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ORIGINAL ARTICLE

A comparative study of sample collection tubes for routine biochemical parameters

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ABSTRACT

Background & Objectives: Turnaround time (TAT) is one of the important indicators of the performance of a clinical laboratory and is the total of the pre-analytical, analytical and post-analytical TAT. Selecting an appropriate sample collection tube can reduce the TAT at the pre-analytical level. Our objective was to compare three sample collection tubes for the biochemical parameters and pre-analytical TAT.

Methods: Samples were collected in plain tube (without clot activator), Becton Dickinson serum separator tube (BD SST^{TM} II) and BD lithium heparin tube from 50 participants and were compared for the pre-analytical TAT and seventeen biochemical parameters. Taking the BD SST^{TM} II tube as a reference, the plain and BD lithium heparin tubes were compared for the tube bias.

Results: Plain tube lactate dehydrogenase (LDH), aspartate transaminase (AST), potassium, and phosphorus were significantly higher ($p<0.05$), while glucose and sodium were significantly lower ($p <0.05$) as compared to the BD SST^{TM} II and bias for these parameters was also clinically significant. BD lithium heparin tube total protein and glucose were significantly higher ($p<0.05$). At the same time, potassium was significantly lower ($p<0.05$) than BD SST^{TM} II, but tube bias for these parameters was clinically insignificant. Pre-analytical TAT was drastically reduced with a plasma tube, followed by BD SST^{TM} II and a plain tube.

Conclusion: Sample collection tubes contribute to the variation in the results of the biochemical parameter and Turnaround time (TAT).

Keywords Anticoagulant, Clot activator, Sample collection tube, Turnaround time, TAT

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INTRODUCTION

Quality, in general, is defined as the product or service that satisfies the needs and expectations of the customer.[1] In the case of clinical laboratories, customers are either clinicians

or patients; the clinician's need would be the right (accurate and precise) report at the right time so that the right decision is made at the right time; for a patient, it would be right report at the right time but also right cost. Delayed reports can lead to delays in critical decisions for patient care and prolonged hospital stay [2], [3] making turnaround time as crucial as the accuracy and precision of a report, which is traditionally used to define the quality of a clinical laboratory. Turnaround time (TAT) is one of the key indicators of laboratory performance, and in clinical laboratories, it is the time from the collection of samples to the reporting of results . [4] The clinical laboratory's turnaround time (TAT) is the sum of pre-analytical, analytical and post-analytical TAT. [4], [5], [6] With the automation of the analyzer, analytical TAT more or less remains constant and doesn't contribute much to the inter-laboratory difference in TAT. It is mainly at pre- and post-analytical levels where laboratories differ in their TAT. Pre-analytical TAT involves sample collection time, sample transport time, clot formation time, centrifugation time, and time taken to dispense (into sample cups) and load the sample on analyzer [4,7].

Pre-analytical TAT can be reduced at the clot formation level by selecting the sample type used for analysis. Using plasma instead of serum samples decreases the TAT by omitting the clotting time. An anticoagulant is required for plasma samples, and out of many anticoagulants in use; lithium heparin is known to cause the least interference in common biochemical parameters analysis [8]. Citrate (blue top) and EDTA (lavender top) are not preferred for chemistry panels because they chelate minerals (e.g. calcium) and interfere with the tests [9,10]. Another way TAT can be decreased at the clotting level is by using collection tubes with clot activators. They reduce the pre-analytical TAT by accelerating the clot formation, thus decreasing the clot formation and centrifugation time. BD serum tube with clot activator, serum separator tube (SST) with gel and rapid serum separator (RST) are examples of the BD vacutainers used for serum samples. These tubes can be directly loaded on the analyzer, omitting the step of the sample dispensing to secondary tubes, thus decreasing the pre-analytical TAT. Since introducing these tubes, a decrease in pre-analytical TAT and pre-analytical error has been reported, further increasing the overall quality of the clinical laboratory.

