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Article · January 2016

DOI: 10.9734/BJMMR/2016/28216

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17(4): 1-17, 2016, Article no.BJMMR.28216
ISSN: 2231-0614, NLM ID: 101570965

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Comparison of the Automatic Non-invasive Express Screening Analyser (ANESA)® for Clinical Analytical Parameters

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Authors' contributions

This work was carried out in collaboration between both authors. Author ASM designed the study, wrote the protocol and wrote the first draft of the manuscript. Author ASM managed the literature searches and statistical analyses. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/28216
Editor(s):
(1) Thomas I. Nathaniel, University of South Carolina, School of Medicine-Greenville, Greenville, SC 29605, USA.
Reviewers:
(1) Leonardo Roever, Federal University of Uberlandia , Brazil.
(2) Aristomenis Exadaktylos, University of Bern, Freiburgstrasse, Switzerland.
Complete Peer review History: http://www.sciencedomain.org/review-history/15727

Original Research Article

Received 9th July 2016
Accepted 2nd August 2016
Published 10th August 2016

ABSTRACT

Background: The objective we evaluated the reliability of some haematological and biochemical parameters performed by a non-invasive auto-analyser (ANESA) with those obtained by the standard method of venipuncture (reference method) in patients who went to the clinical analysis laboratory (Municipal-Hospital of Badalona, Spain).
Methods: A transversal, comparative and parallel (paired) study was carried out. Two methods of study were practiced for the same subject: a) the reference method of venipuncture (conventional clinical analysis) and b) placement of sensors (comparison method: ANESA device). Consecutive patients older than 18 years, who met certain criteria for inclusion were included in the study during an 8 week period in 2014. The parameters studied were: haemogram (7), glucose, lipids (4), transaminases (2), bilirubin, creatinine and urea. Statistical analysis compared averages for paired groups and reliability of the obtained observations (method: intraclass-correlation coefficient (ICC); individual differences: Bland–Altman method), $p<0.05$.
Results: A total of 195 patients were involved, with an average age of 50.8 years; 65.2% were

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women. In paired comparisons, cholesterol (185.4 vs. 179.8; difference: 5.6 mg/dL; p=0.005), cLDL (95.9 vs. 100.5; difference: −4.6 mg/dL; p=0.002) and bilirubin (0.6 vs. 0.5; difference: 0.1 mg/dL; p<0.001) obtained more modest results. Erythrocytes, haemoglobin, haematocrit, platelets, leukocytes, glucose, cHDL, triglycerides, ALT, AST, creatinine and urea reached an ICC>0.90. Lipid parameters (cholesterol: ICC=0.728; cLDL: ICC=0.817) obtained a moderate correlation, whereas lymphocytes (ICC=0.551) and monocytes (ICC=0.546) reached discrete results.

Conclusions: Despite of the study limitations, the automatic non-invasive analyser (ANESA) is shown as a reliable and promising screening method in usual clinical practice for most of the analyzed parameters as an alternative to standard blood extraction. However, more studies are required to strengthen the consistency of the results.

Keywords: Reliability; non-invasive analyser; clinical analysis.

1. INTRODUCTION

Medical diagnosis is a dynamic process that attempts to make ideal decisions in the presence of uncertainty [1-2]. From a functional point of view, a diagnostic test is considered as any procedure done to confirm or discard a presumptive diagnosis in the presence of verisimilitude [2-3]. Nowadays, research into diagnostic tests and their relation to therapeutic innovations are two disciplines which have contributed to greater and faster medical developments [4-7]. In this way, the advantages of diagnostic methods involve the need for practitioners to have the correct information about their characteristics and applicability in their field of work [8]. The clinical laboratory is the place where analytics are performed, and it contributes to studying, preventing, diagnosing and treating patients' health problems [9,10]. Despite routine use, its performance is not without some impact on patients (intolerance to venipuncture), which can even affect its clinical safety (haematomas, infections, phlebitis, etc.) [11,12]. In this regard, effective and non-aggressive diagnostic methods for patients are considered as ideal in everyday medical practice [13,14].

The functional principle of the Automatic Non-invasive Express Screening Analyser (ANESA)® is a non-invasive medical device based on thermal measurement (sensors) at certain biologically active points in an organism [15,16]. Information is processed by USPIH software which is the basis for real-time reports of more than 130 parameters of health status. ANESA is based on correlation between heat generation resulting from *in vivo* chemical reactions of nitrogen, oxygen, hydrogen and carbon and substances without nitrogen [15]. All these processes depend on oxygen supply rate, activity of platelet phospholipids factors, oxygen solubility coefficient, pH and environment temperature. The genetic code manages the cellular elements of blood and biochemical parameters of homeostasis generation [17-19].

The evidence available in literature about comparison between parameters resulting from conventional analysis and those obtained by ANESA are very limited. Most of them are in internal documents or informative publications [20]. Assessment of the ANESA device as a reliable method for determination of biological parameters may create great advantages both for patients and professionals, as well as probable resource savings for the National Health System, so the realisation of this study (pioneering in the Spanish State) is relevant. The objective of the study was an evaluation of the reliability of some haematological and biochemical parameters (haemogram, renal function, hepatic function and lipids), which were obtained from ANESA and by the standard venipuncture method in patients who came to the hospital's clinical laboratory.

2. PATIENTS AND METHODS

2.1 Study Design and Population

A transversal, comparative and parallel (paired) study was carried out, i.e., each patient was examined by both study methods: a) the reference method of venipuncture (usual clinical analysis) and b) placement of sensors (comparison method: ANESA device). The study population consisted of patients of the Municipal Hospital of Badalona, for whom hospital specialists indicated the need for standard blood analysis. The population, which demands attentive care, is mainly urban and belongs to middle to low socioeconomic section of the population.

2.2 Inclusion and Exclusion Criteria

The group of patients was formed consecutively during 8 weeks (February and November, 2014); all patients who met the following characteristics were included in the group: a) age over 18 years old; b) indication by a specialist for routine standard blood analysis (basic health profile or similar), programmed in the Badalona Municipal Hospital clinical analysis laboratory; c) treated in outpatient care, and d) consent to participate in the study voluntarily. Exclusions were: a) displaced subjects or subjects who were outside our responsibility area; b) patients with a preferential or urgent analysis request; c) patients with indication for tests with a specific profile (preoperative, allergies, microbiology, serology, etc.); d) patients in an acute pathological situation (fever or other signs/symptoms) and e) patients with chronic pathology decompensation and/or absence of thermal stabilisation of sensors.

2.3 Theoretical Basis of Device

Entropy is the quantitative measure of disorder in a system [21]. The concept comes out of thermodynamics, which deals with the transfer of heat energy within a system [22]. The two principal laws of thermodynamics apply only to closed systems, that is, entities with which there can be no exchange of energy, information, or material. In addition, a method of the ANESA device is based on correlation of heat generation and produced work in a system of internal circulation of the blood [23]. ANESA device is based on Henry's law and Dalton's law, fluid mosaic model [24], model of low-density lipoproteins [25], and totality of knowledge about structure of cell organelles [26-27]. *Using all those findings, a biotechnology model of correlation of temperature and lipid exchange was developed*. Internal body heat is generated as a result of chemical reaction of nitrogen, oxygen, hydrogen and carbon. The changes of temperatures determine an activation of chemical elements, basically oxygen. Solubility coefficient of oxygen produces alterations on protein and lipid cellular membrane [28-29].

