

## Quality Impact on Diagnostic Blood Specimen Collection Using a New Device to Relieve Venipuncture Pain

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**Abstract** A new device called Buzzy<sup>®</sup> has been recently presented that combines a cooling ice pack and a vibrating motor in order to relieve the venipuncture pain. The aim of this study was to evaluate the impact of Buzzy<sup>®</sup> use during diagnostic blood specimen collection by venipuncture for routine immunochemistry tests. Blood was collected from 100 volunteers by a single, expert phlebotomist. A vein was located on the left forearm without applying tourniquet, in order to prevent any interference from venous stasis, and blood samples were collected using a 20-G straight needle directly into 5 mL vacuum tubes with clot activator and gel separator. In sequence, external cold and vibration by Buzzy<sup>®</sup> was applied on the right forearm—5 cm above the chosen puncture site—for 1 min before

venipuncture and continued until the end of the same procedure already done in the left forearm. The panel of tests included the following: glucose, total cholesterol, HDL-cholesterol, triglycerides, total protein, albumin, c-reactive protein, urea, creatinine, uric acid, alkaline phosphatase, amylase, AST, ALT, *g*-glutamyltransferase, lactate dehydrogenase, creatine kinase, total bilirubin, phosphorus, calcium, magnesium, iron, sodium, potassium, chloride, lipase, cortisol, insulin, thyroid-stimulating hormone, total triiodothyronine, free triiodothyronine, total thyroxine, free thyroxine and haemolysis index. Clinically significant differences between samples were found only for: total protein, albumin and transferrin. The Buzzy<sup>®</sup> can be used during diagnostic blood specimens collection by venipuncture for the majority of the routine immunochemistry tests. We only suggest avoiding this device during blood collection when protein, albumin and transferrin determinations should be performed.

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Reproducibility of results

### Introduction

Laboratory diagnostics is an essential part of the clinical decision making, provided that a high degree of quality is established throughout the total testing process [1]. Continuous monitoring and management of preanalytical errors (i.e., by quality indicators) are crucial for improving the quality of laboratory performance, and are also necessary for all clinical laboratories accredited on the basis of the international organization for standardization 15189 document [2–6]. Moreover, quality indicators in laboratory

medicine are fundamental tools for quantifying the quality of a selected aspect of care by comparing it against a defined criterion [7]. For private laboratories the level of patient satisfaction with the diagnostic blood collection service is a very important quality indicator. A new device called Buzzy<sup>®</sup> has been recently presented that combines a cooling ice pack and a vibrating motor in order to relieve the venipuncture pain in adults and children, thus aimed at increasing patient satisfaction during blood collection [8–10]. The aim of this study was to evaluate the impact of Buzzy<sup>®</sup> use during diagnostic blood specimens collection by venipuncture for routine immunochemistry tests. We hypothesized that a combination of cold and vibration near venipuncture site might be a new source of preanalytical variability.

## Methods

### Study Design

A group of 100 healthy adults of both sexes, volunteers for this study, from a private laboratory called Bioanalise in Teresina city, Piauí, Brazil, were evaluated in one workday. Each volunteer provide an informed consent for being enrolled in this study, which was also carried out in agreement with the Declaration of Helsinki and under the terms of all relevant local legislation.

### Collection of Diagnostic Blood Specimens

The collection of all diagnostic blood specimens was performed from 8.00 to 11.00 AM by a single, expert phlebotomist, according to the phlebotomy guidelines [11, 12]. All volunteers, after 12-hour fasting, were maintained seated for 15 min prior to phlebotomy in order to eliminate possible interferences of blood distribution due to the posture [13]. After that, a vein was located on the left forearm without applying tourniquet using a subcutaneous tissue transilluminator device (Venoscópio IV plus, Duan do Brasil, Sao Paulo, Brazil), in order to prevent any interference from venous stasis [14–16], and blood samples were collected using a 20-G straight needle (BD Vacutainer) directly into 5 mL SST II Advance<sup>®</sup> vacuum tubes with clot activator and acrylic gel separator. To eliminate any potential interference due to either the contact phase or the tissue factor, ~2 mL of blood were preliminarily collected in a discard tube without additive (Vacuette<sup>®</sup>, Greiner Bio-One GmbH, Kremsmünster, Austria). In sequence, external cold and vibration by Buzzy<sup>®</sup> (MMJ Labs, Atlanta, GA, USA) was applied on the right forearm—5 cm above the chosen puncture site—for 1 min before venipuncture and continued until the end of the

same procedure already done in the left forearm (Fig. 1). Buzzy<sup>®</sup> is a reusable 8 × 5 × 2.5 cm plastic bee-like device containing a battery-powered vibrating motor with an 18 g solid frozen ice pack underneath. Blood collection was accurately standardized, including the use of needles and vacuum tubes of the same lot.