Various hospitals in developing countries like India still use plain tubes without clot activators instead of tubes with clot activators or heparin, as they are much cheaper, and many argue whether tube selection affects TAT and biochemical parameters. Another common practice in hospitals using collection tubes with clot activators or anticoagulants is to send the samples for the same chemistry from a patient in different tubes during their stay in the hospital, which again raises the question of inter-tube variation. Through our study, we tried to determine whether the collection tube selection contributes to the variation in the patient's lab results and TAT without causing any significant clinical bias. Our study aimed to compare the performance of three sample collection tubes used in our set-up: BD plasma tube (lithium Heparin), BD serum separator tube (SST^{TM}II advance) and plain tube without clot activators. Our hypothesis was "There is no difference between plain tube (without clot activator), BD SST^{TM} II advance and BD Plasma tube (Heparin)". These tubes

were compared for pre-analytical TAT and standard biochemical parameters done in clinical laboratory.

Materials & Methods:

The study was conducted in the Department of Biochemistry DRPGMC Tanda. The institutional ethical committee approved the study. The study population included 50 healthy patients aged 25-50 from the outpatient department; only individuals whose test requisition by clinician matched the test profile of our study were included. Blood samples were collected from the study subjects under sterile conditions after obtaining consent and distributed into plain tubes (without clot activator), BD SST^{TM} II and BD lithium heparin tubes. The plain serum tube was kept in the stand for the clot formation while BD SST^{TM} II was gently inverted 5-6 times for mixing before keeping it on the stand for clot formation; the BD lithium heparin tube was gently inverted 8-10 times for mixing according to manufacturer's recommendation. Lithium heparin tubes were centrifuged immediately after blood collection at 2000g for 10 minutes at 25˚. Samples in the plain tube (without clot activator) and SST tube were visually observed for clot formation by tilting the tube, and the time of clot formation was noted for each tube. After clot formation, samples in BD SST^{TM}II were centrifuged using fixed angle centrifuge at 25˚C and at 2000g for 10 minutes and plain tubes without clot activator were centrifuged at 3500g for 10min. Pre-analytical TAT for tubes was noted down where pre-analytical TAT included sample collection time, transport time, clotting time, centrifugation time and dispensing time. Using standard reagents, samples from three tubes were then tested for routine biochemistry parameters in the Transasia Erba XL-640 auto analyzer.

Statistical Analysis: Statistical analysis was done using the SPSS V.20.0 software. Data were described by the mean± standard deviation (SD) for normal distribution. Parametric data were compared using a paired Student paired t-test. Level significance for statistical comparison was set as a p-value of <0.05. Clinical significance was judged by comparing the tube bias with the desirable allowable bias.

Tube bias= test tube mean – reference tube mean /reference tube mean x 100

Desired allowable bias [11] = $<0.25\ (CVi^2 + CVg^2_2)^{\frac{1}{2}}$

Where CVi= intra individual variation; CVg= Inter-individual variation

In our study serum, BD SST^{TM} II advance was taken as a reference tube and compared with a plain tube (without clot activator) and BD Plasma tube (heparin).

Result: The average TAT for the pre-analytical phase was 69 min for the plain tube (without clot activator), 47 min for the BD SST^{TM} II and 22 min for the BD Plasma (Heparin) tube. The difference in pre-analytical TAT of the three collection tubes was mainly because of the time taken by the two serum tubes for the clot formation, where the average clotting time for plain tube (without clot activator) was 49min and of BD SST^{TM} II was 27min. The average pre-analytical TAT of three tubes is given in Table 1.

Table 1. 1: Pre-analytical TAT of plain tube (without clot activator), BD SST II™ and BD Plasma (Heparin).

TAT	Plain tube (without clot activator)	BD SST™ II	BD Plasma (Heparin)
Average Pre-analytical TAT (min)	69	47	22

Three tubes were compared for 17 biochemical parameters; taking the BD SST™ II tube as a reference, the plain tube (without clot activator) and the BD Lithium heparin tube were compared for 17 biochemical parameters. A statistically significant difference was observed in LDH, glucose, AST, phosphorus, potassium and sodium between plain serum tube and BD SST™ II; bias for these parameters was also clinically significant (Table 2).

Table 2. 2: Biochemical parameters in a comparison study of BD SST™ II vs Plain tube (without clot activator).

