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ORIGINAL ARTICLE

The Method of Lipemia Clearance Should be Based on the Characteristics and the Method of Testing in the Emergency Laboratory

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SUMMARY

Background: **This study aimed to compare the lipemia removal efficiency of highspeed centrifugation, lipid scavengers, and dilution for biochemical analytes.**
Methods: **We collected 30 cases of lipemic plasma in an emergency laboratory and divided them into 4 aliquots. Lipemia was removed by highspeed centrifugation, lipid scavenger, dilution, and ultracentrifugation, then analytes were measured by an AU5800 analyzer. Taking ultracentrifugation as reference, the efficiencies of the other three methods were evaluated based on the deviation.**
Results: **When highspeed centrifugation was used for lipemia removal, DBIL (18.62%), and Magnesium (6.09%) could not satisfy the criterion. When lipid scavengers were applied to remove lipemia, CRP (-86.70%), TP (-8.29%), CKMB (-44.85%), DBIL (37.96%), Glu (4.20%) and phosphate (14.32%) were not suggested as lipid scavengers. For dilution, nearly half of the analytes could satisfy the criterion, including AMY (2.41%), CRP (5.54%), ALT (2.85%), GGTL (-1.73%), ALP (-0.04%), Glu (-0.84%), LDH (0.06%), CK (0.68%), BUN (3.80%), CREA (-1.54%), UA (5.42%), and magnesium (0.43%).**
Conclusions: **Neither of the methods for lipid removal could satisfy all emergency department tests for lipid removal. This finding suggests that removing lipemia in the clinical laboratory should be based on the characteristics and the method of testing.**
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KEYWORDS

lipid removal, highspeed centrifugation, lipid scavenger, dilution

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INTRODUCTION

With the development of vacuum blood drawing techniques in emergency laboratories, lipemia has become the most frequent preanalytical interference, especially in patients who do not draw blood in the non-fasting state [1]. The mechanism of interference of lipemia includes the interference of light scattering and absorption, saponification, and increasing the background of chemical reaction products [2]. Over the past two decades, the emphasis of laboratory quality control has shifted to the preanalytical procedure that is most prone to error throughout the testing process [3,4]. Most errors are due to preanalytical factors (46 - 68.2% of total errors), while a high error rate (18.5 - 47% of total errors) has been found in the postanalytical stage [5]. Pretreatment before analysis of lipemia should be prioritized. It is important to look for a practical method of eliminating lipemia [6]. Currently, methods of lipemia clearing include ultracentrifugation, highspeed centrifugation, dilution, and lipid scavenger; each of these methods has its own disadvantages.

Ultracentrifugation is considered the recommended method for lipemia clearance, according to the CLSI C56-A document. However, this method is difficult to popularize to most clinical laboratories due to its strict conditions and exorbitant price. Highspeed centrifugation as a method of routine lipid removal is now widely used in the laboratory. Dilution is favored in the laboratory for its efficiency and time savings. Besides, the dilution method is the most effective approach for removing lipids that could satisfy the turnaround time (TAT) requirement. Many biochemical instruments are equipped with automated pre-dilution functions to eliminate interference from lipids. In recent years, a type of non-ionic polymer lipid scavenger has been applied in laboratories [7]. The manufacturer of lipid scavengers claims that they can satisfy the routine emergency requirements except for a few analytes. Verifying the efficacy of the manufacturer's statement of lipid scavengers in specific laboratory settings and instrumentation is important. Surprisingly, only a handful of studies have investigated the effect of this commercial reagent on various biochemical analytes [8,9].

Therefore, we investigated the performance of highspeed centrifugation, dilution, and lipid scavenging in consecutive samples of emergency tests.

