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Comparative Evaluation of Bovine-Brain-Derived Thromboplastin versus Commercial Thromboplastin Reagents for Prothrombin Time and INR: A Pilot Experimental Study at National Polytechnic University Institute Medical Laboratory

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Abstract

Hemostasis is a vital physiological process, and the Prothrombin Time (PT) test with International Normalized Ratio (INR) is central to monitoring coagulation. Variability in PT/INR results persists due to differences in thromboplastin reagents, with bovine-brain-derived thromboplastin widely used in resource-limited laboratories for affordability, but associated with lower sensitivity and batch-to-batch variability. Commercial reagents provide greater consistency but are costly. Comparative evaluation is essential to ensure accuracy, reproducibility, and patient safety. The main purpose of this study was to evaluate the analytical performance of bovine-brain-derived thromboplastin compared to commercial thromboplastin reagents for PT and INR testing, focusing on accuracy, precision, reproducibility, concordance of INR values, and International Sensitivity Index (ISI) calibration. An experimental study design was employed at National Polytechnic University Institute Bamenda, Cameroon. Plasma samples from 10 participants were analyzed using both bovine-brain-derived and commercial thromboplastin reagents. A convenience sampling technique was used to include participants. Laboratory procedures followed standardized protocols for reagent preparation, calibration, and PT/INR testing. Data were analyzed using Microsoft Excel 2013, and SPSS version 20.0 with descriptive statistics (mean, standard deviation, coefficient of variation) and agreement analysis (Pearson correlation). The bovine brain derived reagent produced a

mean PT of 118.9 seconds (SD 77.4; CV 65.1%), while the commercial reagent yielded a mean PT of 63.0 seconds (SD 41.2; CV 65.4%). Reproducibility was wider with the bovine reagent (27 - 254 s) compared to the commercial reagent (18 - 165 s). Logarithmic transformation reduced dispersion but did not eliminate discrepancies, with weak correlation ($r \approx 0.305$, $p \approx 0.392$). The estimated ISI for the bovine reagent was 0.369 compared to 1.2 for the commercial reagent, indicating markedly lower sensitivity. This study confirms that bovine-brain-derived thromboplastin, while affordable and accessible, exhibits poor accuracy, precision, and reproducibility compared to commercial reagents. Commercial thromboplastin reagents provide values closer to expected norms, making them more suitable for routine PT/INR testing and anticoagulation monitoring.

Subject Areas

Evidence Based Medicine

Keywords

Hemostasis, Prothrombin Time, International Normalized Ratio, International Sensitivity Index, Bovine-Brain-Derived Thromboplastin, Commercial Thromboplastin Reagents

1. Introduction

Hemostasis is a tightly regulated physiological process that prevents excessive blood loss following vascular injury through coordinated vasoconstriction, platelet plug formation, and activation of the coagulation cascade [1] [2]. The coagulation cascade comprises the intrinsic, extrinsic, and common pathways, with the extrinsic pathway serving as the primary initiator of coagulation in vivo. This pathway is triggered by the exposure of tissue factor (TF), which binds and activates factor VII, leading to sequential activation of factors IX and X, thrombin generation, and fibrin clot formation [2]-[4]. Because the extrinsic pathway is essential for rapid hemostasis, its functional integrity is routinely assessed using the Prothrombin Time (PT) test, making PT one of the most widely used laboratory assays for evaluating coagulation disorders and monitoring anticoagulant therapy [3] [5].

The Prothrombin Time (PT) and the International Normalized Ratio (INR) are indispensable laboratory parameters for monitoring vitamin K antagonist therapy, diagnosing coagulation abnormalities, assessing liver function, and evaluating bleeding risk before surgical procedures [5]-[8]. The INR was introduced to standardize PT results obtained using different thromboplastin reagents and laboratory instruments by incorporating the ISI, thereby facilitating comparable results across laboratories [6] [8]. Despite this standardization, clinically important variations in PT and INR measurements continue to occur due to differences in reagent sensitivity, calibration procedures, instrumentation, and analytical prac-

tices, potentially resulting in inappropriate anticoagulant dosing and an increased risk of thromboembolic or hemorrhagic complications [7]-[10].