Thermoregulation is sophisticated regulatory process of energy metabolism and hemodynamics, originating from interaction of hippocampus, hypothalamus and pineal gland, basing on energy reactions of adenosin tris fosfato and transmembrane choline-containing phospholipids [30-33]. In this way, thermoregulatory reactions such as sweating and shivering enable the body to keep its core temperature constant. This process depends on the rate of oxygen supply, the activity of phospholipid factor of thrombocytes, solubility coefficient of oxygen, pH medium and temperature. Thermal component of those reactions depends on cholinergic and adrenergic neurotransmitter systems, related to carotid body and formation of charge-transporting interrelation at the level of thyroxin and imidazole protein receptor of a red blood cell and peroxisome proliferator-activated (PPAR) [34-36]. PPAR together with red blood cells takes part in formation of pH of artery blood, according to temperature parameters of interaction of opioid receptors (α, β, γ) in cholinergic and adrenergic regulatory mechanisms of endogenous alcohol synthesis, resulting from the interaction of metabolic processes of cholesterol, vitamin B1 and D, glucose, lactic acid, ubiquitin, intestinal synthetase and α1- trypsin. Temperature and pH of arterial blood are connected with lymphoid myeloid complex, which is presented in all organs and hematopoietic system [35-36].

In summary, metabolic response on the reactions in organism corresponds to the ratio of the sum of temperatures in the carotid bifurcation (carotid body) to a temperature parameter in abdominal area. In this case it is proved that the temperature is the final stage during biochemical and biophysical changes on the level of lysosomes, cytosol and mitochondria. It depends on metabolism of amino acids, phospholipids and cholesterol, and water metabolism. Changes in temperature parameters of mentioned areas are caused by changes in blood circulation and depend on blood circulation in organs, which are controlled by hypothalamus and tyrosine kinases. The method in whole is widely described in monograph "*Thermoregulation of an organism and vegetovascular paroxysms*" [37]. The certificates, patents, allowable limits of performance and quality controls of the device are described in the literature reviewed [38-39].

2.4 Study Groups and Predetermination of Sample Size

A single group of patients was examined by both methods (at first using ANESA and then by conventional blood sampling) to obtain haematological and biochemical parameters (haemogram, renal function, hepatic function and lipid profile). The calculation of the sample size was realised as a function of the variability of the

average of parameters at 10%, assuming a random error of 5% and an estimated accuracy of 1.5%. The minimum number of patients necessary to make the comparison between both methods was 170. The statistical power for the model was higher than 80%.

2.5 Organisational Procedure – Personnel Training

A multidisciplinary working group was established of nine professionals (two nurses, two intern doctors and a family doctor, one laboratory supervisor, three heads of service and one coordinator) for planning the study. A technical training course was conducted for these professionals, in order to learn the physiological, functional and organisational fundamentals of ANESA. Selection of subjects was performed from a basic list (see inclusion/exclusion criteria) of patients scheduled for usual blood analysis. Note that previously the whole hospital had been informed (via corporate intranet) about realisation of the tests especially (personalised information in a group) reception professionals, administrative personnel in the outpatient department, laboratory staff and personnel in the day hospital. Patients who were accepted to participate in the study were informed about the testing procedure by telephone (a week before); they were invited for the planned day of testing (reduction of waiting time) to the hospital (third floor waiting room) and were called out to the testing room every 15 minutes; altogether 8–10 patients per day were tested.

2.6 Preparation of the Patients and Detail of the Procedure

On the day of testing, healthcare staff invited a patient and accompanied him or her to the testing room in the day hospital. There, the patient was informed about the testing procedure again, inclusion and exclusion criteria were checked once more and an informed consent form was offered to the patient for signing. During the test, a doctor and a nurse were always in the room. The patient was placed in a reclining armchair (supine) and was familiarised with the sensors (direct contact) to decrease emotional state. Five sensors were placed on biologically active points: a) bifurcation of the carotid artery left and right (two points); b) axillary region left and right (two points) and c) umbilical region (Fig. 1). Heart rate, age and weight had been determined previously and entered into a computer using a keyboard, along with the gender of the patient. After that, measurement by the ANESA device software was started; after finishing that, blood was sampled.

The estimated time of measurement for each test was 4–9 minutes depending on stabilisation of temperatures for real-time result readings. Those cases in which temperature values were not stabilised adequately were not considered as valid data for inclusion in the analysis and such patients were excluded. The five sensors connected to the analyser measure temperature from the reference points of a patient with an accuracy of not less than 0.5℃. The sensors send temperature parameters to the ANESA central processing unit. Calculation of blood parameter data is done with a special examination algorithm named as the Malykhin-Pulavskyi method (Ukrainian patent No. 3546 A61B5). During examination, there exists no harmful influence from the analyser to patients (non-invasive method). As the analyser determines the influence of environment on a patient's health status, a test is not recommended if: a) the environment temperature is higher than 27℃ or lower than 20℃; b) relative humidity is higher than 80% at 25℃; c) sunshine and/or air conditioning flow are directed at a patient or d) strong electrical or magnetic fields exist in the environment. The device's enclosure was cleaned with a soft well-drained soapy cloth. Disinfection of sensors was done with alcohol wipes (96% alcohol). Subsequently, conventional blood samples were taken (venipuncture): a) EDTA tube for haemogram and b) serum tube for biochemical analysis. According to the usual standard procedure, samples were dispatched to the laboratory, where the results were processed according to usual clinical practice. Materials and devices used for laboratory testing were the following: Vacuette Tube Gel Red 9 mL, Vacuette Tube EDTA K3 Mallow 3 mL, Vacuette Tube Sodium Citrate Blue 3.5 mL, Vacuette Needle 21G×1½, Vacuette Quickshield Safety Tube Holders, Syringe 20cc 3 bodies (BD Plastipak), Needle Luer 20G (BD Microlance), Coagulometer: Automatic autoanalyser IL ACL9000 Elite (Beckman Coulter, USA), Haematology cytometer: Roche Sysmex XT-1800i (Japan) and Biochemical automatic analyser: Hitachi Modular P800/ISE900 (Japan).

