -1.93 to 0.98 Log$_{10}$ IU/mL. HBV DNA tested in artus-DB showed low quantitative values and the differences were high for samples with viral load <4 Log$_{10}$ IU/mL. The Abbott and artus-DSP showed a good agreement with the mean difference of 0.10 Log$_{10}$ IU/mL (CI -0.02 to 0.22) and limits of agreement of -0.91 to 1.11 Log$_{10}$ IU/mL. The mean difference in values between artus-DB and artus-DSP was -0.38 Log$_{10}$ IU/mL (CI -0.56 to -0.19) with limits of agreement...
of -1.82 to 1.06 Log_{10} IU/mL. In comparison to artus-DSP, the HBV DNA levels were lower in artus-DB and showed high difference for most of the samples with viral load <4 Log_{10} IU/mL. (Fig.3)

**HBeAg and HBV DNA detection**

Among 29 HBeAg positive samples, nine samples were not detected by artus-DB. Artus-DSP detected 26 (90%) of those HBeAg positive samples with the viral load in the range of 14-766 IU/mL (median 151 IU/mL). Abbott detected all HBeAg positive samples that missed detection by artus-DB and artus-DSP (<10 to 742 IU/mL, median 71 IU/mL).

**Quantification of HBV DNA specific to genotypes and antiviral resistant mutants**

To determine the difference in HBV DNA quantification among HBV genotypes, the evaluation panel included those with HBV DNA levels >1000 IU/mL in artus-DB that could be amplified in HBVrt PCR. Among 30 samples, genotype A, C and D were identified in 4 (13.33%), 2 (6.67%) and 24 (80%) samples respectively. There was a good correlation for HBV DNA levels between the assays irrespective of HBV genotypes (Fig. 4 and 5). Linear regression analysis was not performed for genotype C as there were only two samples for analysis. However, the Log difference between assays for genotype C ranged between -0.22 to 0.5 log_{10} IU/mL. (Table 3)

Out of these samples two patients on lamivudine and lamivudine adefovir combination were detected with rtM204I mutation and one patient on lamivudine therapy was identified with rtL180M and rtM204V/I mutation. The quantitative difference between the assays for these antiviral resistant mutants ranged between 0.02 to 0.46 Log_{10} IU/mL.
Discussion

In this study we verified the performance specifications of a FDA approved-IVD licensed Abbott real-time HBV assay and CE marked-IVD licensed artus assay for quantification of HBV DNA. Samples for artus real-time PCR were processed in two purification methods with differing technology and sample volume. The Clinical Laboratory Improvement Amendments (CLIA) specifies that clinical laboratories should verify the manufacturer’s performance specifications and confirm that they can be replicated in the respective laboratory (13). Performance characteristics including analytical sensitivity, linear range and accuracy test for comparison-of-methods were performed. Analytical sensitivity for verification of LLD was established using five dilutions of WHO HBV DNA. The samples were tested in replicates of four obtaining 20 data points for each dilution collected over five days. Also, the linearity of assays was established against the minimum required five concentrations across the stated linear range. These data points were according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) and College of American Pathologists (CAP) for validation of quantitative assays (3, 4). In this evaluation, analytical specificity was not performed as it is required mainly for home-brewed assays (2).

Analytical sensitivity determination showed Abbott and artus-DSP real-time systems to detect HBV DNA <10 IU/mL and meet the recommended guidelines for HBV management. Further, correlation analysis showed good correlation with the expected HBV DNA values for Abbott and artus-DSP. In contrast, values for artus-DB were underestimated with the expected values for 100, 50 and 25 IU/mL NIBSC HBV standards with a mean difference of -65.25, -39.68 and -18.78 IU/mL respectively. HBV DNA standards 1 and 10 IU/mL were not included for analysis as these reference standards were not detected in artus-DB and though detected by Abbott, the actual quantitative data was not obtained as it could only show <10 IU/mL for values below the LLD. Our results for LLD indicate that the artus-DB
and artus-DSP system which failed to meet the manufacturer’s claim of 20 IU/mL (artus-DB) and 3.8 IU/mL (artus-DSP) illustrates the importance of evaluation of nucleic acid test systems in the end user laboratories.

Precision and reproducibility analysis of blood plasma bag samples showed Abbott and artus-DSP to be equally reproducible over all ranges tested. Whereas, artus-DB showed a maximum intra-assay variation of 26.85% at 1 Log_{10} IU/mL concentration and the assay was linear and reproducible between 3 and 6 Log_{10} IU/mL. The type of samples used for accuracy or trueness of the results may also influence the determined performance characteristics of the assay. Therefore, the use of blood plasma bag samples in our evaluation ensures the exact reproducibility of results in clinical specimens instead of using standards in different matrix.

