Lampiran 1. Penegasan tentang uji etik pada bab Metode

Lampiran 2. Bukti Komunikasi dengan Peer Review Jurnal:
The Effects of Plasma Prothrombine Time and Activated Partial Thromboplastin Time Based on Different Instruments and Methods

Lampiran 3. Bukti Kaji Etik Penelitian Jurnal:
The Effects of Plasma Prothrombine Time and Activated Partial Thromboplastin Time Based on Different Instruments and Methods

Lampiran 4. Bukti Komunikasi Peer Review Jurnal:
The Effects of Plasma Prothrombine Time and Activated Partial Thromboplastin Time Based on Different Instruments and Methods

Lampiran 5. Bukti Kaji Etik Penelitian Jurnal:
Diagnostic Value of Reticulocyte Hemoglobin and Soluble Transferrin Receptor in Determining The Iron Status of Chronic Kidney Disease with Hemodialysis Patients

Lampiran 6. Bukti Kaji Etik Penelitian Jurnal:
The stability of sample storage for complete blood count (CBC) toward the blood cell morphology

Lampiran 7. Bukti Kaji Etik dan Figure Tampilan Bukti Pemeriksaan Leukosit CD64

The effect of free hemoglobin produced by hemolysis can result in analytical and biological changes. High absorbance will be caused by cell-free hemoglobin from hemolysis at wavelengths used by photo-optical method instruments. Release of cytoplasmic and plasma membrane molecules (e.g., tissue factor, proteases, phospholipids, and adenosine diphosphate) can spuriously activate blood coagulation and platelets.[4] The CLSI guidelines for PPT and APTT testing states: "Samples with visible hemolysis should not be used because of possible clotting factor activation and interference with endpoint measurement."[9]

The Sysmex CS-2100i is a coagulometer that uses the photo-optical method. It minimizes pre-analytical errors by using multi-wavelength scanning and sample liquid-sensing technologies. By using smartly designed PSI technology, the analyzers provide extra operator support; they identify and automatically manage potentially problematic test samples before analysis.[10] According to Tantanate et al,[11] Sysmex CS-2100i (Siemens, Kobe, Japan) is capable of performing good analysis on samples with interference from hemolysis, icterus, and lipemia. The aims of this study were to determine the effect of hemolysis on PPT and APTT tests and to find the plasma hemoglobin cut-off point that could affect the test results. This study may help to reevaluate the policy of rejecting hemolyzed blood samples for coagulation testing.

2. Methods

2.1. Study samples

This study was conducted between November 2014 and February 2015 in the Clinical Pathology Laboratory of the Dr Soetomo General Hospital in Surabaya, Indonesia. The total number of samples was 30 blood samples, which were taken from remaining citrate blood plasma of patients who had been examined for PPT and APTT as part of routine examinations. The inclusion criteria were nonhemolyzed blood samples that had apparently clear plasma, normal PPT and APTT test results, and no icteric and lipemic plasma that could have interfered with the results. Ethical approval was not required because this research had no interaction with the patient and the goal was to create a local laboratory policy on rejection of hemolyzed samples. Informed consent was not required because this research used the remaining samples of patients who were already the subjects of PPT and APTT assays. Age, sex, and patient diagnosis data were recorded from the job list form.

2.2. Methods

This study was an experimental laboratory research project with pre-test and post-test design. The data of PPT and APTT patients who fulfilled inclusion criteria were recorded as baseline data. The remaining samples were then mechanically lyzed by inserting blood into a 3 mL disposable syringe fitted with a 23G needle and then vigorously expelled 2 to 3 times. This procedure resulted in lysis of erythrocytes and measured plasma hemoglobin of <0.8 g/dL. The blood samples next underwent further lysis by expelling with stronger pressure for a total of 4 to 5 times. This resulted in measured plasma hemoglobin of ≥0.8 g/dL. This procedure is a modification of the method proposed by Arora et al[7] and was chosen because the most common cause of hemolysis is mechanical factors occurring during the venipuncture or transportation processes. Determination of plasma hemoglobin was with reference to a level of 0.8 g/dL because this is the limiting level of plasma hemoglobin that will influence the result of APTT according to the Sysmex CS-2100i application sheet.[12] To examine the plasma hemoglobin, lyzed blood samples were centrifuged at 300 rpm for 15 minutes, and then the supernatant was examined for hemoglobin plasma level using a Sysmex XN-1000 (Siemens) hematology analyzer.

Samples were separated according to plasma hemoglobin level. Samples with plasma hemoglobin level <0.8 g/dL belonged to group 1 (n = 30) and samples with plasma hemoglobin level ≥0.8 g/dL belonged to group 2 (n = 30). Both groups were then reexamined for PPT and APTT after hemolysis. All examinations were performed no later than 2 hours after phlebotomy to maintain the stability of coagulation factors. Examinations were performed by the photo optical method using a Sysmex CS-2100i (Siemens) instrument. The reagents used were Dade Actin FSL Activated PTT for APTT and Dade Innovin for PPT. The normal value for PPT was 9 to 12 seconds and APTT was 23 to 33 seconds. The examination of plasma hemoglobin level was performed using Sysmex XN-1000 (Siemen) hematology analyzer. Quality control of this instrument was performed twice a day, in the morning and afternoon, using a plasma control from Sysmex and then once a day with pooled normal plasma.

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. The difference between PPT and APTT values between and within groups was tested with repeated-measures analysis of variance (ANOVA) or Friedman measurements with post hoc tests depending on data distribution. The Shapiro Wilk test was applied to test the data normality. The effect of plasma hemoglobin level on PPT and APTT was analyzed with a linear regression test. The descriptive data were presented as mean ± SD. The receiver operating characteristic (ROC) analysis was applied to evaluate the sensitivity and specificity of plasma hemoglobin levels that could affect PPT and APTT examinations using a confidence interval of 95%. The value of $P < .05$ was considered as statistically significant.

3. Results

The age, sex, and diagnosis of the sample subjects are summarized in Table 1. The age of the patients ranged between 2.6 and 68 years. The diagnoses were variable. However, this did not affect the PPT and APTT value. The mean ± SD of baseline PPT and APTT assays were in the normal range of 10.54 ± 0.67 for PPT and 28.44 ± 2.54 for APTT (Table 2). All groups of PPT and APTT were within normal distribution, so the data were analyzed with repeated-measures ANOVA test. The result of repeated-measures ANOVA test for either PPT or APTT was significant with $P < .001$ for comparison between the groups.

For PPT assays test, the difference of each group was significant except PPT between group 2 and baseline ($P = .14$). The PPT of group 1 had a significantly shorter time than the baseline ($P = .002$) and group 2 ($P = .000$). For APTT assays, group 1 had a significantly shorter APPT than the baseline ($P = .000$), as did group 2 ($P = .000$). In addition, group 2 demonstrated significantly shorter times than group 1 ($P = .003$). The mean ± SD and significance of PPT and APTT results are summarized in Tables 2 and 3.

Linear regression was performed to test the effect of hemolysis on PPT and APTT assays. Therefore, we included all samples in group 1 and 2 to be analyzed. The result for PPT was not significant, $R = 0.294$; $P = .06$. While result for APTT was significant, $R = 0.245$; $P = .02$. The scatter of curve and regression equations is shown in Fig. 1.

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The effects of hemolysis on plasma prothrombin time and activated partial thromboplastin time tests using photo-optical method

Yetti Hernaningsih, MD, PhD[a,*], Jeine Stela Akualing, MD[b]

Abstract

Hemolysis is the most common reason why coagulation test samples are rejected. However, the effects of hemolysis on plasma prothrombin time (PPT) and activated partial thromboplastin time (APTT) are rarely investigated and the results are controversial. This research aims to analyze the effects of hemolysis on PPT and APPT using the photo-optical method.

Nonhemolyzed citrate blood samples (n = 30) with normal PPT and APTT underwent 2-step mechanical lysis and then hemoglobin level measurement was carried out at each step. The first lysis was mild to moderate resulting in a hemoglobin level of <0.8 g/dL. These samples were labeled as group 1. The second step showed more severe lysis, which resulted in a plasma hemoglobin level of ≥0.8 g/dL. These samples were labeled as group 2. Analysis was carried out on the PPT and APTT differences between the 2 groups and baseline, as well as between group 1 and group 2 using repeated-measures analysis of variance (ANOVA). The effects of hemolysis were analyzed using linear regression. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value in PPT and APTT.

Significantly shorter APTT was measured for group 1 than baseline, ($P = .000$), group 2 than baseline ($P = .000$), and group 2 than group 1 ($P = .003$). With regard to PPT results, those for group 1 were significant shorter than baseline ($P = .002$), while those for group 2 were significantly longer than group 1 ($P = .000$). In the correlation assay, the level of hemolysis revealed a mildly significant correlation to APTT ($R = 0.245$; $P = .02$). Cut-off value for PPT was 1.55 g/dL (100% sensitivity and 87.9% specificity), while the value for APTT was 0.95 g/dL (75% sensitivity and 62.5% specificity).

Not all hemolyzed samples should be rejected for PPT and APTT tests using photo-optical methods.