## Processing of Diagnostic Blood Specimens

### Pre-centrifugation and Centrifugation

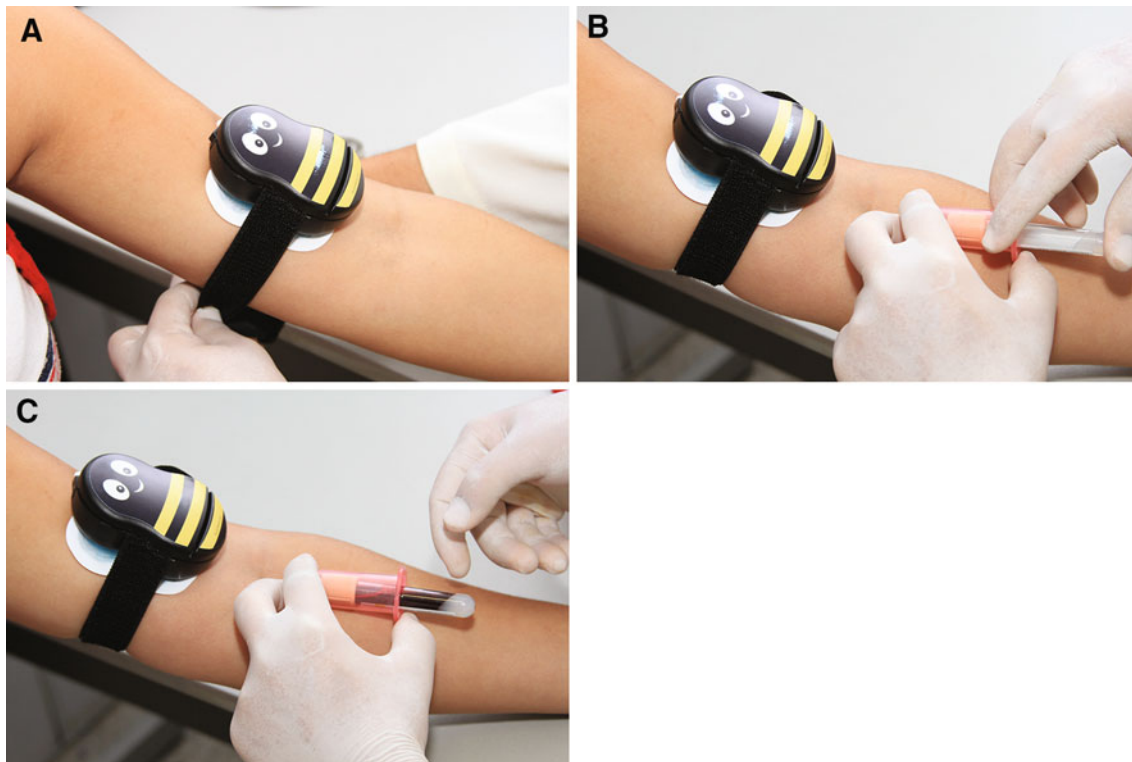
All the serum tubes were left upright for 45 min at room temperature (20 °C) to allow complete blood clotting before centrifugation [17]. Then all samples were centrifuged at 1,500 g for 10 min at room temperature (according to the instructions of the manufacturers).

### Diagnostic Blood Specimens Storage

All serum samples were separated, stored in aliquots and kept frozen at –70 °C until measurement. Samples did not show any sign of hemolysis by visual inspection. No specimen was discarded due to unsatisfactory attempts, difficult venous access, missing veins, manifest hemolysis or lipaemia.