Thromboplastin is the key reagent used in PT testing because it initiates the extrinsic coagulation pathway through tissue factor-mediated activation of factor VII [6] [7]. Thromboplastin reagents may be prepared from biological sources, including bovine brain, rabbit brain, or human placenta, or produced as recombinant commercial formulations. While recombinant and commercial reagents generally offer superior standardization, consistency, and reduced biological risk, they are often expensive and less accessible in low-resource settings. Conversely, bovine brain-derived thromboplastin remains widely used because of its affordability and local availability but is associated with batch-to-batch variability and differences in sensitivity that may influence PT and INR results [6] [7] [10]. Consequently, comparative evaluation of locally prepared bovine thromboplastin against commercial reagents is essential to ensure analytical reliability, quality assurance, and patient safety.

Although the INR system has substantially improved harmonization of coagulation testing, evidence indicates that reagent-related variability remains a major challenge, particularly in resource-limited countries where bovine-derived thromboplastin continues to be used [9]-[12]. In Cameroon, limited local data exist comparing the performance of bovine brain-derived thromboplastin with commercially available reagents, despite ongoing national efforts to strengthen laboratory quality management and standardization [13]-[15]. This evidence gap creates uncertainty in clinical interpretation of PT/INR results and may compromise anticoagulation management. Therefore, this study aimed to compare the performance of bovine brain-derived thromboplastin with commercial thromboplastin reagents for PT and INR determination in order to generate local evidence that could support the selection of accurate, reliable, and cost-effective reagents for coagulation testing in resource-limited settings.

2. Methodology

This pilot experimental laboratory-based analytical evaluation was conducted at the National Polytechnic University Institute (NPUI), Bamenda, Cameroon, between 1 and 30 March 2026 to compare the performance of bovine brain-derived thromboplastin with a commercial thromboplastin reagent for prothrombin time (PT) and international normalized ratio (INR) determination. As a pilot analytical evaluation, a convenience sample of 10 consenting healthy adults (≥18 years) was considered sufficient to generate paired PT and INR measurements for preliminary assessment of agreement and feasibility between the two reagents rather than to establish definitive clinical equivalence. Freshly slaughtered bovine brains (≥450 g, free of hemorrhage) were used for the preparation of the experimental thromboplastin reagent. Individuals with known liver disease, bleeding disorders, or those unwilling to participate were excluded. Venous blood was collected by standard aseptic venipuncture into 3.2% sodium citrate tubes, centrifuged to ob-

tain platelet-poor plasma, and each plasma sample was analyzed in parallel using both the locally prepared bovine brain-derived thromboplastin, extracted following a standardized acetone-extraction protocol, and a commercially available thromboplastin reagent (BIOBASE CoagTHREE Assay Kit). Each plasma sample was analyzed in duplicate, and the mean of the two measurements was used for subsequent analysis. Analytical precision and reproducibility were evaluated using the within-run coefficient of variation of replicate measurements. PT testing was performed on a calibrated coagulation analyzer according to the manufacturer's instructions and standard operating procedures under identical laboratory conditions. The ISI of the locally prepared bovine thromboplastin was calibrated against the commercial reference thromboplastin using paired PT measurements obtained from the study plasma samples. Following WHO recommendations, linear regression analysis of logarithmically transformed PT values was performed, and the regression slope was used to derive the bovine thromboplastin ISI, which was calculated as 0.369. The mean normal prothrombin time (MNPT) established from the healthy participants was used as the reference for INR calculation, with the normal reference PT range defined as 11 - 15 seconds and the normal INR range as 0.8 - 1.2. The INR for each sample was calculated using the standard formula:

$$\text{INR} = (\text{Patient PT} \div \text{Mean Normal PT [MNPT]})^{\text{ISI}}$$

where PT is the patient's prothrombin time, MNPT is the mean prothrombin time of the healthy reference participants, and ISI is the International Sensitivity Index specific to the thromboplastin reagent used. The deviation of each PT result from the normal reference was calculated as:

$$\text{Deviation from normal (\%)} = [(\text{Observed PT} - \text{MNPT}) \div \text{MNPT}] \times 100$$