Abbreviations: APTT = activated partial thromboplastin time, CLSI = Clinical and Laboratory Standard Institute, D = standard deviation, HGB = hemoglobin, OD = optical density, PPT = plasma prothrombin time, ROC = receiver operating characteristic.

Keywords: activated partial thromboplastin time, hemolysis, plasma hemoglobin, plasma prothrombin time, Sysmex CS-2100i

1. Introduction

Plasma prothrombin time (PPT) and activated partial thromboplastin time (APTT) are coagulation tests routinely performed in laboratories to evaluate the function of the coagulation system. The PPT test measures the extrinsic pathway, while APTT measures the intrinsic pathway activities. Both coagulation function tests are affected by preanalytical factors such as the venipuncture process, the dose of citrate anticoagulant, sample transportation, processing, and storing. The interference of hemolysis, icterus, and lipemia are the main problems in coagulation tests that use photooptical detection methods. Errors in preanalytical and analytical phases may interfere with the reliability of results.[1–5]

There are 2 main methods of coagulation measurements, namely the photo-optical method and mechanical method. The optical method detects clot formation through changes in optical density (OD) of the sample. Mechanical clot technology detects clot formation by monitoring the movement of a steel ball inside the test sample using a magnetic sensor.[6]

Hemolyzed blood samples will cause spectral interference in photo-optical method instruments; therefore, this is the most common reason why coagulation tests are rejected. According to the Clinical and Laboratory Standard Institute (CLSI), blood samples that show apparent hemolysis may undergo premature coagulation activity and also disrupt the clot detection by the optical instruments.[3,5]

The rejection of hemolyzed blood samples has become a policy that is applied in most laboratories, hence studies on the effect of hemolysis on coagulation tests have been rare and the results are still controversial. The consequence of hemolyzed blood sample rejection is repeat blood sample collection that causes additional discomfort to patients, delayed test results, and increased laboratory operating costs.[7]

Laga et al[8] in their study explained their findings that PPT and APTT between hemolyzed and nonhemolyzed blood samples did not differ significantly. Arora et al[7] argued that hemolyzed blood samples could be processed for coagulation tests because there was no significant difference between hemolyzed and nonhemolyzed blood samples.

Editor: Wael Alkhiary.

The authors have no conflict of interest.

[a] Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Jawa Timur, [b] Clinical Pathology Laboratory, Tobelo General Hospital, North Halmahera, Indonesia.

* Correspondence: Yetti Hernaningsih, Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Jl. Mayjend Prof. Dr. Moestopo 47 Surabaya, Jawa Timur 60132, Indonesia (e-mail: yetti-h@fk.unair.ac.id).

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Trs: Medicine® MD-D-16-04882: Editor Decision

jeine stela <jeine_stela@yahoo.co.id>
Reply-To: jeine stela <jeine_stela@yahoo.co.id>
To: "yettihernaningsih@gmail.com" <yettihernaningsih@gmail.com>

Sun, Jan 15, 2017 at 6:35 AM

Pada Senin, 31 Oktober 2016 22:11, Medicine <em@editorialmanager.com> menulis:

REQUEST FOR REVISION

Oct 31 2016 11:11AM

RE: MD-D-16-04882, entitled "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method".

Dear Dr Akualing:

Your manuscript has been carefully reviewed, and the reviewer/editorial comments and queries are listed below. Revision and response is necessary before the paper can be considered for further review.

Please submit the revised manuscript via Editorial Manager by Dec 12 2016 11:59PM. If you are unable to revise within this time, please contact the Editorial Office with a request for an extension or your paper will be removed from the editorial process. A request for an extension must be submitted within 60 days of the date of this letter.

All revised manuscripts must include an itemized, point-by-point response to each reviewer, including the reviewer's original comment(s). Specify the changes made to address each of their concerns; include the changes made in the response or indicate their locations in the manuscript. Address each reviewer comment using the reviewer's number. Submit this "Response to Reviewers" as a separate document when uploading the requisite files in the system.

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We look forward to receiving your revised manuscript.

Best Regards,

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COMMENTS TO AUTHOR:

Reviewer #2: This paper is to study the effects of hemolysis on PT and APTT using Photo-Optical Method, and it found that not all hemolyzed samples should be rejected for PPT and APTT is valuable for laboratories to set policy of rejection of hemolysis samples. Although the effect of hemolysis on PT and APTT is still controversial, its impact has become a consensus. A more comprehensive study of the effects of coagulation function should be studied so as to the results are more valuable for clinical applications.

1.The policy of rejection of hemolytic samples according to the effect of indexes on coagulation should be considered comprehensively. Why only PT and APTT were chosen as the research object? It is suggested that the common indicators of coagulation function that TT and FIB should be added to research content, so that the clinical value was greater.

2.The basic information of study population was not given, such as age, sex, and admission diagnosis.

3.The description of the grouping is not clear; please describe the whole grouping process in detail, so as to facilitate the understanding of the results of the subsequent statistical analysis. Why 0.8 g/dL is as separation? Is it from "Sysmex® CS-2100i provides a quite good performance on hemolytic samples and is not affected until the plasma hemoglobin level is 0.8 g/dL [9,10].", please cite the reference in method.

4.Is the method of mechanical hemolysis cited the reference or a standard protocol?
Otherwise, the processing method itself will not affect the results of the study should be proven.

5. Regression linear results are derived from the detection of all the hemolysis samples, please describe in the method.

6. The appropriate description should be added to the figs. and tables.

7. The performance on hemolytic samples by different Coagulation Analysators using Photo-Optical Method should be discussed briefly.

Reviewer #5: The authors investigate the impact on mechanically induced in vitro hemolysis on PPT and aPTT tests. The authors further aimed to determine level of hemolysis, when free hemoglobin levels start to have a significant effect on coagulation test. The investigated topic is of practical importance. However, understanding the paper is sometimes difficult, because English language is not properly used.

Major comments:
1. English language should be thouroghly edited by a native English speaker.
2. Informed consent, IRB approval: it is not clear, whethter the study had approval of the responsible IRB and whether the patients provided informed consent. Please provide details.
3. Methods: the authors include 30 nonhemolyzed samples (as stated in the study samples paragraph) with normal PPT and aPTT times. In the methods section, it is stated that two groups with each 30 samples were assembled. It is not clear to me how the 2 groups wer put together. Please clarify. Maybe a flow chart of what was done could help readers to understand better what has been done.
4. Statistics: In my eyes, statistics are not properly used. Values are compared before and after lysing. This would mean that these are not independent observations. I suggest to use ANOVA repeated measures ANOVA or the Friedman repeated measures test.
5. Table 2: Since I can not figure out how groups 1 and 2 were put together, I do not understand what was compared here. Please clarify.

Minor comments
1. Ref 14: format could be ameliorated.

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #2: Partly

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Partly

Please explain (optional).

Reviewer #2: The policy of rejection of hemolytic samples according to the effect of indexes on coagulation should be considered comprehensively. Why only PT and APTT were chosen as the research object? It is suggested that the common indicators of coagulation function that TT and FIB should be added to research content, so that the clinical value was greater.

Reviewer #3: The authors have revisited the subject of the suitability of using partially hemolysed samples for PPT and aPTT tests. Though this is has been studied and reported several times over the last two decades, the authors of this manuscript have studied samples with two levels of hemolysis and, applied appropriate statistics to prove their hypothesis.

Reviewer #4: (No Response)

Reviewer #5: (No Response)

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2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #2: Yes

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #2: The description of the grouping is not clear; please describe the whole grouping process in detail, so as to facilitate the understanding of the results of the subsequent statistical analysis.

Reviewer #3: Appropriate statistics have been used. One way ANOVA has been appropriately applied to compare PPT and aPTT for non-hemolysed, <0.8 g/dL and ≥0.8 g/dL hemolysis. However, once statistical significant difference is seen, comparison between two groups at a time should be by paired t-test, since the study is comparing the PPT and aPTT parameters before hemolysis and after hemolysis. The authors should see if this can be done and indicated in Table 2.

Further, the correlation coefficients with p values and regression equation for the scatter plots may be given. This will show the extent of association between degree of hemolysis and decrease in aPTT.

Reviewer #4: (No Response)

Reviewer #5: (No Response)

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3. Does the manuscript adhere to standards in this field for data availability?

Authors must follow field-specific standards for data deposition in publicly available resources and should include accession numbers in the manuscript when relevant. The manuscript should explain what steps have been taken to make data available, particularly in cases where data cannot be publicly deposited.

Reviewer #2: No

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Yes

Please explain (optional).

Reviewer #2: The basic information of study population was not given, such as age, sex, and admission diagnosis.

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)

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4. Is the manuscript presented in an intelligible fashion and written in standard English?

Medicine does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors below.

Reviewer #2: Yes

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #2: the manuscript was presented in an intelligible fashion and written in standard English.

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)

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5. Comments to Author (required)

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Reviewer #3: The study, though a subject of debate for many years, is a good one but the statistics applied may be made more rigorous by applying the paired t-test for comparing PPT between non-hemolysed and <0.8 g/dL hemolysis, between non-hemolysed and ≥0.8 g/dL hemolysis and, between <0.8 g/dL and ≥0.8 g/dL hemolysis. Correlation analysis for data plotted in figures 1 and 2 should be included.