MATERIALS AND METHODS

The study was performed in the emergency laboratory of the Zhongshan Hospital Xiamen University in January 2023. Routine emergency biochemical parameters were included in the study. These biochemical indicators may be subject to interference from lipemia during measurement. All biochemical measurements were performed on the Beckman Coulter AU5800 Automated Biochemical Analyzer (Beckman Inst., Jersey City, NJ, USA). The methodology of analytes is listed in Table 1. After routine centrifugation (3,500 revolutions per minute for 15 minutes), the lipemic plasma was divided into four aliquots in order to use different methods to remove lipemia, including ultracentrifugation, highspeed centrifugation, lipid scavenger, and dilution. One aliquot was removed from the lipid by ultracentrifugation by using a Thermo MX 150 Plus centrifuge (Thermo Fisher Scientific, USA). The rotation speed of ultracentrifugation could reach 150,000 revolutions per minute, and the plasma should be centrifuged for at least 10 minutes. The results measured by ultracentrifugation were regarded as the “gold standard”. Highspeed centrifugation was performed in a Sarstedt Microcentrifuge (Sarstedt, North Rhine-Westphalia, Germany) at 121,00 revolutions per minute for 15 minutes. In both of the centrifugations, chylomicron floated on top of the plasma, and the bottom part of the clarified plasma was used for the analytes. One aliquot was removed by a lipid scavenger called LipoClear® (Iris International Inc, Westwood, MA, USA). All steps were performed according to the LipoClear®'s manufacturer instructions; 500 microliters of lipid-blood plasma samples were poured into test tubes of the original manufacturer containing lipid scavenger (100 µL). Then, the tubes were vortexed and left at room temperature for 5 minutes. After, the samples were centrifuged in a routine centrifuge (Xiangyi Hunan China) at 3,500 revolutions per minute for 10 minutes. Finally, the clarified samples were used for analysis, and the results were multiplied by 1.2 to adjust the concentration. The last aliquot of lipemia sample was used for dilution; 100 µL lipidemia samples were diluted with 400 µL ultrapure water at a ratio of 1:5, and the result was multiplied by 5 to revise the dilution of the original results. This study was approved by the Ethics Committee of the Zhongshan Hospital, Xiamen University, following the Helsinki Declaration of 2008. All participants signed informed consent prior to the study.

Statistical analysis

Performance goals: a) Following ISO 5725-6, the acceptable change limit is based on analytical imprecision (CVa), using the formula accepted change limit (ACL) = 2.77 CVa. CVa was obtained from internal conventional data of cumulative QC values at 6 months for each analyte. b) The second approach considers acceptable imprecision based on *in vivo* biological variation. For single- and multiple-point assays, methodological imprecision should be equal to or less than half the mean individual variance (CVb), which should be the goal of short-term laboratory imprecision (≤ 0.5 CVb). CVb of each analyte from the 316 analytes is listed by Ricos et al. [10].

We combined the abovementioned two approaches (analytical and intraindividual imprecisions) by the following formula and defined the total change limit (TCL):

$$\text{TCL} = \sqrt{(2.77CVa)^2 + (0.5CVb)^2}$$

All results were shown as the mean ± standard devia-

tion. Bias from the concentration between ultracentrifugation and other methods of removing lipids was presented as percentage deviation. The mean percentage deviation of each analyte was calculated as follows:
Deviation% = $[(C_x-C_n)/C_n]$ x 100%
C_n represents the means of results obtained by ultracentrifugation, and C_x represents the mean value of other methods of lipid removal in our study to be verified. If the deviation is less than the TCL, the method of lipid removal for that analyte is judged to satisfy the requirements of the quality control. If the deviation is greater than the TCL, the percentage variability is not acceptable. All data analyses were calculated by using Microsoft Excel.

RESULTS

Characteristics of the sample

All plasma was derived from emergency department patients, and the plasma was split into 4 equally divided parts. All samples were native serum, and patient samples without nutritional fat supplementation (total parenteral nutrition) were used for preparation. There were 12 cases of a lipid index of 4 (3.39 - 5.65 mmol/L; intralipid), 8 cases of a lipid index of 3 (2.26 - 3.38 mmol/L; intralipid), and 10 cases of a lipid index equal to 2 (1.13 - 2.25 mmol/L; intralipid). The intralipid related to the turbidity of lipemic blood samples. We measured the triglyceride concentration in serum samples with lipemic indices of 2, 3, and 4. The triglyceride concentration was 8.35 ± 6.35 mmol/L for a lipemic index of 2, 14.87 ± 7.88 mmol/L for a lipemic index of 3, and 16.36 ± 6.34 mmol/L for a lipemic index of 4.
The concentration of triglycerides in all samples was in the range of 5 - 20 mmol/L.