Internal quality control was maintained using normal and abnormal control plasmas, daily analyzer calibration, reagent verification, and adherence to standardized laboratory procedures. Data were analyzed using SPSS version 20 and Microsoft Excel 2013. Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to summarize PT and INR values, while Pearson's correlation analysis was performed to assess the relationship between the two thromboplastin reagents, with statistical significance set at $p \leq 0.05$. Ethical approval and administrative authorizations were obtained from the relevant institutional and regional health authorities.

3. Results

Socio-Demographic Characteristics of participants

Out of the 10 participants, the majority 6 (60.0%) were aged 20 - 29 years, 7 (70.0%) were female, and 8 (80.0%) were single. In terms of education, most 7 (70.0%) held a degree, while 9 (90.0%) were students by occupation. Regarding residence, 6 (60.0%) lived in Mile 7 Nkwen. None reported any known medical condition (Table 1).

Table 1. Distribution of respondents according to socio-demographic characteristics.

Variable	Characteristics	Frequency	Percentage (%)
Age (Years)	<20	2	20.0
	20 - 29	6	60.0
	30 - 39	2	20.0
	40 - 49	0	0.0
	≥50	0	0.0
Total		**10**	**100.0**
Sex	Male	3	30.0
	Female	7	70.0
Total		**10**	**100.0**
Marital Status	Single	8	80.0
	Married	2	20.0
	Divorced	0	0.0
	Widowed	0	0.0
Total		**10**	**100.0**
Educational Level	Secondary	0	0.0
	Diploma	1	10.0
	Degree	7	70.0
	Postgraduate	2	20.0
Total		**10**	**100.0**
Occupation	Student	9	90.0
	Teacher	1	10.0
Total		**10**	**100.0**
Residence	Mile 6 Nkwen	3	30.0
	Bambui	1	10.0
	Mile 7 Nkwen	6	60.0
Total		**10**	**100.0**
Medical Condition	Yes	0	0.0
	No	10	100.0
Total		**10**	**100.0**

Comparison of analytical performance of bovine-brain-derived thromboplastin and commercial thromboplastin reagents in prothrombin time PT and INR testing: accuracy, precision, and reproducibility

Out of the 10 test samples analyzed, the bovine brain-derived thromboplastin consistently showed larger deviations from the normal PT range compared to the commercial reagent, indicating lower accuracy. In contrast, the commercial reagent produced values that were generally closer to expected norms, reflecting better reliability in clinical use (Table 2).

Table 2. Accuracy (closeness to expected PT range) of bovine brain derived and commercial thromboplastin reagent.

PT Bovine (s)	PT Commercial (s)	Deviation from Normal (Bovine)	Deviation from Normal (Commercial)
254	84	+239	+69
52	120	+37	+105
65	84	+50	+69
193	46	+178	+31
70	40	+55	+25
171	165	+156	+150
228	28	+213	+13
74	31	+59	+16
65	18	+50	+3
27	22	+12	+7

Out of the two reagents tested, the bovine brain-derived thromboplastin recorded a higher mean PT of 118.9 seconds with a standard deviation of 77.4, resulting in a coefficient of variation of 65.1%. The commercial reagent showed a lower mean PT of 63.0 seconds with a standard deviation of 41.2, yielding a coefficient of variation of 65.4% (Figure 1).