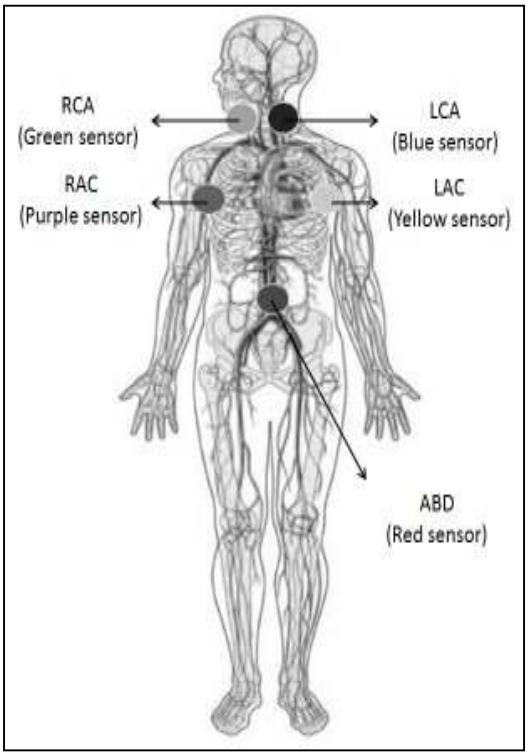


Fig. 1. Detail of ANESA sensor placement on patients

ANESA: Automatic Non-invasive Express Screening Analyser. The five sensors are placed on biologically active points: a) right and left carotid artery bifurcation (two points), b) right and left axillary region (two points) and c) umbilical region

2.7 Studied Parameters

The following blood parameters were determined by the two methods (ANESA and standard laboratory analysis) and compared: haemogram: erythrocytes (10^{12}/L), haemoglobin (g/dL), haematocrit (%), platelets (10^{9}/L), leukocytes (10^{9}/L), lymphocytes (%) and monocytes (%); blood glucose (mg/dL); lipid profile: total cholesterol (high density: cHDL and low density cLDL; mg/L) and triglycerides (mg/dL); hepatic function: alanine aminotransferase (ALT, IU/L), aspartate transaminase (AST, IU/L) and total bilirubin (mg/dL); and renal function: creatinine (mg/dL) and urea (mg/dL). In a prior step, measurement units of the different parameters were brought into correspondence and normalised, as well as their normal reference values.

2.8 Information Confidentiality

Confidentiality of records (anonymous and differentiated) was respected according to the Data Protection Organic Law (15/1999 Law from December 13). All patients were informed about the nature of the study (patient information sheet). They were also informed that all data obtained by ANESA apparatus would be valid only for the study, i.e., only information for estimation of health status and possible medical acts, obtained by standard blood analysismight be taken into account. All participants signed the informed consent form. The study was approved by the Clinical Investigation Ethics Committee of Germans Trías and Pujol University Hospital in Badalona, Spain.

2.9 Statistical Analysis

A descriptive analysis of all evaluation parameters was performed separately, using absolute and relative frequency tables in the case of qualitative variables and statistical averages, standard deviation, Pearson linear correlation, percentiles and/or confidence intervals (IC 95%) in the case of continuous quantitative variables. Distribution normality was verified through a Kolmogorov-Smirnov test. For parameter comparison of both methods (ANESA vs. standard laboratory analysis), a bivariate analysis was done through average comparison for paired groups (T-Student). Internal consistence was analysed by Cronbach's alpha coefficient (based on the average correlation of the items), reliability of the clinical observations through intraclass correlation coefficient (ICC) and analysis of individual differences through Bland–Altman graphs [40]. In the study, an acceptable comparison for ICC values > 90% (level of medical decision) was considered. SPSSWIN version 17 software was used, establishing a statistical significance for values of $p<0.05$.

3. RESULTS

The total number of patients involved was 195. Of those, N=2 (1.0%) refused to participate in the study, N=13 (6.7%) did not meet the initial inclusion criteria, and in N=10 (5.1%) temperature stabilisation was not reached (thermal regulation), which was required to perform the non-invasive test; finally, 172 subjects were analysed. The baseline characteristics of the patients are detailed in Table 1. Average age was 50.8 years old and 65.2% were women.

Table 2 shows comparison of paired averages of parameters (ANESA device vs. standard

laboratory analysis). Distribution of Kolmogorov-Smirnov's normality test is very similar between both study methods (ANESA vs. standard laboratory one). In the patients studied, haematological parameters follow normal distributions, while for biochemical parameters nonlinear distributions with an acceptable comparability between the measuring methodspredominate. The parameters with a higher degree of linear correlation were hepatic tests (AST: r=0.974; ALT: r=0.961) and platelets (r=0.966, p<0.001). In contrast, bilirubin (r=0.724) and total cholesterol (r=0.730) reached moderate correlations. In paired comparisons (average differences between ANESA and standard laboratory blood test), cholesterol (185.4 vs. 179.8; difference: 5.6 mg/dL; p=0.005), cLDL (95.9 vs. 100.5; difference: 4.6 mg/dL; p=0.002) and bilirubin (0.6 vs. 0.5; difference: 0.1 mg/dL; p<0.001) showed more modest results. The rest of the parameters analysed showed an adequate comparability between both methods studied.

Table 1. General characteristics of patients studied

Patient characteristics	Values
Number of subjects	172
Average age, years	50.8 (15.5)
Median (P25–P75) years	49.5 (39.0–58.0)
Gender, women	65.2%
Weight, kg	67.8 (71.7)
Median (P25–P75) years	68.0 (60.0–75.0)
Average radial pulse, per minute	71.6 (10.4)
Median (P25–P75) years	72.0 (64.0–78.0)

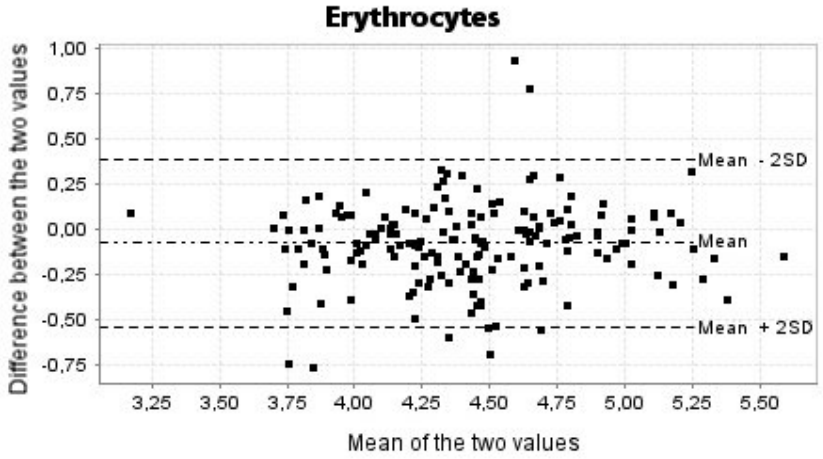
Values expressed in percentages or average (SD: standard deviation) P: percentiles 25 and 75 of the distribution