Reviewer #4: This is a very interesting article in laboratory medicine field, technology study is

important for laboratory tests. The authors investigate the influence of hemolysis for PT and APTT, the effective conclusions has guiding significance for clinical laboratory doctor. The manuscript can be accepted, if the authors successful address the following comments.

1 why the authors choose plasma hemoglobin level of 0.8 g/dL as standard for grouping of hemolysis specimen? Is there a document to support this standard (0.8 g/dL)? Or, when the other hemoglobin concentrations for this grouping of hemolysis specimen, whether PT and APTT still maintain statistically significant? This is a major defect for this article.

2 All samples were from patients with normal PT and APTT, however, whether hemolysis has the influence of for PT and APTT in the samples with abnormal PT and APTT, it is not clear, at least it is a defect for the entire study design.

3 The description in introduction should be further enriched, and reference to previous researchs.

4 Add the results in thrombin time (TT), fibrinogen (FIB) test, and compared with before and after hemolysis, the results may be more interesting.

5 In the method section, exclusion criterias are missing.

6 More sample information should be included such as age, gender and body mass index, since these factors may affect the test results in PT and APTT.

Reviewer #5: The authors investigate the impact on mechanically induced in vitro hemolysis on PPT and aPTT tests. The authors further aimed to determine level of hemolysis, when free hemoglobin levels start to have a significant effect on coagulation test. The investigated topic is of practical importance. However, understanding the paper is sometimes difficult, because English language is not properly used.

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5. Table 2: Since I can not figure out how groups 1 and 2 were put together, I do not understand what was compared here. Please clarify.

Minor comments
1. Ref 14: format could be ameliorated.

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6. If you would like your identity to be revealed to the authors, please include your name here

(optional).

Your name and review will not be published with the manuscript.

Reviewer #2: (No Response)

Reviewer #3: M.G.R. Rajan

Reviewer #4: (No Response)

Reviewer #5: (No Response)

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-List of abbreviations: If not already included, please include a list of abbreviations used in the text as part of the manuscript text file following the title page. Use abbreviations sparingly in the text, and spell them out the first time you use them. Abbreviations used in tables should be spelled out at the bottom of the table.

-Ethical review, Methods section: If not already included, please state in the Methods section that an ethics committee or institutional review board approved the study, and list the board's name. If ethical approval was waived or not necessary, please state the reason. If the study involves patient consent, state explicitly that informed consent was or was not given, and state the reason if not given.

-Funding/Conflict of Interest information: List any source of funding or anything that could be perceived as a conflict of interest in the Acknowledgments section.

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RE: Need extension time for revision MD-D-16-04882

medicine <medicine@wolterskluwer.com> Mon, Mar 20, 2017 at 11:34 PM
To: yetti hernaningsih <yettihernaningsih@gmail.com>

Dear Dr Yetti,

A new revision due date has been entered for the above-referenced submission to Medicine®: Apr 19 2017 11:59PM.

Please make note of the updated deadline.

If you have any questions, please feel free to contact the Editorial Office by replying to this message.

Kind Regards,

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Sent: Sunday, March 19, 2017 12:52 PM
To: medicine <medicine@wolterskluwer.com>
Subject: Need extension time for revision

Dear Patrick Wall

The Editor of Medicine,

I am so sorry for our delaying response to your email about our manuscript revision (Oct 31st 2016) with title: The Effect of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tset Using Photo Optical Method.

First, I have to inform you that dr. Akualing who was corresponding author for our manuscript had mover her office to hospital in Ternate, small island in the end of Indonesia since early October 2016. It caused missing contact between me and her.

Moreover, she had being busy with her hospital accreditation process and prepare her new baby birth. Therefore we have a deal that corresponding author was changed to me, Yetti Hernaningsih, with my email address: yettihernaningsih@gmail.com.

Related with revision of our manuscript, kindly would you give us extension time until 1 month later (April 19th 2017) for revising our manuscript? I hope you would reply me. Thank you for your understanding

Best regards,

Yetti

---

yetti hernaningsih <yettihernaningsih@gmail.com> Tue, Mar 21, 2017 at 5:26 PM
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Thank you very much for your kindness, I note the deadline

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To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

RECEIPT ACKNOWLEDGEMENT

RE: MD-D-16-04882R1
"The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih:

Your revised manuscript has been received by the Medicine® Editorial Office.

Thank you for submitting your revision. The editors will consider the changes and let you know their decision as soon as possible.

With best wishes,

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Your PDF for The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method requires approval

Medicine <em@editorialmanager.com> Thu, Apr 20, 2017 at 1:47 AM
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

PDF REQUIRES APPROVAL

Apr 19 2017 2:47PM

RE: "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih:

The PDF for your submission, "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method," is ready for approval.

If you have not already, please view the PDF file then edit the submission if it needs additional changes, or approve the PDF. This will complete the submission process so the manuscript will be transmitted to the Medicine editorial office.

Use the information below to log into the system at any time to check the status of your submission.

Best regards,

Medicine® Editorial Office
medicine@wolterskluwer.com

Login Information:
http://www.editorialmanager.com/md
Your username is: yetti3210
Your password is: available at this link http://MD.edmgr.com/Default.aspx?pg=accountFinder.aspx&firstname=Yetti&lastname=Hernaningsih&email_address=yettihernaningsih@gmail.com

---

Medicine <em@editorialmanager.com> Thu, Apr 20, 2017 at 2:10 AM
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

PDF REQUIRES APPROVAL

Apr 19 2017 3:10PM
[Quoted text hidden]

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MD-D-16-04882R1: Your Revised Manuscript Has Been Received

Medicine <em@editorialmanager.com> Thu, Apr 20, 2017 at 2:15 AM
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

RECEIPT ACKNOWLEDGEMENT

RE: MD-D-16-04882R1
"The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih:

Your revised manuscript has been received by the Medicine® Editorial Office.

Thank you for submitting your revision. The editors will consider the changes and let you know their decision as soon as possible.

With best wishes,

Medicine® Editorial Office
E-mail: medicine@wolterskluwer.com

Login Information:
http://www.editorialmanager.com/md
Your username is: yetti3210
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Gmail

Please Correct Your Submission to Medicine® MD-D-16-04882R1

Medicine <em@editorialmanager.com>
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

Wed, Apr 26, 2017 at 1:53 AM

re: "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"
MD-D-16-04882R1%

Apr 25 2017 02:53PM

Dear Dr Hernaningsih:

Your submission has been received by the journal Medicine®, but corrections to meet the journal's preferred format are required before the manuscript can be processed.

Please address the following concerns and resubmit your paper:

- Please include a list of abbreviations used in the text as part of the manuscript text file following the title page. Use abbreviations sparingly in the text, and spell them out the first time you use them. Abbreviations used in tables should be spelled out at the bottom of the table.
-: Please state in the manuscript (in the Methods section, if applicable) that an ethics committee or institutional review board approved the study, and list the board's name.
* If ethical approval was waived or not necessary, please state the reason. If the study involves patient consent, state explicitly that informed consent was or was not given, and state the reason if not given.
- Please upload each table and figure as a separate, individual file.
-Figure 3 is cited in the manuscript, but the file is missing.
- Please include all figure legends at the end of the main manuscript document.

Log in to Editorial Manager as an Author, using the log in information below, to make the requested correction(s) and resubmit your paper.

Go to the menu item "Submissions Sent Back To Author" to locate the submission. You may then view your submission, edit your submission, re-build the PDF, and approve the changes. After this process, the submission will be returned to the Editorial Office for review.

Please refer to the Instructions for Authors PDF for detailed guidelines for submission.

Let me know if you have any questions or concerns. Thank you for submitting your work to Medicine®.

With best wishes,

Medicine® Editorial Office
E-mail: medicine@wolterskluwer.com

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Thank you for submitting to the journal Medicine®

Medicine <em@editorialmanager.com>
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

Sat, Apr 29, 2017 at 12:41 AM

RECEIPT ACKNOWLEDGMENT

Apr 28 2017 01:41PM

RE: "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"
MD-D-16-04882R1

Dear Dr Hernaningsih:

Thank you for submitting your manuscript to Medicine®.

For new submissions: Your manuscript number is MD-D-16-04882R1. Please use this number in all future correspondence regarding this manuscript.

For transferred submissions: You will receive a manuscript number in a later note from the editorial office.

Please note all submissions undergo a "technical check" prior to official assignment to an Academic Editor. Some formatting changes may be requested.

Thank you for your support of the journal.

Sincerely,

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E-mail: medicine@wolterskluwer.com

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Gmail

All initial reviews are complete for MD-D-16-04882R1

Medicine <em@editorialmanager.com>
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

Tue, May 16, 2017 at 1:34 AM

AUTHOR NOTIFICATION OF COMPLETED REVIEWS

May 15 2017 02:34PM

RE: MD-D-16-04882R1, entitled "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih:

All of the initial requested reviews for your submission have been received; however, further reviews may be necessary.

You will be notified of the editorial decision regarding the submission as soon as it is received.