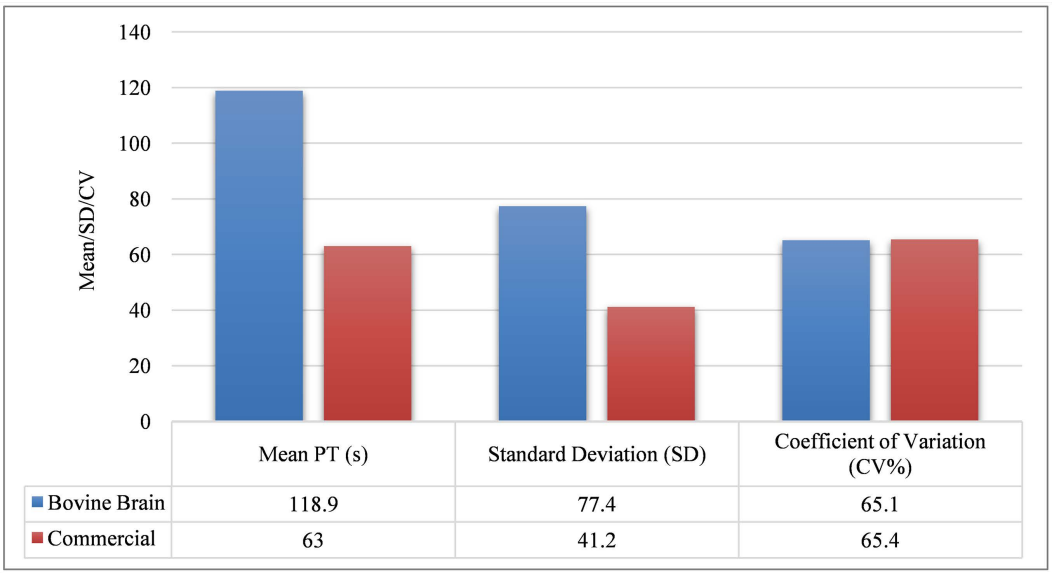

Figure 1. Precision (consistency of replicates) of bovine brain-derived and commercial thromboplastin reagents.

Out of the 10 samples analyzed, the bovine-brain-derived thromboplastin reagent showed a much wider reproducibility range (27 - 254 seconds) compared to the commercial reagent (18 - 165 seconds) (Table 3).

Table 3. Reproducibility of bovine brain-derived vs. commercial thromboplastin reagents (PT range across samples).

Reagent	Minimum PT (s)	Maximum PT (s)	Range (s)
Bovine Brain	27	254	27 - 254
Commercial	18	165	18 - 165

Concordance of INR Values between Bovine Brain Derived and Commercial Reagents

Logarithmic PT test values

Table 4 below demonstrates substantial inter-method variability in PT measurements between bovine brain thromboplastin and the commercial reagent across the ten samples. PT values obtained using bovine thromboplastin are generally higher and more dispersed (27 - 254 s) compared to the commercial reagent (18 - 165 s), although the direction of difference is not uniform across samples, indicating lack of proportional agreement between the two methods. The logarithmic transformation of PT values reduces absolute dispersion and stabilizes variance, yet persistent discrepancies between paired measurements remain, suggesting a non-linear relationship and systematic bias between the reagents.

Table 4. Comparison of PT values and log-transformed results obtained using bovine brain thromboplastin and commercial reagent across samples.

Sample ID	PT bov brain (s)	PT comm (s)	Log PT bov brain	Log PT comm
11	254	84	2.4048	1.9243
3	52	120	1.7160	2.0792
1	65	84	1.8129	1.9243
2	193	46	2.2856	1.6628
5	70	40	1.8451	1.6021
4	171	165	2.2330	2.2175
22	228	28	2.3579	1.4472
6	74	31	1.8692	1.4914
44	65	18	1.8129	1.2553
55	27	22	1.4314	1.3424

Relationship between the logarithmic PT values derived from bovine brain thromboplastin and commercial thromboplastin reagent

The scatter plot (Figure 2) illustrates the relationship between the logarithmic PT values derived from bovine brain thromboplastin and those obtained using a commercial thromboplastin reagent. A positive but weak correlation was observed between the two methods (Pearson's correlation coefficient, $r \approx 0.305$), indicating limited linear agreement in PT values across the two thromboplastin sources. The corresponding regression line ($y = 0.308x + 1.087$) demonstrates a shallow slope, suggesting that increases in log PT values from bovine brain throm-

boplastin are only minimally reflected in the commercial reagent measurements. Statistical analysis revealed that the relationship was not significant ($p \approx 0.392$), confirming that the observed correlation is weak.