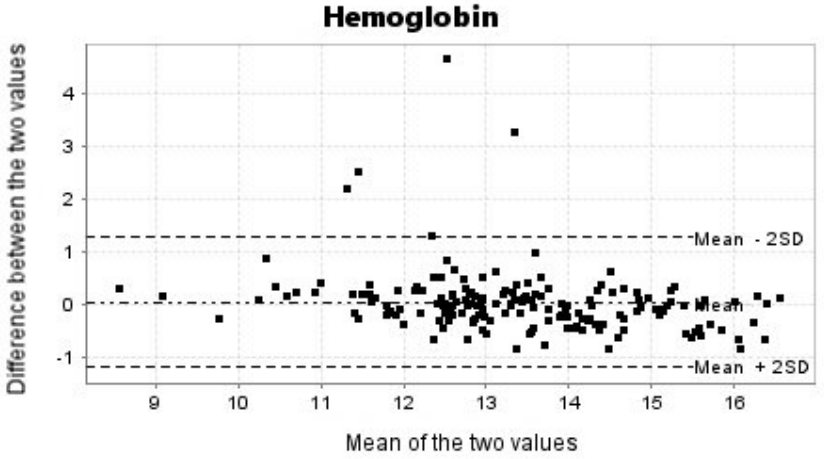
Finally, analysis of the reliability and internal consistency of observations between both measuring methods studied (ANESA device vs. standard laboratory analysis), is described in Table 3. In the 17 studied parameters and comparing both study methods (ANESA device vs. standard laboratory analysis), the relationship between internal consistency and reliability was equivalent. Erythrocytes, haemoglobin, haematocrit, platelets, leukocytes, glucose, cHDL, triglycerides, ALT, AST, creatinine and urea reached an ICC>0.90. Lipid parameters (cholesterol: ICC=0.728; cLDL: ICC=0.817) obtained a more modest correlation; meanwhile lymphocytes (ICC=0.551) and monocytes (ICC=0.546) did not reach expected results. Analysis of the individual differences though Bland–Altman graphs for each of the analysed parameters is shown in Fig. 2. The statistical sub-analysis performed by age and gender average, reliability and consistency of the observations remained without statistically significant differences (similar results).

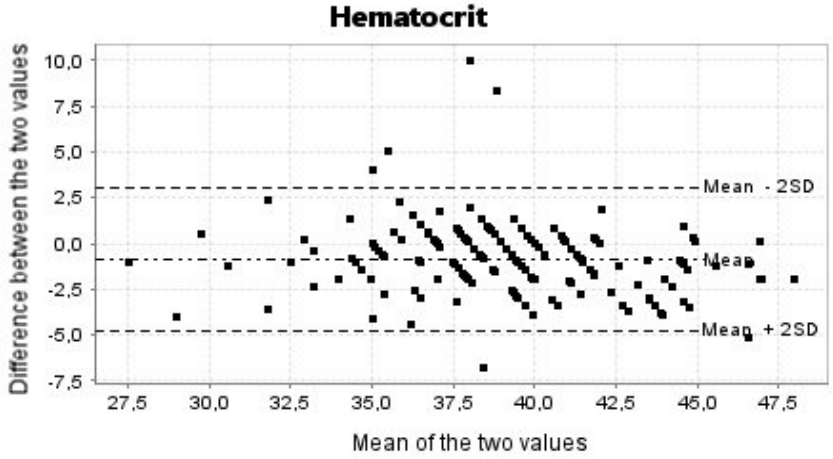
4. DISCUSSION

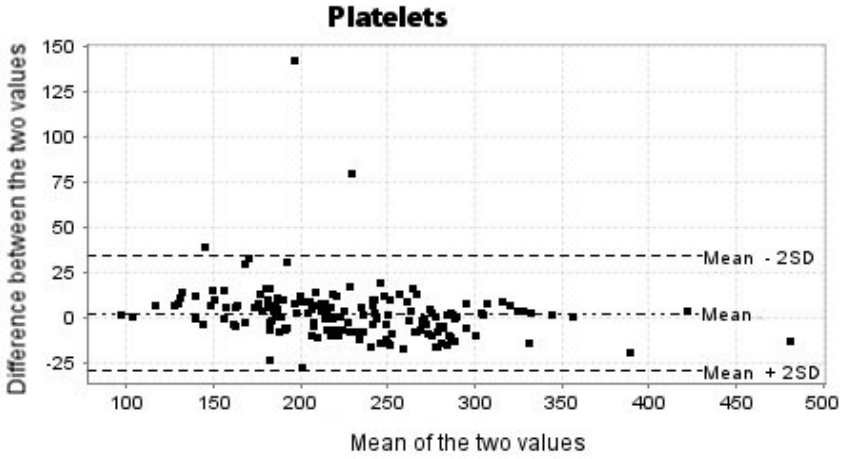
Results showed that the non-invasive ANESA device is a reliable and advantageous method for usual clinical practice in comparison with standard laboratory analysis parameters, being an alternative to the usual blood extraction screening method. It should be noted that few published studies exist which compare these two methods for obtaining parameters in real conditions (which makes the comparison of results difficult), which is why the present study must be interpreted as strong, since it offers relevant information for an alternative to the usual laboratory analysis. However, without an adequate standardisation of methodology for measurement of variables, the results must be interpreted wisely, causing us to be cautious in the validity of the results in general practice.

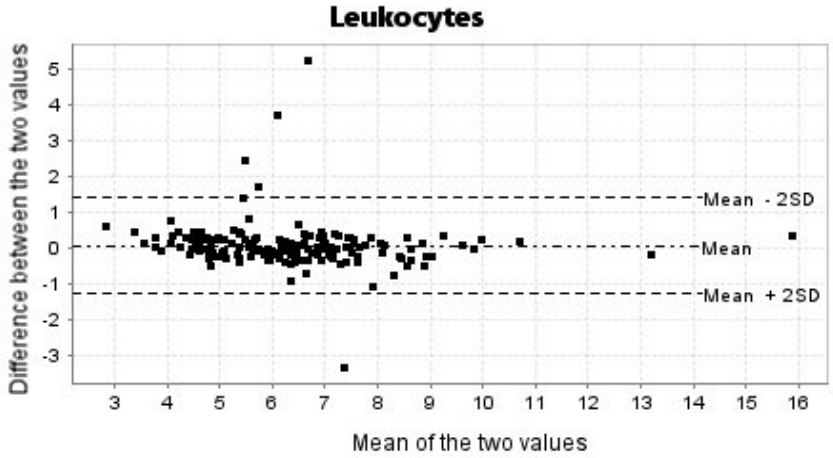
The device could not substitute the usual clinical analysis laboratory, but may be used as a complementary method for patients with noncomplex clinical pathologies (it measures 130 parameters) in primary care centres, special medical institutions, preventive care departments and centres for screening and monitoring of chronic diseases with low complexity (such as dyslipidaemia, diabetes, etc.). In addition, the ANESA device could be very useful in urgent or complex situations as it combines parameters which allow estimation of gas analysis, spirometry or even other analysis as related to cardiac, hepatic, pulmonary or renal disorders. They have not been the objectives of this study, but that is a promising way forward for the future; it offers alternatives that will be analysed and verified.