Performance in different methods of lipemia clearance

As shown in Table 2, the results of the measurements performed by ultracentrifugation, highspeed centrifugation, lipid scavenger, and dilution for lipemia removal were shown as the mean and standard deviation, and the deviation for each analyte was compared with TCL. When highspeed centrifugation was applied to remove the lipemic samples, we found that DBIL (18.62%, TCL = 5.60%) and Magnesium (6.09%, TCL = 3.82%) could not satisfy the criterion of TCL. Meanwhile, many analytes showed a robust stability, such as AMY, CRP, Glu, CK, BUN, calcium, and the deviations of high centrifugation were less than 1%. ALB, AST, ALP, CHE, and LDH had an inferior stability, and the biases were between 1% to 2%.
When lipid scavengers were applied to process the lipemic samples, the greatest bias was found for CRP (-86.70%, TCL = 21.97%), followed by CKMB (-44.85%, TCL = 13.98%), DBIL (37.96%, TCL = 5.60%), phosphates (14.32%, TCL = 3.62%), Glu (4.20%, TCL = 2.89%), and TP (8.29%, TCL = 2.01%), which could not satisfy the TCL criterion. Corresponding to the above analytes, the deviations of AST, CREA, phosphates, calcium, and magnesium were maintained at less than 1%. The biases of ALP, LDH, and calcium maintained between 1% and 2%. Regarding dilution, only half of the analytes could satisfy the criterion of TCL, including AMY (2.41%, TCL = 8.08%), CRP (5.54%, TCL = 21.97%), ALT (2.85%, TCL = 11.62%), GGTL (-1.73%, TCL = 4.19%), ALP (-0.04%, TCL = 10.86%), Glu (-0.84%, TCL = 2.89%), LDH (0.06%, TCL = 4.53%), CK (0.68%, TCL = 7.30%), BUN (3.80%, TCL = 5.60%), CREA (-1.54%, TCL = 4.54%), UA (5.42%, TCL = 6.72%), and magnesium (0.43%, TCL = 3.82%). The rest of the analytes could not satisfy the TCL by dilution.

DISCUSSION

Lipemia interference is a common source of laboratory error for emergency department pretreatment processes, and the frequency is higher than that of hemolysis or jaundice, especially in the emergency laboratory [11]. Verifying the feasibility of lipemia clearing in the emergency department is vital. In our study, highspeed centrifugation may be the best option for lipid removal in emergency laboratories. Only DBIL and Magnesium were not suitable for lipid removal by highspeed centrifugation. For CRP and CKMB, lipid scavengers were strictly prohibited to be used to remove lipids, and the measured values of the abovementioned two analytes were severely unreliable. TP, DBIL, Glu, and phosphates did not satisfy the threshold for the total change limit, when lipid scavengers were applied for lipid removal. Dilution may be the most inappropriate method for lipid clearance; nearly half of the analytes could not satisfy the threshold of the criterion.
When they compared the efficiency of highspeed centrifugation and ultracentrifugation, Saracevic et al. concluded that highspeed centrifugation should replace lipid scavengers for lipemia removal for Glu, phosphates, Magnesium, CKMB, ALP, GGT, ALB, CRP, and troponin T [9]. Dimeski et al. claimed that highspeed centrifugation could have the exact same effect as ultracentrifugation [12]. Calmarza et al. showed that calcium, phosphates, and TP could not satisfy the clinical requirement, when highspeed centrifugation was used [7]. Compared with the abovementioned conclusion, our study showed that Magnesium could not satisfy the criterion, and that the deviation exceeded 5%.
The advantage of lipid scavengers is that they do not require complicated equipment or cumbersome procedures. These advantages are indeed appropriate for emergency laboratories. However, as a type of polar solvent, lipid scavengers may have negative effects on the reaction system of many analytes [13]. Sada et al. published the first report about the clearance of lipid scavengers [14]. In their study, they demonstrated that sodium, TP, and phosphates have clinically significant

Table 1. Analytical methods used in the AU5800 and the evaluation criterion of the dispersion value.