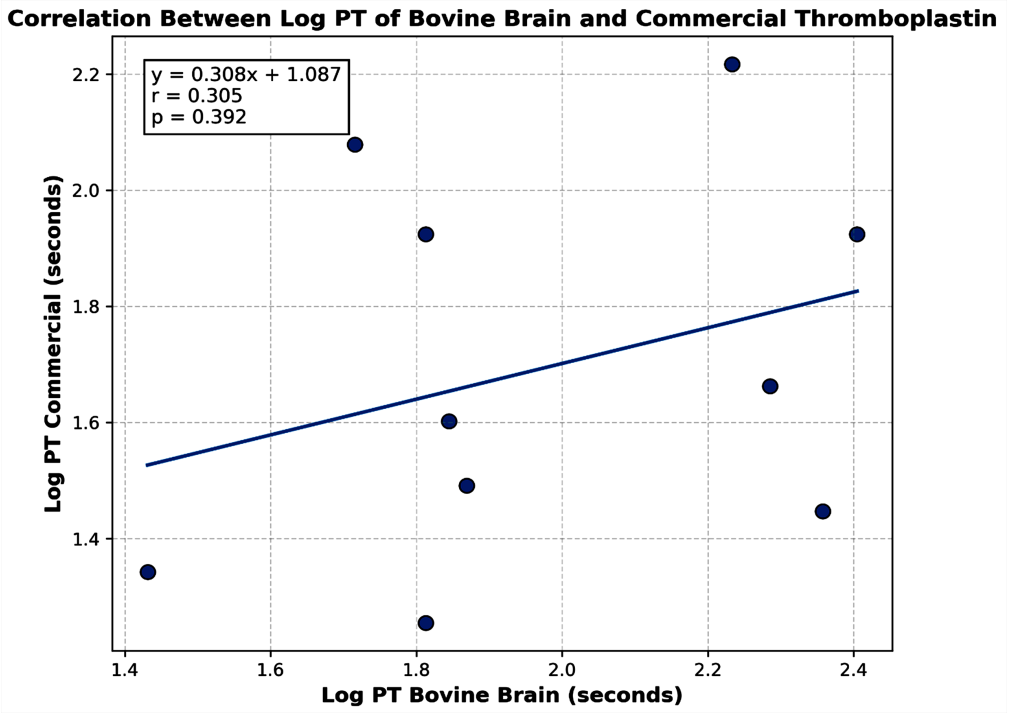

Figure 2. Relationship between the logarithmic PT values derived from bovine brain thromboplastin and commercial thromboplastin reagent.

International Normalized Ratio (INR)

The results in Table 5 demonstrate marked inter-method variability in PT and derived indices between bovine brain thromboplastin and the commercial reagent across all samples. PT values obtained using bovine thromboplastin show wide dispersion (27 - 254 s) and are inconsistently higher or lower than those obtained with the commercial reagent, indicating poor proportional agreement between the two methods. Log transformation of PT and INR values reduces absolute scale differences but does not eliminate the observed inter-method discordance, indicating a non-linear relationship and systematic bias between the two thromboplastin sources (See Figure 3).

Table 5. Comparison INR, and their log-transformed values obtained using bovine brain thromboplastin and commercial reagent samples.

Sample_ID	PT_Bovine	PT_Comm	Log_PT_Bovine	Log_PT_Comm	INR_Bovine	INR_Comm	Log_INR_Bovine	Log_INR_Comm
11	254	84	2.4048	1.9243	2.9954	9.3843	0.4764	0.9724
3	52	120	1.7160	2.0792	1.6681	14.397	0.2222	1.1583
1	65	84	1.8129	1.9243	1.8113	9.3843	0.2580	0.9724
2	193	46	2.2856	1.6628	2.7066	4.5559	0.4324	0.6586