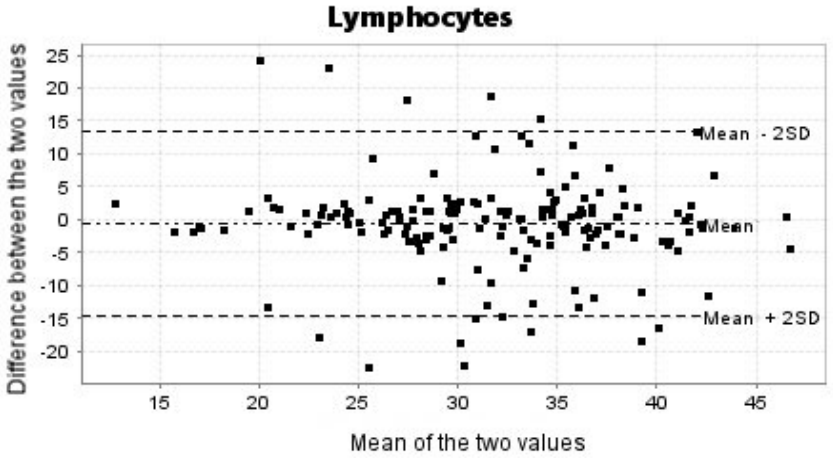

Erythrocytes
Difference between the two values
1,00
0,75
0,50
0,25
0,00
-0,25
-0,50
-0,75
Mean - 2SD
Mean
Mean + 2SD
3,25
3,50
3,75
4,00
4,25
4,50
4,75
5,00
5,25
5,50
Mean of the two values

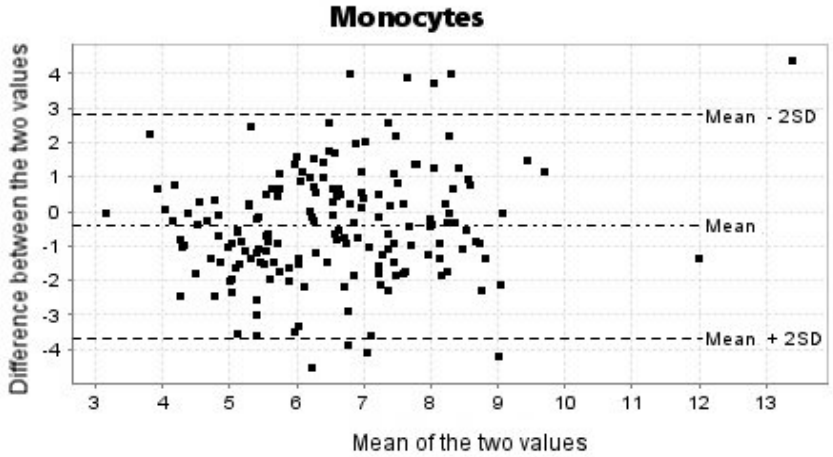

Hemoglobin
Difference between the two values
4
3
2
1
0
-1
Mean - 2SD
Mean
Mean + 2SD
9
10
11
12
13
14
15
16
Mean of the two values

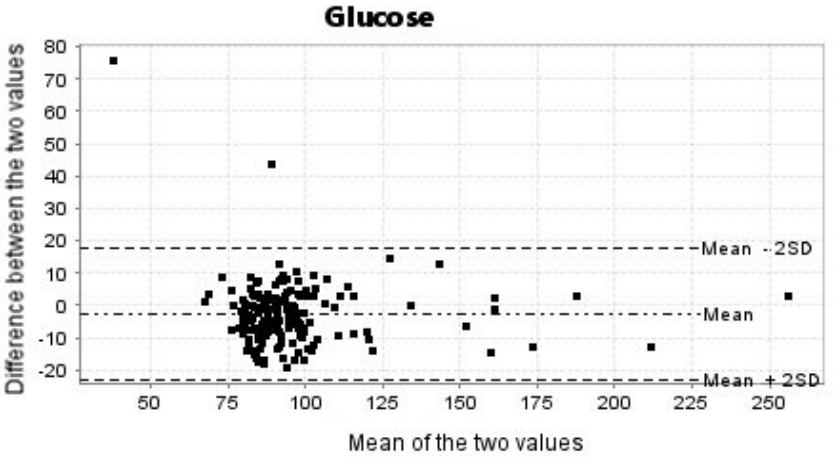

Hematocrit
Difference between the two values
10,0
7,5
5,0
2,5
0,0
-2,5
-5,0
-7,5
Mean - 2SD
Mean
Mean + 2SD
27,5
30,0
32,5
35,0
37,5
40,0
42,5
45,0
47,5
Mean of the two values

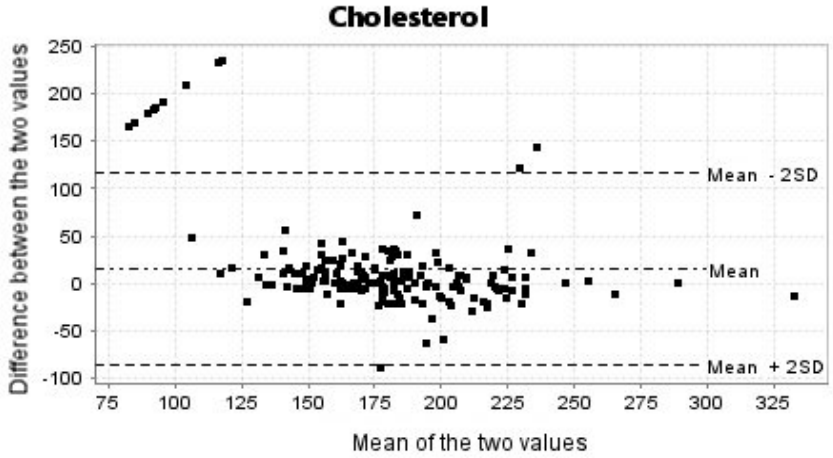

Platelets
Difference between the two values
150
125
100
75
50
25
0
-25
Mean - 2SD
Mean
Mean + 2SD
100
150
200
250
300
350
400
450
500
Mean of the two values

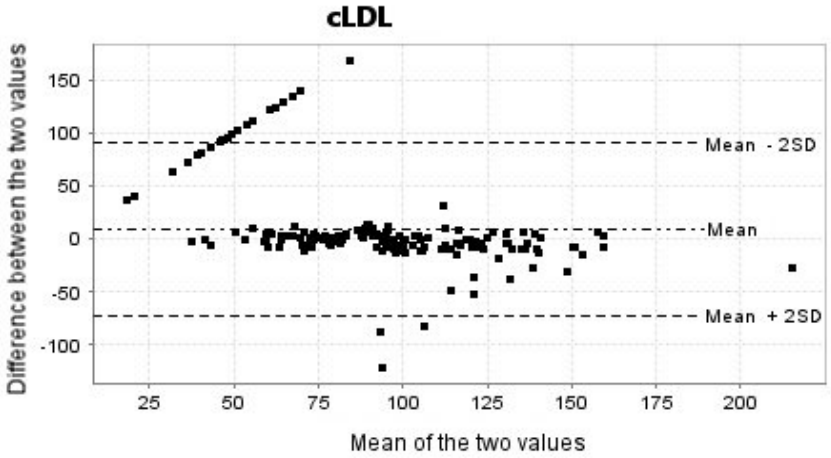

Leukocytes
Difference between the two values
Mean - 2SD
Mean
Mean + 2SD
Mean of the two values