Parameter	Abbreviation	Methodology	Step
Amylase	AMY (U/L)	Velocity method	2
C-reaction protein	CRP (mg/L)	Immunoturbidimetry	2
TP	TP (g/L)	Biuret method	2
Albumin	ALB (g/L)	Bromocresol green method	1
Total bilirubin	TBIL (µmol/L)	Diazo method	1
Direct bilirubin	DBIL (µmol/L)	Diazo method	1
Alanine aminotransferase	ALT (U/L)	Enzyme kinetic method	2
Aspartate aminotransferase	AST (U/L)	Enzyme kinetic method	2
Glutamylaminotransferase	GGTL (U/L)	Enzyme kinetic method	2
Alkaline phosphatase	ALP (U/L)	AMP buffer concentrate velocity method	2
Cholinesterase	CHE (U/L)	Enzyme kinetic method	2
Glucose	Glu (mmol/L)	Hexokinase method	2
Lactate dehydrogenase	LDH (U/L)	Velocity method (L - P)	2
Creatine kinase	CK (U/L)	Enzyme kinetic method	2
Creatine kinase isoenzyme MB	CKMB (U/L)	Enzyme kinetic method	2
Urea nitrogen	BUN (mmol/L)	Urease ultraviolet kinetic method	2
Creatinine	CREA (µmol/L)	Basic picric acid method	2
Uric acid	UA (µmol/L)	Uricase colorimetry	2
Calcium	Calcium (mmol/L)	Arsenazo III method	1
Magnesium	Magnesium (mmol/L)	Dimethyl aniline blue method	1
Phosphorus	Phosphorus (mmol/L)	Phosphomolybdate method	2

Table 2. Data for four different methods of lipid clearance.

Parameter	Ultracentrifugation	Highspeed centrifugation	Lipid scavenger	Dilution	TCL
AMY (U/L)	76.79 ± 10.27	76.18 ± 10.13 (-0.79%)	73.42 ± 10.01 (-4.39%)	78.64 ± 10.52 (2.41%)	8.08%
CRP (mg/L)	13.50 ± 6.39	13.57 ± 6.34 (0.51%)	1.80 ± 0.69 (86.70% *)	14.25 ± 6.30 (5.54%)	21.97%
TP (g/L)	74.31 ± 0.68	75.13 ± 0.73 (1.11%)	68.14 ± 0.74 (-8.29% *)	77.50 ± 1.11 (4.29% *)	2.01%
ALB (g/L)	43.20 ± 0.68	43.76 ± 0.71 (1.28%)	44.18 ± 0.69 (2.27%)	39.47 ± 0.92 (-8.65% *)	2.40%
TBIL (µmol/L)	7.92 ± 0.59	8.37 ± 0.64 (5.76%)	8.07 ± 0.57 (1.95%)	9.07 ± 0.64 (14.53% *)	9.10%
DBIL (µmol/L)	1.25 ± 0.16	1.48 ± 0.18 (18.62% *)	1.72 ± 0.20 (37.96% *)	2.22 ± 0.22 (77.85% *)	5.60%
ALT (U/L)	26.01 ± 2.88	27.42 ± 3.56 (5.44%)	25.46 ± 2.93 (-2.10%)	26.75 ± 2.77 (2.85%)	1.62%
AST (U/L)	27.29 ± 2.86	27.74 ± 2.97 (1.66%)	27.54 ± 2.96 (0.94%)	29.98 ± 2.79 (9.88% *)	6.80%
GGTL (U/L)	99.29 ± 43.23	102.28 ± 44.81 (3.01%)	95.82 ± 40.81 (-3.50%)	97.58 ± 42.35 (-1.73%)	4.19%
ALP (U/L)	111.50 ± 24.63	113.70 ± 24.79 (1.97%)	112.92 ± 24.89 (1.28%)	111.45 ± 24.39 (-0.04%)	10.80%
CHE (U/L)	10,040 ± 376.840	10,188.17 ± 377.57 (1.48%)	10,484.32 ± 398.89 (4.43%)	10,998.83 ± 449.77 (9.55% *)	7.65%
Glu (mmol/L)	7.35 ± 0.87	7.31 ± 0.88 (-0.68%)	7.66 ± 0.92 (4.20% *)	7.29 ± 0.93 (-0.84%)	2.89%
LDH (U/L)	226.72 ± 12.66	223.77 ± 12.45 (-1.30%)	223.31 ± 11.86 (-1.50%)	226.85 ± 12.32 (0.06%)	4.53%
CK (U/L)	131.59 ± 22.22	131.48 ± 22.34 (-0.09%)	128.95 ± 22.49 (-2.01%)	132.48 ± 23.59 (0.68%)	7.30%
CKMB (U/L)	15.11 ± 1.50	15.71 ± 1.62 (3.95%)	8.34 ± 0.96 (-44.85% *)	12.86 ± 1.73 (-14.91% *)	13.98%
BUN (mmol/L)	8.71 ± 1.48	8.76 ± 1.49 (0.52%)	9.14 ± 1.56 (4.84%)	9.04 ± 1.60 (3.80%)	5.60%
CERA (µmol/L)	170.33 ± 50.73	176.63 ±52.49 (3.70%)	170.90 ± 52.63 (0.34%)	167.70 ± 51.05 (-1.54%)	4.54%
UA (µmol/L)	494.67 ± 26.53	484.43 ± 26.98 (-2.07%)	517.43 ± 27.76 (4.60%)	521.50 ± 30.15 (5.42%)	6.72%
Calcium (mmol/L)	2.37 ± 0.02	2.39 ± 0.02 (0.97%)	2.34 ± 0.02 (-1.18%)	2.31 ± 0.03 (-2.45% *)	1.40%
Magnesium (mmol/L)	0.94 ± 0.017	0.99 ± 0.027 (6.09% *)	0.93 ± 0.017 (-0.32%)	0.94 ± 0.018 (0.43%)	3.82%
Phosphates (mmol/L)	1.32 ± 0.086	1.28 ± 0.08 (-2.80%)	1.51 ± 0.089 (14.32% *)	1.23 ± 0.086 (-6.89% *)	3.62%