Continued

5	70	40	1.8451	1.6021	1.8615	3.8525	0.2699	0.5857
4	171	165	2.2330	2.2175	2.5884	21.098	0.4130	1.3242
22	228	28	2.3579	1.4472	2.8783	2.5111	0.4591	0.3999
6	74	31	1.8692	1.4914	1.9001	2.8373	0.2788	0.4529
44	65	18	1.8129	1.2553	1.8113	1.4777	0.2580	0.1696
55	27	22	1.4314	1.3424	1.3096	1.8801	0.1172	0.2742

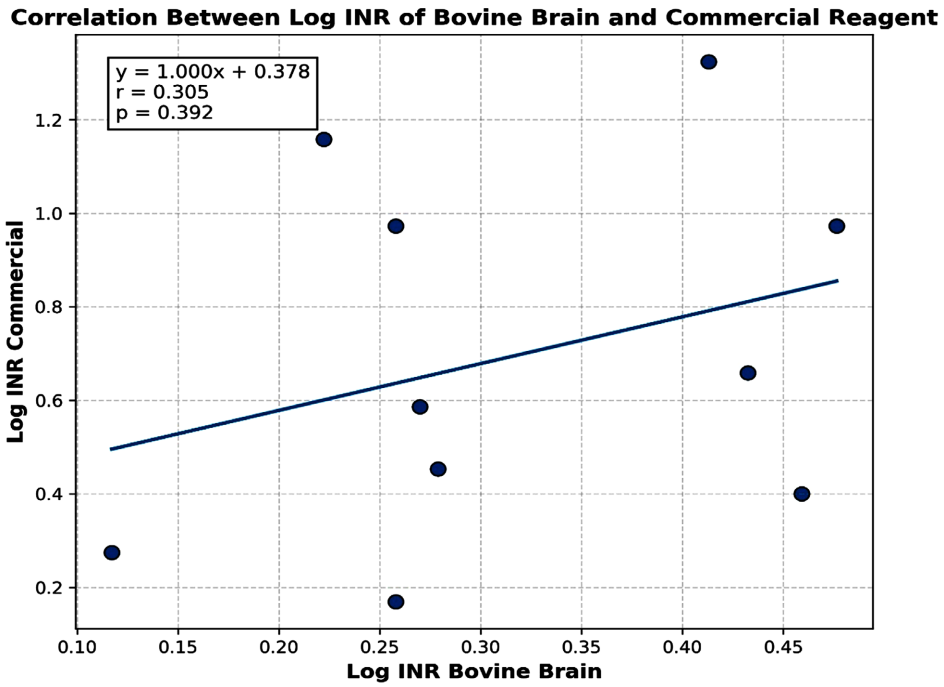

Figure 3. Relationship between the logarithmic INR values derived from bovine brain thromboplastin and commercial thromboplastin reagent.

International Sensitivity Index (ISI)

Table 6 summarizes the comparative analytical performance between the bovine brain thromboplastin reagent and the commercial thromboplastin reagent. The commercial reagent had an assigned ISI of 1.2, while the estimated ISI for the bovine brain reagent was 0.369, indicating markedly lower sensitivity relative to the reference commercial system. Correlation analysis demonstrated a weak positive linear relationship between the two methods (Pearson's r = 0.305), suggesting limited agreement in PT response across samples. Furthermore, the association was not statistically significant (p = 0.3922), indicating that the observed correlation may have occurred by chance and does not provide sufficient evidence of strong concordance between the reagents. The regression equation (y = 0.308x) further supports the presence of poor proportional agreement, with a shallow slope indicating reduced responsiveness of the bovine reagent relative to the commercial thromboplastin. The mean logarithmic values also differed between the two systems (0.3185 vs 0.6968).

Table 6. Comparative analytical performance between the bovine brain thromboplastin reagent and the commercial thromboplastin reagent.