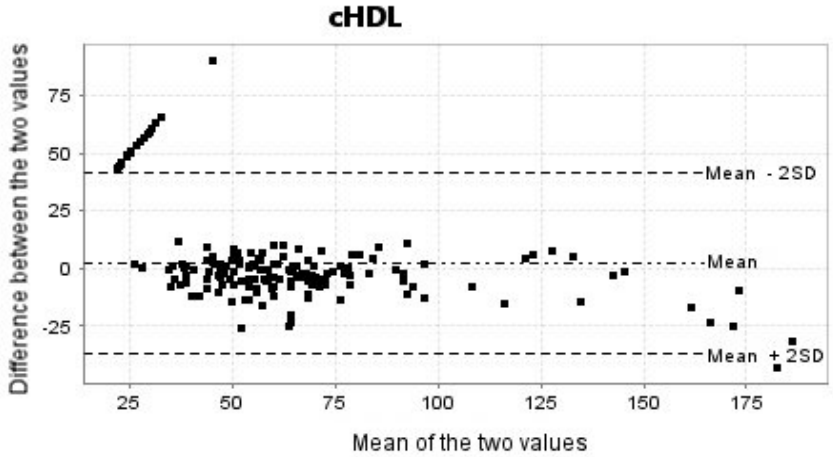

Lymphocytes
Difference between the two values
Mean - 2SD
Mean
Mean + 2SD
Mean of the two values

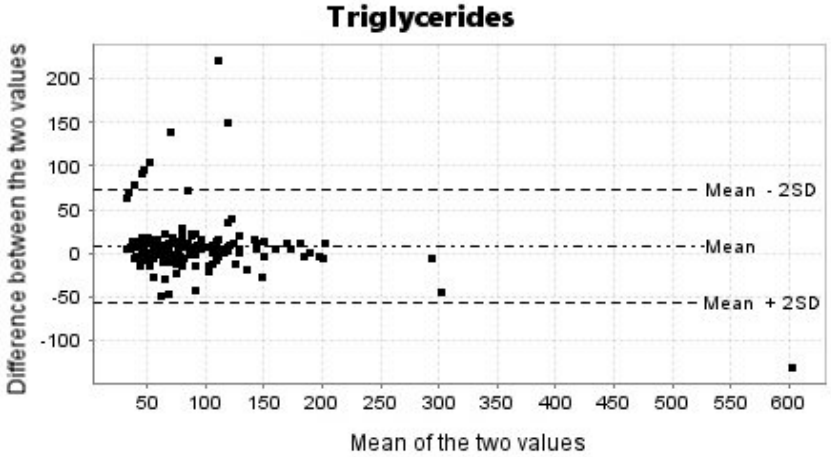

Monocytes
Difference between the two values
Mean - 2SD
Mean
Mean + 2SD
Mean of the two values

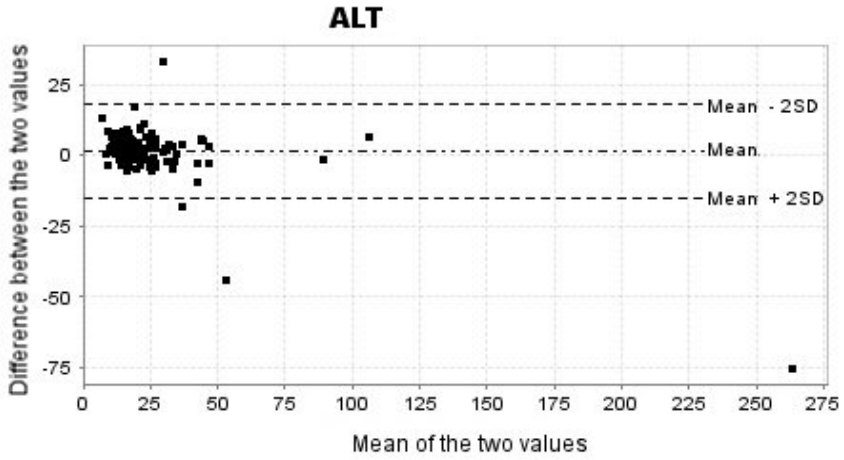

Glucose
Difference between the two values
Mean - 2SD
Mean
Mean + 2SD
Mean of the two values