### Laboratory Testing

All frozen serum aliquots were thawed at the same time. The clinical chemistry and immunochemistry tests were performed in duplicate immediately after thawing on the same instrument Cobas<sup>®</sup> 6000 <c501> and <e601> module (Roche Diagnostics GmbH, Penzberg, Germany), according to the manufacturer's specifications and using proprietary reagents. The panel of tests included the following: glucose (GLU), total cholesterol (COL), HDL cholesterol (HDL), triglycerides (TG), total protein (TP), albumin (ALB), c-reactive protein (CRP), urea, creatinine (CRE), uric acid (UA), alkaline phosphatase (ALP), amylase (AMYL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), *g*-glutamyltransferase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin (TBil), phosphorus (P), calcium (Ca), magnesium (Mg), iron (Fe), sodium (Na), potassium (K), chloride (Cl), lipase, cortisol, insulin, thyroid-stimulating hormone (TSH), total triiodothyronine (T3), free triiodothyronine (FT3), total thyroxine (T4), free thyroxine (FT4) and haemolysis index (HI). The instrument was calibrated against appropriate proprietary reference standard materials and verified with the use of proprietary quality controls. Our evaluation of the within-run precision by internal quality control on the Cobas<sup>®</sup> 6000 <c501> and <e601>



**Fig. 1** Using the Buzzy<sup>®</sup> device during diagnostic blood specimen collection by venipuncture **a** Buzzy<sup>®</sup> application 1 min before venipuncture **b** venipuncture **c** diagnostic blood specimen collection by venipuncture with vacuum tube system

module (Roche Diagnostics GmbH) showed low coefficients of variation— $CV_A$  (Table 1).

#### Statistical Analysis

The significance of the differences between samples was assessed by paired Student's *t* test after checking for normality (with D'Agostino-Pearson's omnibus test). As non-normal distribution was found for HDL, CRP, CRE, lipase, AST, GGT, TBil, Fe, Cl, GLU, insulin, FT3 and FT4 results were assessed by Wilcoxon ranked-pairs test using licensed statistical software (GraphPad Prism<sup>®</sup> version 5.01, La Jolla, CA, USA). A *p* value <0.05 was considered statistically significant. Mean % differences were determined according to the formula: *mean % difference* = [(Buzzy procedure + Gold standard procedure)/Buzzy procedure] × 100 Finally, the biases from gold standard and Buzzy-venipuncture procedure (mean % differences) were compared with the current desirable quality specifications, derived from biological variation [18, 19] according to the formulae:

$$CV_A < 0.5 CV_W$$

$$|BA| < 0.25(CV_W^2 + CV_G^2)^{0.5}$$

where  $CV_A$  is the percent analytical coefficient of variation,  $CV_W$  is the within subject biological variation,  $CV_G$  is the between subject biological variation, BA is the bias.

#### Results

Since our aim was to ascertain whether any differences could be observed when Buzzy was employed vs the standard procedure and whether they might be clinically relevant, we based the criteria for evaluating the analytical performance upon desirable quality specifications as suggested [18], by employing the above reported formulae.

Statistically significant differences between standard (without tourniquet) and Buzzy-venipuncture procedure (adequately assessed as reported in Methods by paired Student's *t* test or Wilcoxon ranked-pairs test, *p* value <0.05) were found for: COL, HDL, TG, TP, ALB, UREA, ALP, AMYL, GGT, CK, transferrin, cortisol and TSH (Table 1). The main analytes shown increased concentration when cold and vibration by Buzzy<sup>®</sup> were applied before diagnostic blood specimen collection (Table 1). Moreover clinically significant differences were found only for: TP, ALB, transferrin, AST and TBil (the last two without statistical significance).