Sincerely,

Medicine® Editorial Office
E-mail: medicine@wolterskluwer.com

Login Information:
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Medicine® MD-D-16-04882R1: Editor Decision

Medicine <em@editorialmanager.com> Thu, May 25, 2017 at 1:18 AM
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

REQUEST FOR REVISION

May 24 2017 02:18PM

RE: MD-D-16-04882R1, entitled "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih:

Your manuscript has been carefully reviewed, and the reviewer/editorial comments and queries are listed below. Revision and response is necessary before the paper can be considered for further review.

Please submit the revised manuscript via Editorial Manager by Jul 05 2017 11:59PM. If you are unable to revise within this time, please contact the Editorial Office with a request for an extension or your paper will be removed from the editorial process. A request for an extension must be submitted within 60 days of the date of this letter.

All revised manuscripts must include an itemized, point-by-point response to each reviewer, including the reviewer's original comment(s). Specify the changes made to address each of their concerns; include the changes made in the response or indicate their locations in the manuscript. Address each reviewer comment using the reviewer's number. Submit this "Response to Reviewers" as a separate document when uploading the requisite files in the system.

Authorship

Medicine® considers the final author list to be complete at the time of the first revision submission. Please be sure to check that all authors are properly listed on the revision submission, this includes the spelling of an author's name, their designated degrees, and order of authors listed.
Medicine® has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

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* If your manuscript is accepted for publication, payment of the article processing charge (APC) must be completed by visiting: http://wolterskluwer.qconnect.com. Upon entering the site for the first time, authors will be prompted to create a user ID and password. The APC for *Medicine*® is $1400 for the Creative Commons 4.0 International licenses, with the exception of the CCBY license, which is $1750. The publication fee must be paid within 30 days of article acceptance by credit card by the author, funding agency, or institution. Payment must be received in full for the article to be published.

To submit your revision, go to http://www.editorialmanager.com/md and login as an Author. Click on the menu item "Submissions Needing Revision" to obtain your submission record and begin the revision process.

We look forward to receiving your revised manuscript.

Best Regards,

Medicine® Editorial Office
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COMMENTS TO AUTHOR:

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Yes

Please explain (optional).

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)

---

2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #3: The use of paired t-test between two groups at a time is appropriate. However, the authors can also mention the results of the one-way ANOVA, which they have carried out. My comments were not to substitute paired-t test in place of ANOVA, but to do the paired t-test, after ANOVA. ANOVA results can be a part of the Table 3. ANOVA results are shown by arranging he mean values of the groups in ascending order and underlining the means that are not statistically different, i.e., where $p>0.05$. This is the conventional method of reporting one way ANOVA results.

Reviewer #4: (No Response)

Reviewer #5: (No Response)

---

3. Does the manuscript adhere to standards in this field for data availability?

Authors must follow field-specific standards for data deposition in publicly available resources and should include accession numbers in the manuscript when relevant. The manuscript should explain what steps have been taken to make data available, particularly in cases where data cannot be publicly deposited.

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Yes

Please explain (optional).

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)

---

4. Is the manuscript presented in an intelligible fashion and written in standard English?

Medicine does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors below.

Reviewer #3: No

Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #3: The Authors have made an effort to get the manuscript whetted for standard English, yet there is much

lacking in the English language used. The authors should look into this. Incorrect English usage should not result in misinterpretation of the methods and results study.

Reviewer #4: (No Response)

Reviewer #5: (No Response)

---

5. Comments to Author (required)

Reviewer #3: The Authors have made considerable efforts to incorporate the suggestions from the Reviewers. Most of the technical queries have been addressed, but the use of English language needs improvement to avoid misinterpretation of results.

Reviewer #4: I agreed with the paper to publish in Medicine.

Reviewer #5: The authors have taken into account the reviewer suggestions. I still have some comments to be addressed.

Major comments:

1. The authors investigate 30 samples at three timepoints: at baseline, after introducing mild hemolysis, and after introducing stronger hemolysis. This is a comparison of more than 2 groups. A paired t-test is not the method of choice for this statistical problem. A repeated measures ANOVA or a Friedman test is the suitable statistical test for this kind of analysis. Comparison of groups can be post hoc by means of several tests.

2. I still suggest language editing. An example, second sentence in the results section: "The diagnosis was vary but did not affect the PPT and APTT value."

3. The ROC-curve analysis is not clear to me: was the outcome alteration of PPT? How would that alteration be defined? Sensitivity and specificity to exert an effect of hemolysis on PPT change? This seems not clear to me. Is this kind of analysis appropriate to the problem in question? Please explain more in detail, what has been done.

---

6. If you would like your identity to be revealed to the authors, please include your name here (optional).

Your name and review will not be published with the manuscript.

Reviewer #3: M.G.R. RAJAN

Reviewer #4: (No Response)

Reviewer #5: (No Response)

Editorial Formatting Comments

-Title page: Be sure the title page lists all author names, degrees, and affiliations.

-Title: Be sure the title includes any specific terms as directed in the reporting guidelines for your type of article (for example, "case report" should be in the title of a CARE-compliant article). The following guidelines specify terms that

should be in the title: CARE, CHEERS, CONSORT, PRISMA.

-Abstract: Be sure to use a structured abstract, with headings. Use the specific headings listed in the guidelines checklist if your report is based on the CARE, CHEERS, CONSORT, or PRISMA guidelines.

-List of abbreviations: If not already included, please include a list of abbreviations used in the text as part of the manuscript text file following the title page. Use abbreviations sparingly in the text, and spell them out the first time you use them. Abbreviations used in tables should be spelled out at the bottom of the table.

-Ethical review, Methods section: If not already included, please state in the Methods section that an ethics committee or institutional review board approved the study, and list the board's name. If ethical approval was waived or not necessary, please state the reason. If the study involves patient consent, state explicitly that informed consent was or was not given, and state the reason if not given.

-Funding/Conflict of Interest information: List any source of funding or anything that could be perceived as a conflict of interest in the Acknowledgments section.

-Acknowledgments: If you list anyone by name in the Acknowledgments section, please confirm that the person gives permission to be named.

-License to Publish: If not already submitted, complete and submit a copy of the Open Access-License to Publish (LTP). The LTP is available to download from the home page of our website, under Forms. Be sure to select the kind of license you would like to use if the paper is accepted. (The different kinds of licenses determine how others can use your work after publication, varying from not restrictive at all to very restrictive.) Fill out all schedules (parts of the form). The corresponding author can sign the form on behalf of all authors; we need only one copy of the form. The form can be filled out and signed electronically, then uploaded as a submission item.

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Medicine® MS# MD-D-16-04882R2: Editor Decision

Medicine <em@editorialmanager.com> Fri, Aug 11, 2017 at 10:45 PM
Reply-To: Medicine <medicine@wolterskluwer.com>
To: Yetti Hernaningsih <yettihernaningsih@gmail.com>

CC: jeine_stela@yahoo.co.id

ACCEPTANCE NOTIFICATION

RE: MD-D-16-04882R2, entitled "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"

Dear Dr Hernaningsih,

It is a distinct pleasure to inform you that your manuscript has been accepted for publication in Medicine®.

* Per journal office policy, please note editorial changes may be made to your manuscript to conform to the journal's established style. These changes will be grammatical and stylistic changes only.

* Payment of the article processing charge (APC) (or a request for an invoice) must be completed by visiting: http://wolterskluwer.qconnect.com. Upon entering the site for the first time, authors will be prompted to create a user ID and password.

* Once payment of the APC is received (or an invoice is requested), proofs of the article should be distributed within 4-5 weeks.

Thank you for contributing this notable addition to academic literature through the vehicle of Medicine®!

Sincerely,

Medicine® Editorial Office
E-mail: medicine@wolterskluwer.com

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yetti hernaningsih <yettihernaningsih@gmail.com> Thu, Aug 17, 2017 at 9:28 PM
Draft To: "adm@ppjpi.unair.ac.id" <adm@ppjpi.unair.ac.id>

[Quoted text hidden]

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Return proof article

yetti hernaningsih <yettihernaningsih@gmail.com>
To: medicine <medicine@wolterskluwer.com>

Sun, Sep 10, 2017 at 6:17 PM

Article: MD-D-16-04882R2 (The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method)

Dear Editor,

Here I return my approval article. (attach file)

Thank you very much

Best regards,

Yetti Hernaningsih

Proof MD-D-16-04882.pdf
332K

MD

Manuscript No. MD-D-16-04882

MEDICINE

Dear Author,

During the preparation of your manuscript for typesetting, some queries have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin as neatly as possible or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to the Production Editor.

QUERIES: to be answered by AUTHOR/EDITOR?