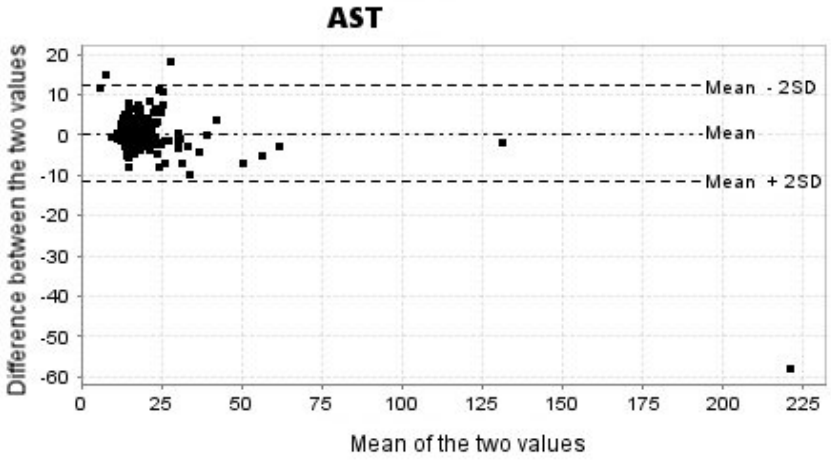

Cholesterol
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD

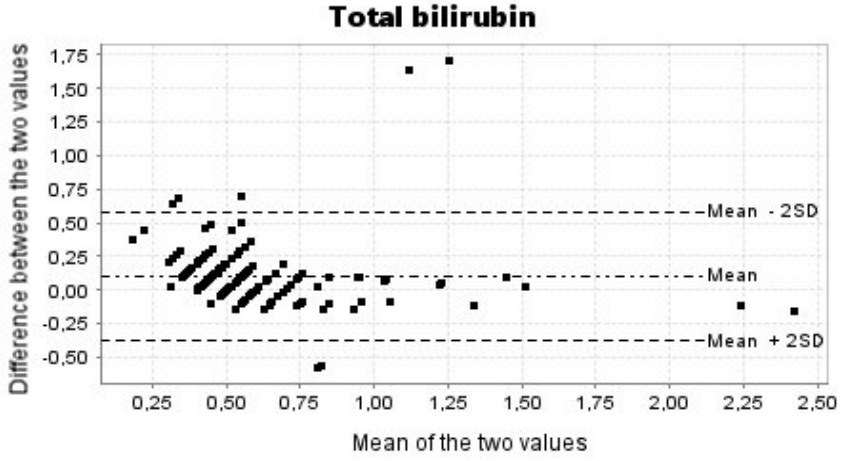

cLDL
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD

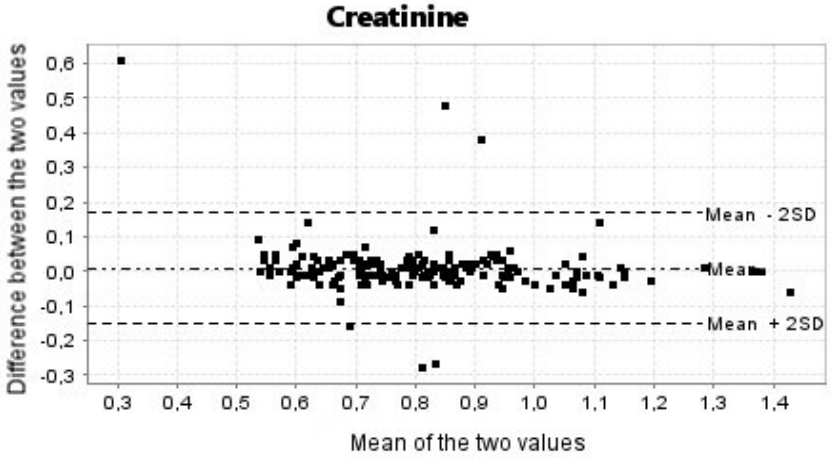

cHDL
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD


Triglycerides
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD


ALT
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD


AST
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD


Total bilirubin
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD


Creatinine
Difference between the two values
Mean of the two values
Mean - 2SD
Mean
Mean + 2SD

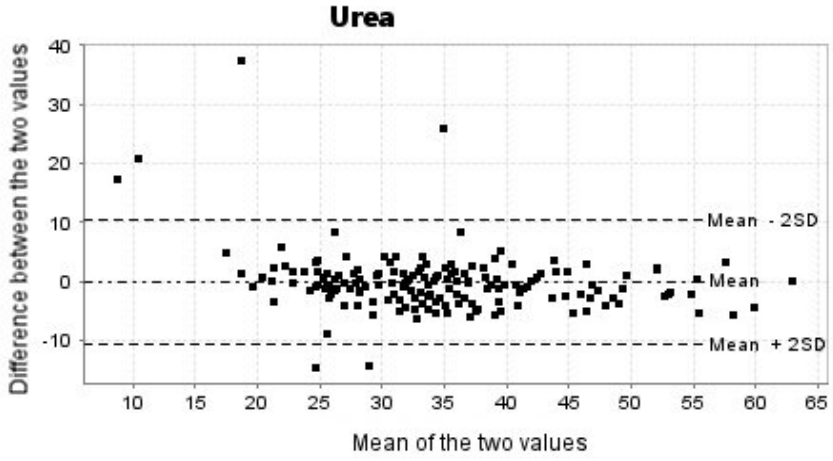


Fig. 2. Analysis of the individual differences through Bland and Altman´s graphs for each analyzed parameter

cLDL: cholesterol linked to low density lipoproteins
cHDL: cholesterol linked to high density lipoproteins
ALT: alanine aminotransferase
AST: aspartate transaminase

Table 2. Average comparison for paired parameters (ANESA device vs. usual laboratory analysis)

Pair wise comparison[1]	Analysed parameters	K-S ANESA[2] p	K-S Reference[3] p	ANESA[4] method	Usual[4] method	Average difference	p*	r
Pair 1	Erythrocytes, 10^{12}/L	0.539	0.854	4.4 (0.4)	4.5 (0.4)	−0.1 (0.2)	0.221	0.893
Pair 2	Haemoglobin, g/dL	0.499	0.665	13.4 (1.4)	13.3 (1.6)	0.0 (0.6)	0.506	0.921
Pair 3	Haematocrit, %	0.320	0.803	38.7 (3.6)	39.5 (4.0)	−0.8 (2.0)	0.081	0.899
Pair 4	Platelets, 10^9/L	0.420	0.620	229.5 (57.0)	227.4 (60.9)	2.1 (15.9)	0.078	0.966
Pair 5	Leukocytes, 10^9/L	0.510	0.740	6.3 (1.7)	6.3 (1.8)	0.1 (0.7)	0.250	0.925
Pair 6	Lymphocytes, %	0.616	0.849	31.3 (7.1)	31.9 (7.6)	−0.6 (7.0)	0.228	0.752
Pair 7	Monocytes, %	0.236	0.239	6.3 (1.8)	6.8 (1.6)	−0.4 (1.6)	0.081	0.753
Pair 8	Glucose, mg/dL	<0.001	<0.001	97.0 (23.7)	98.0 (23.4)	−2.0 (8.9)	0.061	0.938
Pair 9	Cholesterol, mg/dL	0.180	0.319	185.4 (33.6)	179.8 (35.7)	5.6 (25.6)	0.005	0.730
Pair 10	cLDL, mg/dL	0.228	0.296	95.9 (27.7)	100.5 (31.2)	−4.6 (17.8)	0.002	0.823
Pair 11	cHDL, mg/dL	<0.001	<0.001	68.5 (29.0)	70.6 (32.3)	−2.1 (9.7)	0.091	0.955
Pair 12	Triglycerides, mg/dL	<0.001	<0.001	90.3 (56.0)	87.6 (63.4)	2.6 (21.0)	0.105	0.946
Pair 13	ALT, IU/L	<0.001	<0.001	22.1 (19.3)	20.7 (24.7)	1.4 (8.2)	0.064	0.961
Pair 14	AST, IU/L	<0.001	<0.001	21.6 (16.9)	21.5 (20.8)	0.1 (5.8)	0.820	0.974
Pair 15	Bilirubin, mg/dL	<0.001	<0.001	0.6 (0.3)	0.5 (0.3)	0.1 (0.2)	<0.001	0.724
Pair 16	Creatinine, mg/dL	0.137	0.221	0.8 (0.2)	0.8 (0.2)	0.0 (0.1)	0.411	0.930
Pair 17	Urea, mg/dL	0.208	0.129	35 (9.1)	35.6 (9.5)	−0.5 (3.9)	0.069	0.914

[1] Average comparison for paired groups (t-Student test samples)

[2] K-S: Kolmogorov-Smirnov normality test; ANESA method: Automatic Non-invasive Express Screening Analyser; p: statistical significance of K-S

[3] K-S: Kolmogorov-Smirnov normality test; usual method (blood extraction; clinical analysis); p: statistical significance of K-S

[4] Expressed values as average (SD: Standard Deviation) for each analysed parameter. Comparison of ANESA vs. usual clinical laboratory analysis

** Statistical significance of the average comparison (paired groups)*

r: Pearson's linear correlation coefficient

cLDL: cholesterol linked to low density lipoproteins

cHDL: cholesterol linked to high density lipoproteins

ALT: alanine aminotransferase

AST: aspartate transaminase

Table 3. Reliability analysis and internal consistence of observations between studied measurement methods (ANESA device vs. usual laboratory analysis)