**Table 1** Impact of Buzzy® on routine immunochemistry laboratory testing

Tests	Units	Desirable Bias (%)	CVa	Diagnostic blood specimen collection procedures			Mean % difference	p value
				Buzzy®	Gold standard			
COL**	(mmol/L)	4.0	1.8	4.73 ± 0.7	4.58 ± 0.7	3.2	<b>0.0002</b>	
HDL*	(mmol/L)	5.2	4.3	1.35 (1.11–1.64)	1.30 (1.07–1.63)	3.7	<b>0.0079</b>	
TG**	(mmol/L)	10.7	2.0	1.55 ± 0.6	1.51 ± 0.6	2.6	<b>0.0101</b>	
TP**	(g/L)	1.2	1.2	80.1 ± 4.4	78.9 ± 3.6	<b>1.5</b>	<b>0.0244</b>	
ALB**	(g/L)	1.3	1.2	48.9 ± 3.7	47.9 ± 3.4	<b>2.0</b>	<b>0.0135</b>	
CRP*	(mg/L)	21.8	1.3	50.0 (50.0–50.1)	49.8 (49.8–50.0)	0.4	0.7500	
UREA**	(mmol/L)	5.5	2.6	9.35 ± 1.8	9.64 ± 1.7	–3.1	<b>0.0004</b>	
CRE*	(µmol/L)	3.8	2.5	73.4 (61.9–108.7)	72.5 (61.9–105.2)	1.2	0.7764	
UA**	(µmol/L)	4.9	1.0	299.7 ± 92.5	300.2 ± 89.2	–0.2	0.8494	
ALP**	(µkat/L)	6.4	2.7	1.19 ± 0.3	1.14 ± 0.3	4.2	<b>0.0232</b>	
Lipase*	(µkat/L)	10.1	2.8	2.12 (1.34–2.91)	2.08 (1.30–2.93)	1.9	0.2483	
AMYL**	(µkat/L)	7.4	0.8	1.29 ± 0.3	1.24 ± 0.3	3.9	<b>0.0069</b>	
AST*	(µkat/L)	5.4	1.2	0.49 (0.37–0.60)	0.44 (0.37–0.61)	<b>10.2</b>	0.8217	
ALT**	(µkat/L)	12.0	1.3	0.61 ± 0.2	0.58 ± 0.2	4.9	0.1253	
GGT*	(µkat/L)	10.8	1.6	0.54 (0.37–0.81)	0.53 (0.37–0.80)	1.8	<b>0.0232</b>	
LDH**	(µkat/L)	4.3	1.5	7.32 ± 1.0	7.19 ± 1.2	1.8	0.1132	
CK**	(µkat/L)	11.5	3.3	2.25 ± 1.5	2.14 ± 1.4	4.9	<b>0.0035</b>	
TBil*	(µmol/L)	11.4	2.2	10.3 (5.1–13.7)	8.6 (5.1–13.7)	<b>16.5</b>	0.1736	
P**	(mmol/L)	3.2	3.0	1.30 ± 0.2	1.32 ± 0.2	–1.5	0.0717	
Ca**	(mmol/L)	0.8	0.7	2.37 ± 0.1	2.36 ± 0.1	0.4	0.5320	
Mg**	(mmol/L)	1.8	1.2	0.81 ± 0.07	0.81 ± 0.06	0.0	0.7192	
Fe*	(µmol/L)	8.8	2.6	14.1 (12.6–18.0)	14.9 (12.4–17.2)	–5.7	0.6817	
Transferrin**	(g/L)	1.3	1.2	2.31 ± 0.3	2.27 ± 0.3	<b>1.7</b>	<b>0.0266</b>	
Na**	(mmol/L)	0.3	1.0	144.3 ± 1.9	144.3 ± 1.8	0.0	1.000	
K**	(mmol/L)	1.8	1.5	4.0 ± 0.4	4.0 ± 0.3	0.0	0.6590	
Cl*	(mmol/L)	0.5	1.0	102 (101–103)	102 (101–103)	0.0	0.2755	
GLU*	(mmol/L)	2.2	1.5	4.66 (4.27–5.11)	4.66 (4.33–5.11)	0.0	0.9987	
Cortisol**	(nmol/L)	12.5	3.7	223.9 ± 99.0	198.4 ± 104.2	11.4	<b>0.0317</b>	
Insulin*	(pmol/L)	15.5	5.9	66.0 (30.0–125.8)	66.4 (24.2–110.5)	–0.6	0.3757	
TSH**	(mU/L)	7.8	3.5	1.33 ± 0.6	1.28 ± 0.6	3.8	<b>0.0074</b>	
T3**	(nmol/L)	4.8	2.1	2.01 ± 0.2	2.00 ± 0.2	0.5	0.2723	
FT3*	(pmol/L)	4.8	2.2	0.054 (0.050–0.059)	0.055 (0.052–0.059)	–1.8	0.6909	
T4**	(nmol/L)	3.0	1.3	90.7 ± 14.4	89.6 ± 14.5	1.2	0.1661	
FT4*	(pmol/L)	3.3	1.4	13.4 (12.0–15.2)	13.2 (11.7–15.2)	1.5	0.3265	
HI*	NA	NA	0.8	4.07 ± 0.22	4.02 ± 0.20	1.2	0.7573	

The bold *p* values are statistically significant ( $p < 0.05$ ) and bold mean % differences represent clinically significant variations, when compared with desirable bias [19]

\* Non-normal distribution; the values are presented as median (interquartile range); *p* value represents the significance by Wilcoxon ranked-pairs test

\*\* Normal distribution; the values are presented as mean ± standard deviation; *p* value represents the significance by paired student's *t* test