Parameters	BD SST (Mean ±SD)	Plain tube (without clot activator) (Mean ± SD)	Bias %	p-value <0.05*	Desirable bias %
Glucose (mg/dl)	98.50±2.47	96.20±2.61	2.33	0.001*	2.30
Urea (mg/dl)	37.70±3.37	37.54±3.26	0.42	0.18	5.57
Creatinine (mg/dl)	1.03±0.06	1.03±0.07	0	0.40	4.00
T Bil (mg/dl)	1.23±0.10	1.21±0.11	1.62	0.21	9.00
AST (U/L)	33.50± 3.50	35.90± 3.60	7.1	0.002*	6.54
ALT (U/L)	33.06±2.59	32.60±2.83	1.39	0.10	11.48
ALP (U/L)	108.43±4.89	107.82±4.52	0.56	0.12	6.72
Total protein (g/dl)	6.79±0.21	6.81±0.21	0.30	0.08	1.40
Albumin (g/dl)	4.51±0.38	4.48±0.36	0.66	0.15	1.43
LDH (U/L)	276.01 ±9.70	293.00± 9.80	6.0	0.001*	4.30
Cholesterol (mg/dl)	141.02±6.6	139.54±6.9	1.04	0.19	4.10
Triglycerides (mg/dl)	132.82±5.7	131.78±5.2	0.78	0.25	9.60
Calcium (mg/dl)	9.99±0.14	9.97±0.17	0.20	0.08	0.80
Phosphorus (mg/dl)	4.09±0.24	4.23±0.34	3.42	0.01*	3.38
Sodium (mmol/l))	139.0±4.7	137.9±4.80.	0.79	0.03*	0.20
Potassium (mmol/l)	3.83±0.10	3.92±0.10	2.30	0.001*	1.80
Chloride (mmol/l)	108.07±0.63	108.00±0.76	0.03	0.57	0.50

BD SST™ II and BD lithium heparin tubes were comparable for most biochemical parameters except glucose, potassium and total protein, where a statistically significant dif-

ference was found. Still, tube bias was clinically insignificant (Table 3).

Table 3. 3: Analytical data of biochemical parameters in a comparison study of BD SST™ II vs BD Heparin-Lithium tube.

Parameters	BD SST™II (Mean ±SD)	BD Lithium Heparin Tube (Mean ± SD)	Bias %	P value <0.05*	Desirable bias %
Glucose (mg/dl)	98.50±2.47	99.20±2.30	0.71	0.001*	2.30
Urea (mg/dl)	37.70±3.37	37.56±3.30	-0.37	0.37	5.56
Creatinine (mg/dl)	1.03 ± 0.06	1.03±0.07	0	0.26	4.00
T Bil (mg/dl)	1.23±0.10	1.22±0.10	-0.81	0.40	9.00
AST (U/L)	33.01±3.5	32.00±3.5	-3.0	0.24	6.54
ALT (U/L)	33.06±2.59	32.92±2.87	-0.42	0.56	11.48
ALP (U/L)	108.43±4.89	107.74±4.17	-0.63	0.89	6.72
Total protein (g/dl)	6.79±0.21	6.82±0.22	0.45	0.04*	1.40
Albumin (g/dl)	4.51±0.38	4.52±0.37	0.22	0.15	1.43
LDH (U/L)	276± 9.7	274±9.2	-0.76	0.12	4.30
Cholesterol (mg/dl)	141.02±6.6	139.6±6.1	-1.00	0.16	4.10
Triglycerides (mg/dl)	132.82±5.7	131.24±5.3	-1.18	0.10	9.60
Calcium (mg/dl)	9.99±0.14	9.98±0.17	-0.10	0.14	0.80
Phosphorus (mg/dl)	4.09 ±0.24	4.11±0.26	0.48	0.16	3.38
Sodium (mmol/l))	139.0±4.7	138.8±4.6	-0.41	0.47	0.20
Potassium (mmol/l)	3.83±0.10	3.79±0.10	-1.04	0.04*	1.80
Chloride (mmol/l)	108.07±0.63	108.10±0.59	0.02	0.71	0.50

DISCUSSION:

Sample collection tubes have been reported to affect the pre-analytical TAT by altering the clotting time. Still, this reduction in TAT should not be at the expense of compromising the quality of patient reports.