QUERY NO.	QUERY DETAILS	RESPONSE
<AQ1>	Please confirm whether surnames/family names (red) have been identified correctly in the author byline.	<AQ1>Corrrection for coathor: Jeine Stela Akualing
<AQ2>	Please check and confirm authors' affiliations for correctness.	<AQ2> aDepartment of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Jawa Timur, Indonesia ; bClinical Pathology Laboratory, Tobelo General Hospital, North Halmahera, Indonesia.
<AQ3>	Please check and confirm author's correspondence for correctness.	<AQ3> Author's name is correct, email address: yetti-h@fk.unair.ac.id (this is my institution email)
<AQ4>	Please provide the complete correspondence details including the zip code for the city in the correspondence address.	<AQ4> Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Jl. Mayjend Prof. Dr. Moestopo 47 Surabaya, Jawa Timur, Indonesia, 60132
<AQ5>	Please check the author group 'Alvaro et al' for correctness.	<AQ5> Yes, correctness: Laga et al
<AQ6>	Please provide the complete manufacturing details for 'Sysmex CS-2100i', 'IBM SPSS version 20'.	<AQ6> Correctness: Sysmex® CS-2100i (Siemens, Kobe, Japan) IBM SPSS Statistics for Windows, Version 20.0. Armonk,NY:IBM Corp.
<AQ7>	Please provide the complete manufacturer details for 'Diagnostica Stago, Inc'.	<AQ7> Diagnostica Stago, Inc. (Asni eres sur Seine, France)
<AQ8>	Please provide the exact vol. no. for ref [5].	<AQ8> Ref 5: Freitas F. What's new about sample quality in routine coagulation testing? Bioanalise/ANO 2015;XI(1):5-6.
<AQ9>	Please provide the complete bibliographic details for refs [9,12].	<AQ9> Ref 9: NCCLS. Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fifth Edition. NCCLS document H3-A5 [ISBN 1-56238-515-1]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003. Ref 12: Sysmex Corporation. Application sheet for aPTT with Dade® Actin® FSL Activated PTT Reagent (Global Assays). Valid from Software version: 00-61: 1-7
<AQ10>		<AQ10> Please make correct: The reagents used were Dade® Actin® FSL Activated PTT for APTT and Dade® Innovin® for PPT.

Yes, I have made it correct as I explained above

6. If you would like your identity to be revealed to the authors, please include your name here (optional).

Your name and review will not be published with the manuscript.

Reviewer #2: (No Response)

Reviewer #3: M.G.R. Rajan

Reviewer #4: (No Response)

Reviewer #5: (No Response)

Editorial Formatting Comments

-Title page: Be sure the title page lists all author names, degrees, and affiliations.

-Title: Be sure the title includes any specific terms as directed in the reporting guidelines for your type of article (for example, "case report" should be in the title of a CARE-compliant article). The following guidelines specify terms that should be in the title: CARE, CHEERS, CONSORT, PRISMA.

-Abstract: Be sure to use a structured abstract, with headings. Use the specific headings listed in the guidelines checklist if your report is based on the CARE, CHEERS, CONSORT, or PRISMA guidelines.

-List of abbreviations: If not already included, please include a list of abbreviations used in the text as part of the manuscript text file following the title page. Use abbreviations sparingly in the text, and spell them out the first time you use them. Abbreviations used in tables should be spelled out at the bottom of the table.

-Ethical review, Methods section: If not already included, please state in the Methods section that an ethics committee or institutional review board approved the study, and list the board's name. If ethical approval was waived or not necessary, please state the reason. If the study involves patient consent, state explicitly that informed consent was or was not given, and state the reason if not given.

-Funding/Conflict of Interest information: List any source of funding or anything that could be perceived as a conflict of interest in the Acknowledgments section.

-Acknowledgments: If you list anyone by name in the Acknowledgments section, please confirm that the person gives permission to be named.

A. B.

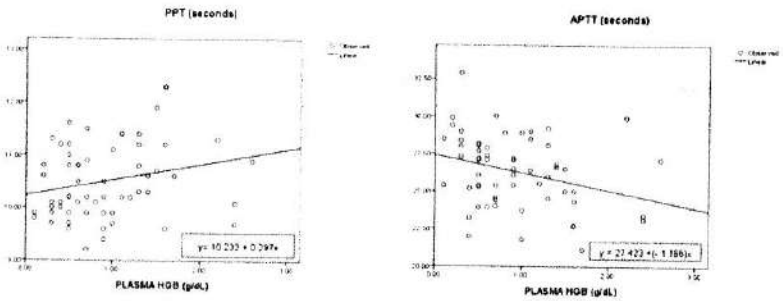


Figure 1. Regression linear curve of plasma hemoglobin level's effects on (A) PPT with R=0.294; p=.059; and (B) APTT with R=0.245; p= .023

Reviewer #4: (No Response)

Reviewer #5: (No Response)

3. Does the manuscript adhere to standards in this field for data availability?

Authors must follow field-specific standards for data deposition in publicly available resources and should include accession numbers in the manuscript when relevant. The manuscript should explain what steps have been taken to make data available, particularly in cases where data cannot be publicly deposited.

Reviewer #2: No

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Yes

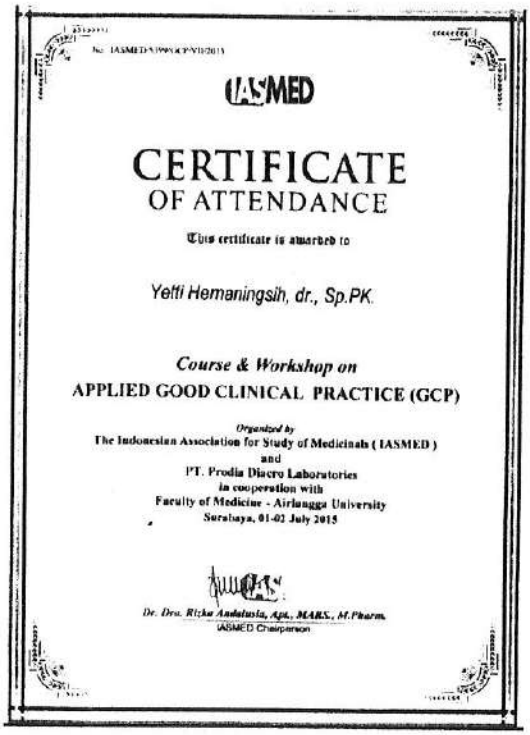
Please explain (optional).

Reviewer #2: The basic information of study population was not given, such as age, sex, and admission diagnosis.

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)



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CERTIFICATE
OF ATTENDANCE

This certificate is awarded to

Yetti Hemaningsih, dr., Sp.PK.

Course & Workshop on
APPLIED GOOD CLINICAL PRACTICE (GCP)

Organized by
The Indonesian Association for Study of Medicinals (IASMED)
and
PT. Prodia Diacro Laboratories
in cooperation with
Faculty of Medicine - Airlangga University
Surabaya, 01-02 July 2015

Dr. Dra. Ricka Andalusia, Apt., MARS., M.Pharm.
IASMED Chairperson

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- The Principles of ICH-GCP & its Implementation in Clinical Trial
- The Roles of Ethical Committee/IRB
- Study Protocol & Study Protocol Amendments
- Clinical Trial Design
- The Roles of Principal Investigator in a Clinical Trial
- Clinical Trial Procedures and Preparation in Indonesia
- Investigator Brochure & Essential Documents
- Adverse Event(s) & Serious Adverse Event(s) in Clinical Trial
- The Roles of Clinical Research Coordinator, Site Preparation and Drug Accountability
- Clinical Trial Monitoring & Source Document Verification (SDV)
- The Roles & Responsibilities of Sponsor and CRO
- Subject Recruitment, Retention & Compliance
- Audit & Inspection in Clinical Trials
- Workshops

Prof. Dr. dr. Riawio Setiabudy, Sp.FK(K)
Advisor of GCP Course Program

Well, about informed consent, the rules in our country that we use the remaining samples, we allowed to not requested the informed consent. This policy has stated in KNEP (Pedoman Operasional Komisi Etik Penelitian Kesehatan di Indonesia), unfortunately, I was difficult to get the original book. I only got the lecture in ppt form when I take Good Clinical Practice course from Prof. Riawan Setiabudy

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DI INDONESIA

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Jakarta
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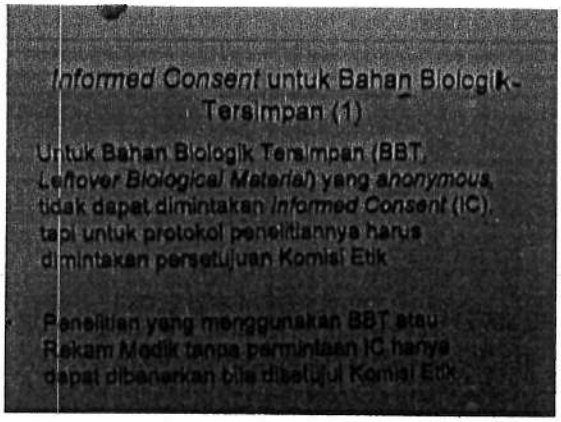


Informed Consent untuk Bahan Biologik-Tersimpan (1)

Untuk Bahan Biologik Tersimpan (BBT, *Leftover Biological Material*) yang *anonymous*, tidak dapat dimintakan *Informed Consent* (IC), tapi untuk protokol penelitiannya harus dimintakan persetujuan Komisi Etik

Penelitian yang menggunakan BBT atau Rekam Medik tanpa permintaan IC hanya dapat dibenarkan bila disetujui Komisi Etik

appropriately applied to compare PPT and aPTT for non-hemolysed, <0.8 g/dL and ≥0.8 g/dL hemolysis. However, once statistical significant difference is seen, comparison between two groups at a time should be by paired t-test, since the study is comparing the PPT and aPTT parameters before hemolysis and after hemolysis. The authors should see if this can be done and indicated in Table 2.