NA not available [19], ALB albumin, ALP alkaline phosphatase, ALT alanine aminotransferase, AMYL amylase, AST aspartate aminotransferase, Ca calcium, CK creatine kinase, Cl chloride, COL total cholesterol, CRE creatinine, CRP c-reactive protein, Fe iron, FT3 free triiodothyronine, FT4 free thyroxine, GGT *g*-glutamyltransferase, GLU glucose, HDL HDL-cholesterol, HI haemolysis index, K potassium, LDH lactate dehydrogenase, Mg magnesium, Na sodium P phosphorus, TBil total bilirubin, TG triglycerides, TP total protein, TSH thyroid-stimulating hormone, T3 total triiodothyronine, T4 total thyroxine, UA uric acid

## Discussion

For a long time the preanalytical phase has been considered as the “dark side of the moon” [20–27]. Presently in order to start a “light-side” period in the preanalytical phase and in patient safety, the attention of the laboratory professionals has been focused on some procedures previously regarded as consolidated, such as: (i) furniture changes among different manufacturers of syringes for blood gas analyses, which can represent new sources of laboratory variability; similar considerations apply to not validated vacuum tubes [28–31]; (ii) transport boxes unable to guarantee the maintenance of the temperature during blood specimens transportation [32]; (iii) traditionally accepted although incorrect paradigms ranging from the filling of vacuum tubes to the mixing procedures which appear unsupported by accurate experimental verification; e.g., recently it has been observed that there is no apparent need to mix all blood specimens after collection into vacuum tube systems by venipuncture [33, 34]. On the other hand, apparently incorrect vigorous mixing of the primary blood vacuum tubes immediately after collection does not promote laboratory variability [35]; more so, no clinical impact has been observed in routine and specialized coagulation laboratory testing when the vacuum tubes are incompletely filled (when filled more than 90 % but <100 %) [36]. Obviously the ability of the phlebotomist to put the patient at ease is considered very important by outpatient [37]. Oatey and Stiller after evaluating inpatients showed that 28 % agree that generally, the venipuncture procedure is painful [38]. The new tool called Buzzy<sup>®</sup> reportedly relieves the sensation of pain during venipuncture [8–10]. However our results showed statistically significant increase of several analytes when the blood specimens were collected using Buzzy<sup>®</sup> in comparison with the standard procedure (Table 1). Nevertheless, clinically significant differences, due to results consistently and systematically higher after Buzzy procedure than after gold standard were observed only for TP, ALB, transferrin, AST and TBil—the last two without statistical significance—when comparison is made with the current quality specifications for bias, derived from biological variation [19, 39]. Obviously the quality specifications derived from biological variation [19] are considered both very important and useful in the daily practice by the quality managers of the medical laboratories [40–43]. Even in this case caring physicians unaware of the real patient situation might initiate (or delay) appropriate treatments as a consequence of the use of this new device. Direct skin cooling causes a vasoconstriction [44, 45]. From a practical point of view, the cold-induced hemoconcentration [46] promotes the exit of water, diffusible ions and low molecular weight substances from the vessel thereby increasing the

concentration of various blood analytes at the punctured site thus potentially influencing the laboratory results interpretation (e.g. TP, ALB and transferrin). As known, calcium is the fifth most common element in the body and the most prevalent cation. Moreover this cation is present in three physicochemical states in plasma: (i) 50 % is free (ionized); (ii) 10 % is complexed with small diffusible inorganic and organic anions (e.g. bicarbonate, lactate, phosphate and citrate); (iii) 40 % is bound to plasma proteins (where ~80 % is associated with albumin and the remaining 20 % associated with globulines) [47]. This explains why the hemoconcentration due to Buzzy application during diagnostic blood specimen collection by venipuncture can affect ALB results without significant effects on calcium concentration, since calcium is only partially bound to proteins. Fuller et al. [48] in a systematic review showed that vibration increases muscle perfusion with the magnitude of increase positively related to the vibratory load applied. Our results showed that the vibration promoted by Buzzy<sup>®</sup> could have an effect on the muscle (see CK), but possibly without clinical impact when comparing Buzzy<sup>®</sup> versus gold standard procedure, as no clinically significant differences are observed.

In conclusion the Buzzy<sup>®</sup> can be used during diagnostic blood specimens collection by venipuncture for the majority of the routine immunochemistry tests. We only suggest to avoid this device during blood collection when TP, ALB and transferrin determinations should be performed. Future investigations should be planned to cover other areas of clinical laboratory (e.g. haematology and coagulation).

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**Conflicts of interest** No potential conflicts of interest relevant to this article were reported.

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