Parameters	Coefficients*	Values	CI 95%	Test F
Erythocytes, 10^{12}/L	Intraclass correlation	0.902	0.885–0.928	22.507
	Cronbach's Alpha	0.920	0.891–0.941	
Haemoglobin, g/dL	Intraclass correlation	0.916	0.887–0.937	22.741
	Cronbach's Alpha	0.956	0.940–0.967	
Haematocrit, %	Intraclass correlation	0.904	0.881–0.922	23.755
	Cronbach's Alpha	0.927	0.902–0.945	
Platelets, 10^9/L	Intraclass correlation	0.964	0.951–0.973	54.183
	Cronbach's Alpha	0.982	0.975–0.986	
Leukocytes, 10^9/L	Intraclass correlation	0.925	0.899–0.944	44.200
	Cronbach's Alpha	0.961	0.947–0.971	
Lymphocytes, %	Intraclass correlation	0.551	0.437–0.647	3.451
	Cronbach's Alpha	0.710	0.608–0.785	
Monocytes, %	Intraclass correlation	0.546	0.432–0.643	3.409
	Cronbach's Alpha	0.707	0.603–0.783	
Glucose, mg/dL	Intraclass correlation	0.938	0.916–0.953	31.058
	Cronbach's Alpha	0.968	0.956–0.976	
Cholesterol, mg/dL	Intraclass correlation	0.728	0.648–0.792	6.361
	Cronbach's Alpha	0.843	0.786–0.884	
cLDL, mg/dL	Intraclass correlation	0.817	0.755–0.864	9.920
	Cronbach's Alpha	0.899	0.861–0.927	
cHDL, mg/dL	Intraclass correlation	0.950	0.932–0.963	38.873
	Cronbach's Alpha	0.974	0.965–0.981	
Triglycerides, mg/dL	Intraclass correlation	0.938	0.917–0.954	31.464
	Cronbach's Alpha	0.968	0.957–0.977	
ALT, IU/L	Intraclass correlation	0.932	0.909–0.949	28.427
	Cronbach's Alpha	0.965	0.952–0.974	
AST, IU/L	Intraclass correlation	0.954	0.938–0.966	42.487
	Cronbach's Alpha	0.976	0.968–0.983	
Bilirubin, mg/dL	Intraclass correlation	0.724	0.644–0.788	6.236
	Cronbach's Alpha	0.840	0.783–0.881	
Creatinine, mg/dL	Intraclass correlation	0.929	0.906–0.947	27.329
	Cronbach's Alpha	0.963	0.951–0.973	
Urea, mg/dL	Intraclass correlation	0.913	0.885–0.935	22.115
	Cronbach's Alpha	0.955	0.939–0.966	

**Reliability: intraclass correlation coefficient type C using one definition of consistency; the inter-measure variance is excluded from denominator variance. A mixed-effect model of two factors was used in which the effects of people are random and the effects of measures are fixed*

CI: confidence intervals of 95%

F: Fisher-Snedecor's F distribution

cLDL: cholesterol linked to low density lipoproteins

cHDL: cholesterol linked to high density lipoproteins

ALT: alanine aminotransferase

AST: aspartate transaminase

Available evidence in our country does not exist, hindering comparison of results. One interesting hypothesis states that the results obtained by both methods are comparable (*in vivo*: ANESA; *in vitro*: clinical laboratory). To our knowledge, the answer is complex, but it is the unique alternative available so far. There are specific factors inherent to the *in vivo* ANESA method which could affect the chain of chemical reactions that occur in human body cells, on the hydrodynamic properties of blood, gas exchange, gas solubility and diffusion. Moreover, *in vitro* tests are usually performed in a laboratory at a standard temperature and pH. Other parameters (for example enzymes) are determined at other temperatures (20 or 25℃). In that case, a manufacturer of reagents determines other normal values for the parameter or gives a table or additional coefficients for conversion [41]. There is another

group of active factors like temperature, pressure, gas concentration and presence of salts which have no effect or very little effect on blood parameters which are compared. This group contains blood parameters like haemoglobin, erythrocytes, leukocytes, etc. So, comparing results which are received invivo and invitro must be very similar. Other factors like pH and salt concentration do have an effect on blood parameters which are compared [42]. In general, the peak of each enzyme depends on temperature and pH. So, intake of numerous medications or dietary supplements may have repercussions for the reported data of patients. Finally, normal values, which are different for people from different places in the world, play a great role in the comparison of *in vivo* and *in vitro* results for clarification of normal and pathological states. Concentration of human blood depends on altitude and O_2 concentration [43].

The statement above could be comparable in the context of the obtained results from the study. In our case, in people with noncomplex clinical pathologies, erythrocytes, haemoglobin, haematocrit, platelets, leukocytes, glucose, cHDL, triglycerides, ALT, AST, creatinine and urea reached optimal results, whereas lymphocytes and monocytes did not reach expected results. The last may be caused by a lack of conversion in the ANESA's algorithms or by random effects. A special mention must be made about lipid parameters, which obtained a modest correlation. According to the opinion of scientific associations, lipid parameters have a high variability margin, so their interpretation must be performed taking into account potential modifying factors. So, factors affecting ANESA's algorithm as well as the results should be improved in order to reduce the variability margin compared with standard laboratory analysis [44-45].

4.1 Study Limitations

Possible limitations of the study are disease complexity, possible bias of classification of patients (inter-individual variability) and effective measurement of variables (*in vivo* vs. *in vitro*). Moreover, some bias may occur because of: a) an imperfect reference test, and as there is no good reference test, the one available test is used (although this test does not classify well and does not always differentiate healthy and sick correctly), and all reference tests are subject to a variability margin (technical, inter-individual, etc.) and b) differences in result interpretation. This study was realized with patients attending outpatient care (scarce clinical complexity), so this situation should be considered as a limitation of the study. Lipids results were slightly discordant. This fact may be due to several factors: a) a random phenomenon, b) a lack of reliability in the method, c) the own biological variability of the biochemical parameters analyzed in the laboratory [46], and / or other unmeasured variables in the study. However, the most important limitation is a lack of external validity of the study, so the generalisation of results must be interpreted cautiously. In our study, the ICC was used to compare quantitative data. Although it is a valid method for analysis; It could have also used the regression model Passing-Bablok (homogeneity of variances is required) [47]. Another study limitation is the lack of comparison with literature due to there is no published recent studies, for the moment.

4.2 Future Directions

In future researches we should answer these inaccuracies. It is an investigation field with a high potential in clinical practice. The device's merits, such as use of a non-invasive procedure, with results in real time and at very low cost, are only some of the advantages of this type of device.

5. CONCLUSION

Despite of the study limitations, the automatic non-invasive analyser (ANESA) is shown as a reliable and promising screening method in usual clinical practice for most of the analyzed parameters as an alternative to standard blood extraction. However, more studies are required to strengthen the consistency of the results.

ETHICAL APPROVAL

The study was approved by the Clinical Investigation Ethics Committee of Germans Trías and Pujol University Hospital in Badalona, Spain (BSA-ANESA-2014-01; REF. CEI. PI-14-030).

ACKNOWLEDGEMENTS

Badalona Serveis Assistencials multidisciplinary work group: Anna Maria Padrós Fluviá, Ángel Luis Ballesteros Álvarez, Francesc Blanch Grifol, Joaquim Vila Planas, Lidia Ortega Martín, Sandra Arco Rodríguez, Xavier Frías Garrido, Soledad Velasco Velasco and Estefanía Delgado.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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