Yes, thank you for your correction. I had done it in new manuscript.

Table 2. Descriptive analysis of plasma hemoglobin; PPT and APTT before and after lysis test results

Parameter	Mean±SD		
	Before Lysis (Baseline)	After Lysis	
		Group 1	Group 2
Plasma HGB (g/dL)		**0.46 ± 0.18 (0.10 – 0.70)**	**1.38 ± 0.48 (0.80 – 2.60)**
PPT (seconds)	10.54 ± 0.67 (9.10 – 11.90)	10.38 ± 0.62 (9.20 – 11.60)	10.62 ± 0.79 (9.40 – 12.30)
APTT (seconds)	**28.44 ± 2.54 (23.80 – 33.00)**	**26.76 ± 2.38 (22.0 – 32.90)**	**25.90 ± 2.34 (21.10 – 29.90)**

SD=standard deviation; HGB = hemoglobin

Table 3. Significance of PPT and APTT test results

Parameter	*P*
PPT	
PPT baseline and group 1	**0.002**
PPT baseline and group 2	**0.143**
PPT group 1 and 2	**0.000**
APTT	
APTT baseline and group 1	0.000
APTT baseline and group 2	0.000
APTT group 1 and 2	0.003

Further, the correlation coefficients with p values and regression equation for the scatter plots may be given. This will show the extent of association between degree of hemolysis and decrease in aPTT.

Yes, thank you for your correction. I had done it in new manuscript (regression equation embedded in scatter plots figure, while p value was stated in part of Results).

specimen, whether PT and APTT still maintain statistically significant? This is a major defect for this article.
Answer:
Yes, thank you. I have explained as above

2 All samples were from patients with normal PT and APTT, however, whether hemolysis has the influence of for PT and APTT in the samples with abnormal PT and APTT, it is not clear, at least it is a defect for the entire study design.
Comment:
Thank you for your good comments. In fact, hemolysis samples in patients give the influence in PPT and APTT, usually prolonged PPT and APTT. Even in application sheeth state that plasma HGB 0.8 mg/dL as limit to give effect, but in fact minimal hemolysis will influence trhe result of PPT and APTT. Therefor we want to know the exact value of plasma HGB that will affect PPT and APTT. So, we start with normal plasma and make artificial blood lysis.

3 The description in introduction should be further enriched, and reference to previous researchs.
Answer:
Yes, thank you for your suggestion. I have fixed the introduction in new manuscript. I have added the reference of Tatana et al. beside Alvaro et al. and Arora et al. in part of Introduction

4 Add the results in thrombin time (TT), fibrinogen (FIB) test, and compared with before and after hemolysis, the results may be more interesting.
Answer:
Yes. may be in the next research

5 In the method section, exclusion criterias are missing.
Answer:
We are apologize for less understanding of your statement. In the old manuscript, we have written the exclusion criteria, hewever if you want to skip this criteria, I have omitted it in the new manuscript method section.
The old manuscript:

2. MATERIALS AND METHODS

2.1 Study samples

This study was conducted at the laboratory of Clinical Pathology, Dr. Soetomo General Hospital, Surabaya, Indonesia. We studied 30 nonhemolytic blood samples with normal PPT and APTT results. The study samples were selected from all blood specimens that were submitted for coagulation tests at our laboratory, between January - March 2015. The blood samples were collected in tubes that contained 3.2% sodium citrate; the ratio of blood to citrate was 9:1. Icteric and lipemic samples were excluded.

The new manusript:

2.1 Study samples

This study was conducted in November 2014 untill February 2015 in the Clinical Pathology Laboratory, Dr Soetomo General Hospital Surabaya. The total number of samples were 30 blood samples, which taken from remaining of citrate blood plasma of

patients who have been examined for PPT and APTT as a routinely examinations. The inclusion criteria were nonhemolysis blood samples that apparent clear plasma with normal PPT and APTT test results, no icterio and lipemic plasma that may interfere the results.

6 More sample information should be included such as age, gender and body mass index, since these factors may affect the test results in PT and APTT.
Answer:
Yes, we have added the data of patients as table 1, including age, sex and diagnosis. Unfortunately, we do not have the data of body mass index. We apologize about it.

Reviewer #5: The authors investigate the impact on mechanically induced in vitro hemolysis on PPT and aPTT tests. The authors further aimed to determine level of hemolysis, when free hemoglobin levels start to have a significant effect on coagulation test. The investigated topic is of practical importance. However, understanding the paper is sometimes difficult, because English language is not properly used.

Major comments:
1. English language should be thouroghly edited by a native English speaker.
2. Informed consent, IRB approval: it is not clear, whethter the study had approval of the responsible IRB and whether the patients provided informed consent. Please provide details.
3. Methods: the authors include 30 nonhemolyzed samples (as stated in the study samples paragraph) with normal PPT and aPTT times. In the methods section, it is stated that two groups with each 30 samples were assembled. It is not clear to me how the 2 groups wer put together. Please clarify. Maybe a flow chart of what was done could help readers to understand better what has been done.
4. Statistics: In my eyes, statistics are not properly used. Values are compared before and after lysing. This would mean that these are not independent observations. I suggest to use ANOVA repeated measures ANOVA or the Friedman repeated measures test.
5. Table 2: Since I can not figure out how groups 1 and 2 were put together, I do not understand what was compared here. Please clarify.

Minor comments
1. Ref 14: format could be ameliorated.
Answer:

data that supports the conclusions. Experiments must have been conducted rigorously, with appropriate controls, replication, and sample sizes. The conclusions must be drawn appropriately based on the data presented.

Reviewer #2: Partly

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: Partly

Please explain (optional).

Reviewer #2: The policy of rejection of hemolytic samples according to the effect of indexes on coagulation should be considered comprehensively. Why only PT and APTT were chosen as the research object? It is suggested that the common indicators of coagulation function that TT and FIB should be added to research content, so that the clinical value was greater.

Reviewer #3: The authors have revisited the subject of the suitability of using partially hemolysed samples for PPT and aPTT tests. Though this is has been studied and reported several times over the last two decades, the authors of this manuscript have studied samples with two levels of hemolysis and, applied appropriate statistics to prove their hypothesis.

Reviewer #4: (No Response)

Reviewer #5: (No Response)

2. Has the statistical analysis been performed appropriately and rigorously?

Reviewer #2: Yes

Reviewer #3: Yes

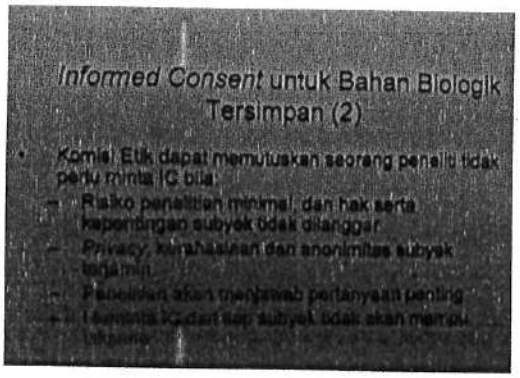
Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #2: The description of the grouping is not clear; please describe the whole grouping process in detail, so as to facilitate the understanding of the results of the subsequent statistical analysis.

Reviewer #3: Appropriate statistics have been used. One way ANOVA has been



Translation in English:

Operational guidelines of ethical research committee on health in Indonesia
Informed Consent for Saved Biologic Materials (1):
1. For biologically stored material (BBT), leftover biological material) anonymous, can not be requested Informed Consent (IC), but for the research protocol should be requested approval of the Ethics Commission
2. Research using BBT or Medical Record without IC request can only be justified if approved by the Ethics Committee

Informed Consent for Saved Biological Material (2):
The Ethics Commission may decide that a researcher should not ask IC if:
1. The risk of research is minimal, and the rights and interests of the subject are not violated
2. Privacy, secrecy and anonymity of the subject are guaranteed
3. Research will answer important questions
4. Asking IC from each subject will not be able to do

3. Methods: the authors include 30 nonhemolyzed samples (as stated in the study samples paragraph) with normal PPT and aPTT times. In the methods section, it is stated that two groups with each 30 samples were assembled. It is not clear to me how the 2 groups wer put together. Please clarify. Maybe a flow chart of what was done could help readers to understand better what has been done.
Answer:
Yes, I have describe more clear in Methods section in new manuscript. Here the flow chart. Thank you very much for sugestion that very usefull to make understanding the reader.

Baseline	30 specimens that fulfilled the criteria (clear plasma, normal results of PPT and APTT)
	↓
Group 1	erythrocytes lyzed artificial (pushed out from 3 ml spuit) 2-3 times
	↓
	measured plasma HGb (< 0.8 g/dL)
	↓
	sentrifuge for getting plasma
	↓
	measured PPT and APTT

The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests using Photo-ptical Methods

<u>**Abstract**</u>

Objective: Hemolysis is the most common reason why coagulation test samples are rejected. However, the effects of hemolysis on PPT and APTT are rarely investigated and the results are controversial. This research aims to analyze the effects of hemolysis on PPT and APPT using photo-optical methods.