The results of the values (means ± SD) for each parameter from highspeed centrifugation, dilution, ultracentrifugation sample, and lipid scavenger. The mean percentage of deviation between ultracentrifuged sample and other methods are shown in the next line of mean and standard deviation. * The asterisk indicates that those indicators exceed TCL's criteria and are, therefore, not suitable for this method of lipid removal.

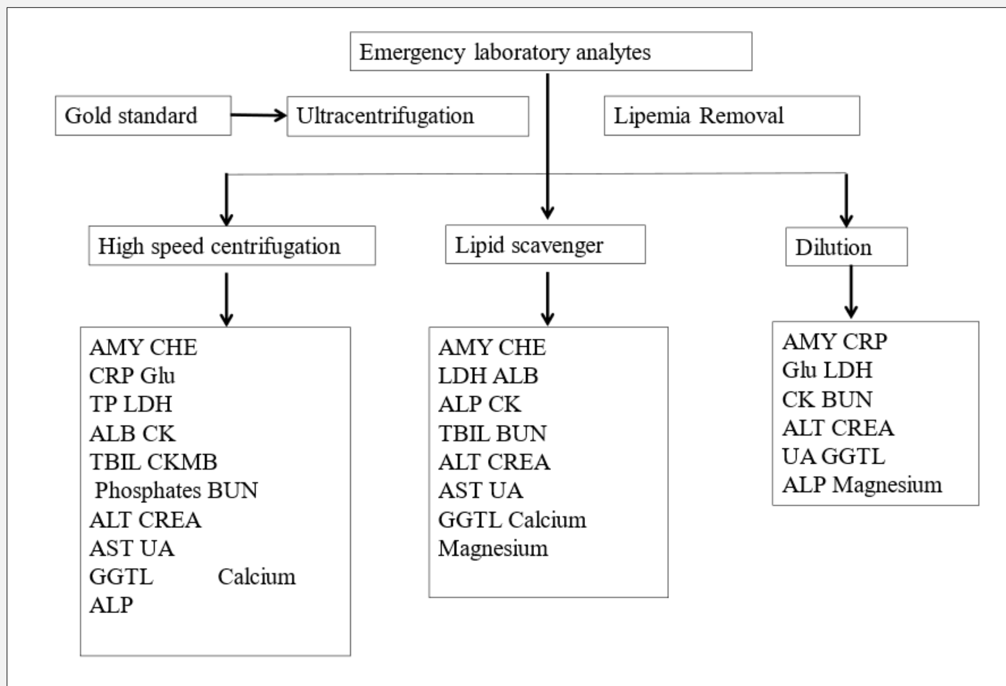

Figure 1. Clinical trial design.