Comparison of clinical samples showed the Abbott system to be very sensitive detecting 18(20%) and 5(6%) of samples more than artus-DB and artus-DSP. Moreover, Abbott detected all 29 samples that are positive for HBeAg as HBV DNA positive, whereas 9 (31%) and 3 (10%) of HBeAg positive samples that are likely to be positive for HBV DNA was missed out by the artus-DB and artus-DSP respectively. Therefore, the sensitivity of artus-DB, artus-DSP and Abbott for the detection of HBV DNA with respect to HBeAg positivity was 69%, 90% and 100% respectively. The HBV DNA results obtained by artus-DB were consistently lower in 74(82%) and 54(60%) samples tested by Abbott and artus-DSP. The Bland-Altman plot showed artus-DB to underestimate HBV DNA levels relative to Abbott and artus-DSP systems for samples with viral load <4 Log_{10} IU/mL. Viral loads were not uniformly distributed when comparing artus-DSP and artus-DB systems. However, there existed a good level of agreement between Abbott and artus-DSP. There was no substantial difference in quantification among the circulating HBV genotypes and antiviral resistant mutants tested in all three systems.
The main reason for difference in sensitivity between these assays could be due to the difference in sample volume, i.e., 200µl for artus-DB and 500µl for Abbott and artus-DSP. Also, the final elution volume can make a substantial difference in the obtained DNA concentration. Therefore, DNA prepared from high sample volume and re-suspended in low elution buffer enhances the detection rate in low viral load samples. The effect of sample volume on the sensitivity of HBV detection was also shown by Allain & Candotti (1). The other reason may also be the different target region used for detection. This argument is supported by one sample not detected in Abbott system being positive in artus-DB and artus-DSP. Due to the inadequacy in sample volume, the reasons for Abbott negative and artus-DB/DSP positive results were not analysed. Though Abbott and artus-DSP employed different principle for sample processing and targets different region for amplification, the results for the clinical samples correlated very well. The mean difference in quantification between Abbott and artus-DSP was less than the clinically relevant difference of 0.5 Log_{10} IU/mL and showed a good level of agreement. Therefore, Abbott and artus-DSP systems can also be interchangeably used for therapeutic monitoring.

In summary, the Abbott real-time HBV PCR is a sensitive and highly reproducible system for quantification of HBV DNA. With automation technology it reduces the hands-on-time and carry-over contamination in a high-throughput laboratory. Likewise, artus real-time system in combination with DSP purification system (artus-DSP) is a reliable and sensitive HBV DNA quantification system. Both these systems show comparable performance than artus-DB and meet the current guidelines for assays used in the management of hepatitis B. Our study also illustrates the importance of validation of commercial assays in individual laboratories before implementation for routine testing.
Conflicts of interest

None

Source of funding

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References


Figure legends

Figure 1. Correlation analysis using the expected NIBSC HBV DNA concentration (Log\(_{10}\) IU/mL) and the corresponding test results in the three systems. Each point represents the mean Log\(_{10}\) IU/mL of 20 data points tested in quadruplicates over 5 days. The bars represent ± 1 SD.

Figure 2. Correlation of HBV DNA levels in clinical samples measured by artus-DB, Abbott and artus-DSP systems.

Figure 3. Bland-Altman analysis showing the differences in quantification between artus-DB, Abbott and artus-DSP systems.

Figure 4. Correlation between measurements of DNA levels by artus-DB, Abbott and artus-DSP systems for HBV genotype A.

Figure 5. Correlation between measurements of DNA levels by artus-DB, Abbott and artus-DSP systems for HBV genotype D.
Table 1: Lower limit of detection by probit analysis

<table>
<thead>
<tr>
<th>NIBSC HBV DNA (IU/mL)</th>
<th>No. of replicates</th>
<th>No. Positive (%)</th>
<th>Probit value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>artus-DB</td>
<td>Abbott</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
<td>15 (75%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>25</td>
<td>20</td>
<td>13 (65%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>3 (15%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>0</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Probit value (95% CI)</td>
<td>82 (56 to 179)</td>
<td>1.43</td>
<td>9 (5 to 31)</td>
</tr>
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Table 2: Precision and reproducibility of Abbott, artus-DB and artus-DSP systems

<table>
<thead>
<tr>
<th></th>
<th>Intra-assay&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Interassay&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>Abbott HBV DNA</td>
<td></td>
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<tr>
<td>(Log&lt;sub&gt;10&lt;/sub&gt; IU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>2</td>
<td>1.91-2.04</td>
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<tr>
<td>3</td>
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<td>0.04-0.18</td>
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<td>6.19-6.31</td>
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<td>artus-DB HBV DNA</td>
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<tr>
<td>(Log&lt;sub&gt;10&lt;/sub&gt; IU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.26-1.61</td>
<td>0.31-0.42</td>
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<td>(Log&lt;sub&gt;10&lt;/sub&gt; IU/mL)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>3</td>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>6.1-6.29</td>
<td>0.02-0.21</td>
</tr>
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</table>

<sup>a</sup> HBV DNA concentrations (Log<sub>10</sub> IU/mL) of five blood plasma bag units are shown as estimated by the three assays

<sup>b</sup> Samples were tested in triplicates over 3 days
### Table 3: Quantification difference by HBV genotypes between the real-time systems

<table>
<thead>
<tr>
<th>HBV Genotype</th>
<th>Mean Log$_{10}$ IU/mL (SD)</th>
<th>Difference in Log$_{10}$ IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>artus-DB Abbott artus-DSP</td>
<td>(artus-DB) (Abbott) – (Abbott) – (artus-DSP)</td>
</tr>
<tr>
<td>A (n=4)</td>
<td>4.54 (1.45) 4.76 (1.63)</td>
<td>-0.22 0.16 0.05</td>
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<tr>
<td>C (n=2)</td>
<td>5.00 (0.55) 5.28 (0.08)</td>
<td>-0.27 -0.22 0.50</td>
</tr>
<tr>
<td>D (n=24)</td>
<td>5.88 (1.67) 5.87 (1.70) 5.88 (1.53)</td>
<td>0.01 -0.01 0.01</td>
</tr>
</tbody>
</table>