Plain tube (without clot activator) vs BD SST™ II: There was a significant difference in the pre-analytical TAT between the two tubes despite both of them being the serum tubes because BD SST™II as compared to plain tube has silica as clot activator, which accelerates the clot formation and decreases the pre-analytical TAT at the level of clot formation. Discrepancy observed in the biochemical parameters (AST, LDH, glucose, potassium, sodium and phosphorus) of these two serum tubes may be due to longer serum-clot contact time

and hemolysis as a result of mechanical stress inflicted by the higher g force in case of the plain tube.

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With the increase in serum-clot contact time, serum glucose concentration has been reported to decrease due to increased cellular consumption of glucose via glycolysis, [12 14] . To counter this, sodium fluoride tubes have been introduced, stabilizing the glucose concentration by inhibiting glycolysis [15] Serum potassium has been reported to increase with the increase in serum-clot contactg time, [12 14] and results from the net effect of glycolysis and passive diffusion[16,17] . During the initial phase, when glycolysis is active, potassium moves into the cells, causing a decrease in its serum concentration. As serum-clot contact time prolongs, the rate of glycolysis diminishes, and passive diffusion of potassium from cells takes over, causing an increase in serum potassium concentration. Serum phosphates have also been reported to increase with increased serum-clot contact time. Organic phosphates in the cells are hydrolyzed to produce the inorganic phosphates, which leak out of the cells, increasing serum phosphate concentration[12,14] Serum aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) have also been reported to increase with the increase in serum-clot contact time [12] , [14] . Various studies done on the effect of serum-clot contact time on biochemical parameters had similar observations; Ono et al. [13] found statistically significant changes in ALT, AST, LDH, glucose, sodium, potassium, calcium, and inorganic phosphorus; Zhang et al. [12] found significant changes in potassiu, glucose and phosphorus. Similar results were observed by Rehak and Chiang [14] where they stored the samples for 24h at different temperatures before serum-clot separation and found significant changes in creatinine, glucose, inorganic phosphorus, potassium, AST, and ALT. Although we didn't find any significant changes in ALT, creatinine and calcium, the rest of the findings were consistent with the above studies. BD SST^{TM} II tube, apart from having silica as a clot activator, also has gel, which acts as a barrier between the serum and clot, avoiding the above variation because of serum-clot contact time.

Plain serum tubes (without clot activator) require longer or higher centrifugation speed to get clearer serum separation from a clot. Increased time or speed of centrifugation further increases the cellular content leakage rate, resulting in a relative increase in the concentration of these parameters in serum[18,21] . It can also cause hemolysis due to mechanical stress inflicted by higher g force, further aiding in the discrepancy of these serum parameters. Probable mechanisms of interference by hemolysis are: increase in the concentration of parameters due to release from the cell [22] ; spectral interference [20,23] , chemical interference [24] and interference due to dilutional effect[22] . The chemical constituents which are in higher concentration inside the cell are released during hemolysis, causing an increase in concentration of these parameters; LDH, AST, potassium and phosphates are higher in cells and are released during the hemolysis, resulting in false high-value of these parameters [18,20,26] . The dilutional effect of hemolysis is seen for the parameters whose concentration is lower inside the cell, such as sodium, chloride and glucose [22,25] . Spectrophotometric interference as a result of hemolysis is seen for the parameters whose absorption spectrum

overlaps with that of the oxyhemoglobin and deoxyhemoglobin, which have a maximum absorption at 415 nm with a detection range between 320 nm and 450 nm and between 540 nm and 589 nm respectively [20,27] . Lipase, albumin and GGT are the few such parameters that are prone to be affected by the spectral interference of hemoglobin[20,25] . Interference by hemolysis depends on the degree of hemolysis, and certain parameters such as LDH, potassium and AST have been reported to be affected even at lower degrees[25].

Another problem which has been reported with the plain tube (without clot activator) is the re-appearance of the fibrin clot during analysis, which could lead to erroneous sample results, blockage of the sample probe and an increased number of sample repeat runs leading to re-ordering of the fresh samples from the same patient. This increases the financial burden on patients due to the re-ordering of the same tests and the hospital laboratory due to increased use of consumables for the same set of tests, increasing the overall cost of a test.