errors when lipid scavengers are used. Anderson et al. found that lipid scavengers influence phosphates, but TP is not in the range of interference [15]. Vermeer et al. spiked Intralipid® into three types of serum pools to obtain 400 mg/dL of lipemia samples. They concluded that GGT, CRP, and CKMB could not recover after using lipid scavengers [16]. Gerard Steen et al. agreed with Vermeer et al. that CRP and DBIL were not applicable with LipoClear® [17]. Consistent with the above-mentioned conclusions, our study suggested that lipid scavengers should not be used for CRP and CKMB. And the data also showed that DBIL, phosphates, and TP also caused an unacceptable deviation. The CRP was used as an analyte in the AU5800 analyzer immunity transmission turbidity, and is the only analyte that was measured by turbidity in this study. Lipid scavengers may have an effect on the turbidity of the reaction. CKMB is also not suggested for application as a lipid scavenger, because lipid scavengers may affect the antigen-antibody reaction of CK-M monomers. DBIL could not attain clinical criteria in the AU5800 biochemical analyzer, regardless of the methods applied, possibly because DBIL had a very short linear scope. Phosphate reagents are a one-step procedure in AU5800 biochemical reactions. The reagents themselves have a deep background color. Lipid scavengers may affect the color of the original substrate. Immunosorbent reagents were not suitable for using lipid scavengers for lipid removal. Interference of lipid scavengers with CKMB measurements is now largely universally accepted. Lipid scavengers are equally ineffective for antigen-antibody binding and may affect immunology reaction systems.

Dilution seems to be superior to the other methods of lipemia removal for their turnaround time. With the development of automated biochemical analyzers, many instruments are equipped with auto dilution functions. Laboratory operators may blindly believe the results of automated dilution, and few may query the accuracy of the dilution. This study showed that TP, ALB, TBIL, DBIL, AST, CHE, CKMB, calcium, and phosphates should not be diluted to eliminate lipemia. However, some analytes, such as ALT, AST, TBIL, and DBIL, which are usually reviewed because of lipids, should be given more attention when these analytes enter the dilution revision state. Dilution could add to the imprecision of the results and have a matrix effect on the entire reaction system. Furthermore, chylomicrons still exist in the reaction system and affect scattered light or turbidity. Dilution was the worst performing of the three different methods for removing lipemia, and many analytes used by dilution should be rechecked by highspeed centrifugation or lipid scavengers.

There are some limitations to this study. First, only 30 lipemia samples were included in this study, so the sam-

ple size of lipemia should be expanded in further studies to obtain more accurate conclusions, and the subtypes of lipemia should be further subdivided. Second, this article mainly analyzed emergency laboratory analyses, and many analytes used to diagnose acute coronary syndrome and sepsis, such as cardiac troponin T (TNT) and procalcitonin (PCT), were not included in this study. Third, a greater variety of biochemical instruments with different models and methodologies should be included in further studies to obtain more comprehensive data.

In conclusion, the method of lipemia clearance should be based on the characteristics and the method of the analytes. As shown in Figure 1, lipid scavengers are not suitable for lipemia removal from samples for analytes like CRP, TP, DBIL, GLU, CKMB, and phosphates. Highspeed centrifugation was not suitable for Magnesium and DBIL. Nearly half of the analytes can satisfy the criterion for dilution, including AMY, CRP, ALT, GGTL, ALP, Glu, LDH, CK, BUN, CREA, UA, and magnesium.

Ethics Approval:

This study was approved by the Ethics Committee of the Zhongshan Hospital Xiamen University and is in accordance with the Declaration of Helsinki (2008).

Declaration of Interest:

The authors declare that they have no financial and personal relationships with other people or organizations that could inappropriately influence their work. There is no professional or other personal interest of any nature or kind in any product, service and/or company, that could be construed as influencing the position that they´re presented in or the review of the manuscript. All authors agreed to the submission, and they declare that the manuscript has neither been published in whole nor in parts nor has it been submitted anywhere else.

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