Parameter	Value
Commercial ISI	1.2
Estimated Bovine ISI	0.369
Pearson r	0.305
p-value	0.3922
Regression equation	y = 0.308x + 1.087
Mean Log INR (Bovine)	0.3185
Mean Log INR (Commercial)	0.6968

4. Discussion

The present study evaluated the analytical performance of a locally prepared bovine brain-derived thromboplastin reagent in comparison with a commercial thromboplastin reagent for Prothrombin Time and International Normalized Ratio testing. The study population was predominantly composed of young adults, females, students, and individuals without known medical conditions. This demographic profile was expected because healthy volunteers were intentionally recruited to establish the mean normal prothrombin time (MNPT), thereby minimizing the influence of underlying diseases on coagulation parameters. Similar approaches have been recommended for reagent validation studies, where healthy individuals provide an appropriate baseline for assessing analytical performance rather than disease prevalence [16] [17].

The comparison of PT values demonstrated that the commercial thromboplastin reagent exhibited superior analytical performance compared with the bovine brain-derived reagent. Although the commercial reagent generally produced shorter PT values and lower variability than the bovine reagent, several commercial INR values were unexpectedly above the normal reference range (0.8 - 1.2) despite all participants being apparently healthy. This apparent inconsistency may be explained by analytical rather than biological factors, including the use of a locally established MNPT, the assigned ISI, instrument-reagent interactions, or minor pre-analytical variation during specimen processing. Consequently, the commercial reagent should be interpreted as producing results that were closer to the expected reference values relative to the bovine reagent, rather than uniformly within the normal range. In contrast, the bovine reagent consistently generated markedly prolonged PT values and correspondingly higher INR estimates, indicating reduced analytical accuracy and a tendency to overestimate coagulation times. These findings are consistent with previous reports showing that biological thromboplastins prepared from animal tissues are susceptible to variations in tissue factor concentration, phospholipid composition, extraction procedures, and storage conditions, all of which influence reagent responsiveness [7] [10] [16]. Commercial thromboplastins, although manufactured under standardized conditions with carefully calibrated ISI values, may still exhibit minor analytical variation due to local calibration proce-

dures and laboratory-specific testing conditions, but generally provide greater analytical consistency and improved clinical reliability than locally prepared reagents [8] [11].

The precision analysis further demonstrated that both reagents exhibited relatively high coefficients of variation (approximately 65%), although the bovine reagent produced substantially higher mean PT values and greater variability across samples. While the coefficients of variation were comparable, the markedly higher PT values observed with the bovine reagent indicate poorer analytical performance in absolute clinical terms. This variability is likely attributable to inconsistencies during tissue extraction, differences in thromboplastin concentration, and the heterogeneous nature of biological reagents. Previous investigations have similarly reported that locally prepared tissue-derived thromboplastins demonstrate greater analytical variability than recombinant or commercial reagents because of unavoidable biological and manufacturing differences [10] [16] [18].

Reproducibility analysis also demonstrated clear differences between the two reagents. The bovine brain-derived thromboplastin produced a much wider PT range (27 - 254 seconds) than the commercial reagent (18 - 165 seconds), indicating greater variability between measurements. Good reproducibility is an essential characteristic of coagulation reagents because clinicians rely on serial PT and INR measurements to adjust anticoagulant therapy accurately. The greater dispersion observed with the bovine reagent suggests reduced analytical stability, possibly resulting from batch-to-batch differences in tissue factor activity or incomplete standardization of the extraction process. Similar findings have been reported by investigators evaluating tissue-derived thromboplastins, who concluded that commercial recombinant reagents consistently demonstrate superior reproducibility because of tighter manufacturing controls and standardized calibration procedures [11] [16] [19].

The logarithmic transformation of PT values reduced data dispersion but did not eliminate the discrepancies between the two analytical methods. Although transformation stabilized variance, substantial differences between paired measurements persisted, indicating the presence of systematic rather than random analytical bias. This finding suggests that the differences between the bovine and commercial reagents cannot be explained solely by measurement scale but rather reflect fundamental differences in reagent sensitivity and responsiveness. Previous studies have similarly demonstrated that logarithmic transformation improves statistical analysis without correcting systematic analytical bias between thromboplastin reagents of different origins [11] [19].