BD SST^{TM} II vs BD Heparin lithium tube: A significant decrease in pre-analytical TAT is seen in the case of the plasma sample, as there is no need to wait for the clot formation. The plasma sample requires an anticoagulant and differs from the serum sample in clotting factors used up in clot formation in the case of the serum sample [28,29] . Therefore, any differences in the biochemical parameters of these two tubes could be attributed to the sample matrix, serum-clot contact time and anticoagulant. Our study showed a statistically significant difference in the total protein concentration of BD SST^{TM} II and BD lithium heparin tube, although the difference was not clinically significant. Higher plasma protein could be because of the fibrinogen used up in clot formation in serum samples [28,29] . Glucose was another parameter for which the difference between these tubes was found statistically significant but not clinically significant. The glucose concentration decreases in the sample by 5-7% per hour due to glycolysis by the cellular components [15]. Additional effect due to anticoagulants has been reported by some studies in the case of plasma samples where glucose was found to be lower in plasma than serum, probably due to cellular fluid shift by anticoagulant[30,32] . It is recommended to use plasma over serum samples to measure glucose [33] for the diagnosis of diabetes, as plasma can be centrifuged promptly without waiting for the blood to clot. Our study found serum glucose level to be lower than the plasma, but the difference was not clinically significant. The probable cause of the decrease in serum glucose concentration could be cellular consumption of glucose due to serum-clot contact time, which was avoided in the case of the lithium heparin tube by separating the plasma immediately after the centrifugation without waiting for the clot formation.Potassium concentration was significantly lower in the plasma sample compared to the serum sample, although tube bias was not clinically significant. Higher serum potassium could be because of the release of potassium during clot formation. Our study also found the mean value of LDH, AST and potassium to be higher in serum than in plasma tubes, although the difference was not statistically significant. The mean value of LDH, potassium and AST in serum is slightly higher than in plasma, which may be because of the release of these constituents from cells during clotting [12,14]. Generally, serum samples are preferred for chemistry testing because our chemistry reference intervals are based on serum, not plasma. Plasma has

the advantages of shorter processing and centrifugation time, decreasing the TAT, which is crucial in an emergency sample.

CONCLUSIONS:

We conclude that the plain tubes without clot activators give rise to significant clinical bias for various routine biochemistry parameters. The sample collection tubes (serum/-plasma) do contribute to the variation in the results of certain biochemical parameters, which might or might not be clinically significant depending upon the tube used. We recommend that during individual patient's hospital stays, samples for chemistry should always be collected into the same tube (heparin or red top) to avoid inter-tube variation. This will ensure that parameter variations are attributed to the patient or disease rather than related to the choice of anticoagulant. For example, suppose the first chemistry panel is submitted in a lithium heparin tube. In that case, all subsequent chemistry tests should be submitted in heparin to allow more accurate comparison between sequential results. Selection of the right sample collection tube can decrease the TAT drastically, which is crucial in the case of samples from the emergency department as it helps make critical decisions at the right time and improves the efficiency of the emergency department by decreasing the duration of patient stay.

ABBREVIATIONS:

TAT: Turnaround time

AST: Aspartate transaminase

LDH: Lactate dehydrogenase

ALT: Alanine transaminase

SST: Serum separator tube

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Table 4.

Contributor Role	Degree of contribution		
	Lead	Equal	Supporting
Conceptualization	AD		
Data Curation	AD		
Formal Analysis	AD		BG
Fund Acquisition	–		
Investigation	AD		
Methodology	AD		
Project Administration	AD		
Resources	AD		
Software	AD		
Supervision	AD		
Validation	AD		BG
Visualization	AD		
Writing Original Draft	AD		BG
Writing review and Editing	AD		BG

DECLARATIONS:

Authors' contributions:

Conflict of interest:

The authors declare no conflict of interest.

Ethical approvals:

Study is approved by Institutional Ethical Committee.

Data availability:

The data that support the findings of this study is available from the corresponding author upon reasonable request.

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