Methods: Nonhemolytic citrate blood samples (n=30) with normal PPT and APTT were [illegible] each steps. The first lysis was mild to moderate and [illegible] g/dL, then we called them as group 1. The next step was [illegible] more severe [illegible] plasma hemoglobin levels > 0.8 g/dL, then we called them as group 2. The differences of PPT and APTT between [illegible] and baseline, group 1 and 2 [illegible] and the effects of hemolysis were analyzed using *paired t-test* and linear regression, respectively. The ROC curve analysis was made for [illegible] the cut off in PPT and APTT.

Results: There were shorter significant difference for APTT between group 1 to baseline (p=0.000), group 2 to baseline (p=0.000), group 2 to group 1 (p=0.003). For PPT results, group 1 have significant shorter than baseline (p=0.02), hence group 2 have longer significant than group 1 (p=0.000). In correlation assay, the level of hemolysis revealed mild significant correlation to APTT (R=0.245, p=0.023). Cut off value for PPT was 1.55 g/dL (sensitivity 1.000 and specificity 0.879), while APTT was 0.95 g/dL (sensitivity 0.750 and specificity 0.625).

2. Informed consent, IRB approval: it is not clear, whethter the study had approval of the responsible IRB and whether the patients provided informed consent. Please provide details.

Answer:

Yes, IRB should be approved by ethic committee, however we did not do it in that time because the ethical clearance requirement in our institution was still not well sosialized like recently, after good clinical practice (GCP) has been well sosialized and GCP becomes prerequirement of scientist before doing research. Something that relieve my research is this study only took the remaining specimen, not directly contact with patients, also I hide the identities of patients.

2.2 Methods

This study was experimental laboratory with pre-test and post-test design. The data of PPT and APTT patients that fullfilled for inclusion criteria were recorded as a baseline data. The remaining samples then mechanically lysed by inserting blood into the disposable syringe 3 mL, needle 23G and vigorously moderate pressure pushed out in a quick motion and this was performed 2-3 times. This procedure resulted lysis with plasma hemoglobin < 0.8 g/dL at the measurement. The blood sample next underwent further lysis by adding stronger pressure pushed out with total 4-5 times. It resulted the plasma hemoglobin ≥ 0.8 g/dL. This procedure is the modification of method proposed by Arora et al. [7]. This method was chosen because the most common cause of hemolytic is mechanical factors, occur during venipuncture or transportation process. Determination of plasma hemoglobin in the level 0.8 g/dL because this is the limit level of plasma hemoglobin that will influence the result of APTT according to Sysmex CS-2100i that was stated in application sheet [12]. To examine the plasma hemoglobin, lysed blood samples were centrifuged at 300 rpm for 15 minutes, then the supernatant were examined for hemoglobin plasma level using Sysmex® XN-1000 (Siemen) hematology analyzer.

4.Is the method of mechanical hemolysis cited the reference or a standard protocol? Otherwise, the processing method itself will not affect the results of the study should be proven.

Answer:

Yes, it regards the reference number 7 (Arora et al.) and we make little modification technic to make lysis with plasma HGB < 0.8 g/dL then further lysed to make plasma HGB level > 0.8 g/dL

5. Regression linear results are derived from the detection of all the hemolysis samples, please describe in the method.

Answer:

Thank you for your suggestion, and we had added this statement in the result (we apologize to not input it at methods because we think it more relevant in results)

3. RESULTS

The age, sex and diagnosis of the samples were shown in table 1. The age of the patients range between 2.6 and 68 years old. The diagnosis was vary but did not affect the PPT and APTT value. The mean±SD of baseline PPT and APTT assays were in the normal range 10.54 ± 0.67 for PPT and 28.44 ± 2.54 for APTT. All groups of PPT and APTT were in normal distribution. The result of paired t-test for APTT assay, both group 1 either group 2 shorter than baseline, group 2 shorter than group 1 (table 2).

Comparison between the groups based on paired t-test in PPT assays were significant except PPT between group 2 and baseline (p=.143). The PPT group 1 have significant shorter value than baseline (p= .002) while group 2 have significant longer value than group 1 (p=.000). For APTT assays, all comparisons were significant difference, specimens of group 1 have significant shorter APPT than baseline (p=.000), as well as group 2 to baseline (p=.000); while group 2 has significant shorter APTT than group 1 (p=.003). Data significance of PPT and APTT results were shown in table 3.

Linear regression were performed to test the effect of hemolysis on PPT and APTT assay. Therefore we included all samples in group 1 and 2 to be analyzed. The

Table 1. Characteristic of samples

Sample	Sex	Age (years)	Diagnosis
1.	F	22	Post sectio cesaria
2.	F	60	Carsinoma mammae
3.	M	11	Multiple fractures of skull and facial bone
4.	M	59	Hydronefrosis
5.	F	61	Hypertensi Heart Disease
6.	M	57	Cellulitis
7.	F	54	Calculus of kidney and ureter
8.	F	36	Carsinoma ovarium
9.	F	59	Carsinoma mammae
10.	F	16	Chronic kidney disease
11.	M	56	Calculus of kidney and ureter
12.	F	61	Hypertension heart diseaase, diabetes mellitus
13.	M	40	Non hodgkin lymphoma
14.	F	37	Carsinoma mamae
15.	F	61	Carsinoma cervix, hyperkalemia
16.	F	12	Idiopathic thrombocytopenic purpura
17.	F	56	Carsinoma mammae
18.	F	67	Unstable pelvis, closed fracture of acetabulum dextra, closed fracture of ramus pubis dextra, internal bleeding
19.	F	50	Diabetes mellitus
20.	M	60	Unstable angina, arteri coronary syndrome medium high risk
21.	M	47	Post debulking mass region pedis
22.	F	40	Hemangioma
23.	M	29	Lung tuberculosis
24.	M	2.6	Atrial septal defect, ventricular septal sefect
25.	M	32	Carcinoma of tongue
26.	F	18	Calculus of kidney and ureter
27.	F	40	Carsinoma mammae
28.	M	4	Acute lymphoblastic leukemia
29.	F	64	Hypertensi, diabetic retinopathy
30.	M	68	Hypertension heart disease

M male, F female

3.The description of the grouping is not clear; please describe the whole grouping process in detail, so as to facilitate the understanding of the results of the subsequent statistical analysis. Why 0.8 g/dL is as separation? Is it from "Sysmex® CS-2100i provides a quite good performance on hemolytic samples and is not affected until the plasma hemoglobin level is 0.8 g/dL [9,10].", please cite the reference in method.

Answer:

We grouped the sample in two group below and upper 0.8 g/dL was based on the limit plasma Hb that influence the test according to Application sheet for APTT of Sysmex CS-2000i/CS-2100i as reference number 10 page 2 (shown in a print screen).

Application Sheet for aPTT with
Dade® Actin® FSL Activated PTT Reagent

Performance Characteristics

Precision (CV%)

	mean value sec	Within Run %	Between-run %	Total %
Control Plasma N	27.2	0.4	1.3	1.3
Ci-Trol 3	63.8	0.9	0.5	1.0

Within run precision was calculated with Control Plasma N and Ci-Trol 3 in 20-fold determination. Between-run precision and total precision were calculated with Control Plasma N and Ci-Trol 3 over 5 days in 10-fold.
Acceptable variability (imprecision) should be such that the within device/lab CV of the analytical system on the same lot of control plasma is less than 5 %.

Method Comparison

Predicate Device	unit	n	Regression Equation	r
Dade® Actin® FSL Activated PTT Reagent on CA-1500 System	sec	42	y = 1.003x - 0.01	0.998

Interference Studies

No interferences up to ...	
Triglycerides (mg/dL)	288*
Hemoglobin (mg/dL)	800
Bilirubin (mg/dL)	48

* Data from SIEMENS evaluation

Yes. I had made clear in grouping method and added the reference in part of Methods in new manuscrpt. Thank you for your correction.

COMMENTS TO AUTHOR:

Important notification to editor:
We made some correction in statistic analysis:

1. To comparison between group, we used paired t-test to substitute anova test as a rewiewer suggestion.
2. In regression linear and ROC. We repeat analysis because in fisrt analysis the statistician has analyzed all the data including baseline. The right way that the data should be group 1 and 2 only. However, the new statistical analysis results do not changes the conclusion.

Thank you for making attention.

Reviewer #2: This paper is to study the effects of hemolysis on PT and APTT using Photo-Optical Method, and it found that not all hemolyzed samples should be rejected for PPT and APTT is valuable for laboratories to set policy of rejection of hemolysis samples. Although the effect of hemolysis on PT and APTT is still controversial, its impact has become a consensus. A more comprehensive study of the effects of coagulation function should be studied so as to the results are more valuable for clinical applications.

1.The policy of rejection of hemolytic samples according to the effect of indexes on coagulation should be considered comprehensively. Why only PT and APTT were chosen as the research object? It is suggested that the common indicators of coagulation function that TT and FIB should be added to research content, so that the clinical value was greater.

Answer:
Thank you for your suggestion. Your input is very valuable, unfortunately TT and FIB are not routinely as coagulation function in our country. In our country and hospital, routine coagulation test is PPT and APTT so we do not think and performed TT and FIB test to be included in our research at that time. Therefor your suggestion may be very usefull in the next research.