Correlation analysis further demonstrated only a weak positive relationship between PT values obtained with the two reagents ($r = 0.305$), with the association failing to reach statistical significance ($p = 0.392$). This weak correlation indicates poor analytical agreement and suggests that PT values generated by one reagent cannot reliably predict values obtained with the other. Similar observations have been reported in international multicenter evaluations of thromboplastin rea-

gents, where significant differences in tissue factor source, phospholipid composition, and calibration resulted in weak inter-method agreement despite use of the INR system [9]-[11]. The shallow regression slope observed in the present study further supports the limited proportional agreement between the two analytical systems.

The INR comparison likewise demonstrated substantial discordance between the bovine and commercial thromboplastin reagents. Although the commercial reagent consistently produced lower INR values than the bovine reagent, several commercial INR values remained above the expected reference interval for healthy individuals. This observation most likely reflects analytical factors related to MNPT estimation, ISI calibration, or instrument-reagent interactions rather than true coagulation abnormalities among the study participants. Nevertheless, the bovine reagent consistently yielded substantially higher INR values than the commercial reagent, demonstrating greater analytical bias and poorer agreement with expected reference values. These findings support earlier reports indicating that, although the INR system was developed to harmonize PT measurements across laboratories, it cannot completely eliminate variability arising from differences in thromboplastin sensitivity, ISI calibration, instrument-reagent interactions, and local laboratory calibration procedures [8] [9]. Consequently, laboratories using different thromboplastin reagents may still generate clinically different INR values despite applying the standardized calculation formula.

One of the most important findings of this study was the markedly lower estimated ISI of the bovine brain-derived thromboplastin (0.369) compared with the assigned ISI of the commercial reagent (1.2). Since ISI reflects reagent responsiveness relative to the international reference preparation, the lower estimated ISI indicates that the locally prepared reagent responded differently to coagulation factor deficiencies and therefore lacked equivalence with the standardized commercial system. The World Health Organization and the International Society on Thrombosis and Haemostasis recommend rigorous local calibration of thromboplastin reagents before routine clinical use because inaccurate ISI assignment may lead to erroneous INR values and inappropriate anticoagulant dosing [12] [20]. The findings of this study reinforce the importance of local reagent validation before implementation in routine patient care.

From a clinical perspective, the poor agreement observed between the two reagents has important implications for anticoagulation monitoring. Overestimation of PT or INR may result in unnecessary reduction or discontinuation of anticoagulant therapy, thereby increasing the risk of thromboembolic complications, whereas underestimation may expose patients to excessive anticoagulation and potentially life-threatening bleeding events [5] [8]. Although locally prepared bovine brain-derived thromboplastin offers a potentially affordable alternative in resource-limited settings, its current analytical performance indicates that further optimization of extraction procedures, calibration, and quality assurance is necessary before it can be recommended for routine diagnostic use. Future studies involving larger

sample sizes, multiple reagent batches, international reference thromboplastins, and Bland-Altman agreement analysis would provide more comprehensive evidence regarding its suitability for clinical implementation [11] [16] [20].

5. Conclusion

This study demonstrated that the commercial thromboplastin reagent outperformed the locally prepared bovine brain-derived thromboplastin in PT and INR testing, exhibiting greater analytical accuracy, reproducibility, and overall reliability. The bovine brain-derived reagent showed marked variability, weak agreement with the commercial reagent ($r = 0.305$, $p = 0.392$), and a substantially lower estimated ISI, indicating that it cannot currently be considered an equivalent substitute for routine clinical coagulation testing. Although bovine brain-derived thromboplastin remains a potentially cost-effective alternative for resource-limited settings, further optimization of its preparation, calibration, and standardization is required before it can be safely adopted for clinical use.

6. Study Limitations

The study was limited by the small sample size ($n = 10$), which may have reduced the statistical power and generalizability of the findings. The evaluation was conducted using a single batch of locally prepared bovine thromboplastin and one commercial reagent, preventing assessment of batch-to-batch variability and performance across different commercial brands. Agreement analysis was limited to correlation analysis, and more robust methods such as Bland-Altman analysis and testing on anticoagulated patient samples were not performed.

Conflicts of Interest

The authors declare no conflicts of interest.

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