2.The basic information of study population was not given, such as age, sex, and admission diagnosis.

Answer:
Yes, we have embedded the patient characteristic that comprise of age, sex and diagnosis as table 1 in new manuscript.

4. Is the manuscript presented in an intelligible fashion and written in standard English?

Medicine does not copyedit accepted manuscripts, so the language in submitted articles must be clear, correct, and unambiguous. Any typographical or grammatical errors should be corrected at revision, so please note any specific errors below.

Reviewer #2: Yes

Reviewer #3: Yes

Reviewer #4: Yes

Reviewer #5: No

Please explain (optional).

Reviewer #2: the manuscript was presented in an intelligible fashion and written in standard English.

Reviewer #3: (No Response)

Reviewer #4: (No Response)

Reviewer #5: (No Response)

5. Comments to Author (required)

Reviewer #2: This paper is to study the effects of hemolysis on PT and APTT using Photo-Optical Method, and it found that not all hemolyzed samples should be rejected for PPT and APTT is valuable for laboratories to set policy of rejection of hemolysis samples. Although the effect of hemolysis on PT and APTT is still controversial, its impact has become a consensus. A more comprehensive study of the effects of coagulation function should be studied so as to the results are more valuable for clinical applications.

1.The policy of rejection of hemolytic samples according to the effect of indexes on coagulation should be considered comprehensively. Why only PT and APTT were chosen as the research object? It is suggested that the common indicators of coagulation function that TT and FIB should be added to research content, so that the clinical value was greater.
Answer:
Yes, thank you. I have explained as above

2.The basic information of study population was not given, such as age, sex, and admission diagnosis.

Answer:
Yes, thank you. I have explained as above

3.The description of the grouping is not clear; please describe the whole grouping process in detail, so as to facilitate the understanding of the results of the subsequent statistical analysis. Why 0.8 g/dL is as separation? Is it from "Sysmex® CS-2100i provides a quite good performance on hemolytic samples and is not affected until the plasma hemoglobin level is 0.8 g/dL [9,10].", please cite the reference in method.
Answer:
Yes, thank you. I have explained as above

4.Is the method of mechanical hemolysis cited the reference or a standard protocol? Otherwise, the processing method itself will not affect the results of the study should be proven.
Answer:
Yes, thank you. I have explained as above

5. Regression linear results are derived from the detection of all the hemolysis samples, please describe in the method.
Yes, I had done it in new manuscript. Thank you for your sugestion

6. The appropriate description should be added to the figs. and tables.
Yes, I had given more explanation in part of Results about tables and figures in new manuscript. Thank you for your sugestion

7. The performance on hemolytic samples by different Coagulation Analysators using Photo-Optical Method should be discussed briefly.
Answer:
Yes, I had added it in the last paragraph of discussion. Thank you

Reviewer #3: The study, though a subject of debate for many years, is a good one but the statistics applied may be made more rigorous by applying the paired t-test for comparing PPT between non-hemolysed and <0.8 g/dL hemolysis, between non-hemolysed and ≥0.8 g/dL hemolysis and, between <0.8 g/dL and ≥0.8 g/dL hemolysis. Correlation analysis for data plotted in figures 1 and 2 should be included.
Yes, I had done it in new manuscript. Thank you for your sugestion

Reviewer #4: This is a very interesting article in laboratory medicine field, technology study is important for laboratory tests. The authors investigate the influence of hemolysis for PT and APTT, the effective conclusions has guiding significance for clinical laboratory doctor. The manuscript can be accepted, if the authors successful address the following comments.

1 why the authors choose plasma hemoglobin level of 0.8 g/dL as standard for grouping of hemolysis specimen? Is there a document to support this standard (0.8 g/dL)? Or, when the other hemoglobin concentrations for this grouping of hemolysis

6. The appropriate description should be added to the figs. and tables.
Answer:
Yes, I had added it in new manuscript, especially in part of results. Thank you for your suggestion

7. The performance on hemolytic samples by different Coagulation Analysators using Photo-Optical Method should be discussed briefly.
Answer:
Yes, I had added it in the discussion (third paragraph from the last paragraph) in new manuscript. Thank you for your suggestion

to lengthening PPT in this particular research are still difficult to be explained because there was no coagulation factor assay conducted.

Woolley et al. in their research the effect of hemolysis on PPT and APTT using instrument with mechanical detection technology, STA-Compact-Max® analyser with different reagent of Stago revealed the result no significant difference was observed between hemolysed versus nonhemolysed samples group in all reagents. In contrast, APTT was statistically significantly shorter in hemolysed versus nonhemolysed samples with two of three test reagents. However, this different in one of two reagents was not clinically significant. No correlation was observed between the level of hemolysis and the result variation for all assays whatever the reagent used [15]. This result support that instrument with photo optical detection method using multiple wavelength method can overcome the spectral interference that become a limitation of photo optical method to date.

Plasma hemoglobin levels that are capable of affecting PPT and APTT were observed as well in this study. According to literature, Sysmex® CS-2100i provides a quite good performance on hemolytic samples and is not affected until the plasma hemoglobin level is 0.5 g/dL for PPT and 0.8 g/dL for APTT [12]. Statistical analysis

Reviewer #5: The authors investigate the impact on mechanically induced in vitro hemolysis on PPT and aPTT tests. The authors further aimed to determine level of hemolysis, when free hemoglobin levels start to have a significant effect on coagulation test. The investigated topic is of practical importance. However, understanding the paper is sometimes difficult, because English language is not properly used.

Major comments:
1. English language should be thouroghly edited by a native English speaker.
Answer:
Well, thank you. I has made so much editing in writing and we have proofread it in Foreign Language Centre of Airlangga University (Pusat Bahasa Universitas Airlangga/PBUA). I hope it will make this manuscript able to fullfill the requirement of standardized english for international journal. This is, the first page of proofread of PBUA, they gave stamp in the right buttom corner.
However, if this translation is felt not satisfactory, we will be ready to improve again if this article was accepted.

Group 2 → further lyzed by pushing out stronger 3-5 times (from 3 mL disposible spuit) → measured plasma HGb (≥ 0.8 g/dL) → sentrifuge for getting plasma → measured PPT and APTT

4. Statistics: In my eyes, statistics are not properly used. Values are compared before and after lysing. This would mean that these are not independent observations. I suggest to use ANOVA repeated measures ANOVA or the Friedman repeated measures test.

Answer:

Yes, thank you for your correction. This research design considers to before and after comparison design (using the same sample), therefor paired t-test was exact test. I had changed the statistic in new manuscript.

5. Table 2: Since I can not figure out how groups 1 and 2 were put together, I do not understand what was compared here. Please clarify.

Answer:

I hope flow chart in answering question number 3 can clarify this question

Minor comments

1. Ref 14: format could be ameliorated.

Answer:

Yes, I have done it in new manuscript. Thank you for your correction

The old version:

14. Plumhoff EA, Masoner D, Dale JD. Preanalytic laboratory errors: Identification and prevention. December 2008. Ref type: electronic citation.

The new version in new manuscript

16. Plumhoff EA, Masoner D, Dale JD. Preanalytic laboratory errors: Identification and prevention. Mayo Clinic, Mayo medical Laboratories, preq.in/images/mayo.pdf; December 2008, (accessed 04.02.15).

Reviewer's Responses to Questions

Comments to the Author

1. Is the manuscript technically sound, and do the data support the conclusions?

The manuscript must describe a technically sound piece of scientific research with

re: "The Effects of Hemolysis on Plasma Prothrombin Time and Activated Partial Thromboplastin Time Tests Using Photo-Optical Method"
MD-D-16-04882R1%

Apr 25 2017 02:53PM

Dear Dr Hernaningsih:

Your submission has been received by the journal Medicine®, but corrections to meet the journal's preferred format are required before the manuscript can be processed.

Please address the following concerns and resubmit your paper:

- Please include a list of abbreviations used in the text as part of the manuscript text file following the title page. Use abbreviations sparingly in the text, and spell them out the first time you use them. Abbreviations used in tables should be spelled out at the bottom of the table.
Yes, I have done it in new manuscript, thank you

-: Please state in the manuscript (in the Methods section, if applicable) that an ethics committee or institutional review board approved the study, and list the board's name.
* If ethical approval was waived or not necessary, please state the reason. If the study involves patient consent, state explicitly that informed consent was or was not given, and state the reason if not given.

Thank you very much. Now, we have stated in part of method section

- Please upload each table and figure as a separate, individual file.
Yes, I will do it, thank you

-Figure 3 is cited in the manuscript, but the file is missing.
Yes, thank you for your correction. I have made a mistake in writing, I mean figure 2 in that sentences. I have make correct. Thank you.

- Please include all figure legends at the end of the main manuscript document.
  Yes, I will do it

Log in to Editorial Manager as an Author, using the log in information below, to make the requested correction(s) and resubmit your paper.

Go to the menu item "Submissions Sent Back To Author" to locate the submission. You may then view your submission, edit your submission, re-build the PDF, and approve the changes. After this process, the submission will be returned to the Editorial Office for review.

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