Reviewer Assessment **Open Access**

M. Schenk, G. Mueller, T. O. Greiner, Ch. Fahrner, A. Koenigsrainer, and Ch. Thiel

Pull-off characteristics of double-shanked compared to single- shanked ligation clips: an animal study

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***Corresponding author: Martin Schenk**
University of Tuebingen, Tuebingen, Germany
E-mail: martin.schenk@med.uni-tuebingen.de

Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Mar 18, 2016

Reviewer Recommendation Term:	Revise with Major Modifications
Overall Reviewer Manuscript Rating:	70

Custom Review Question(s)	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	2
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	4
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

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Comments to Author:

The authors compared two standard single-shanked clips with respect to axial and radial pull-off forces to a novel double-shanked titanium clip from Aesculap. For this purpose, they clipped arteries of two defined size ranges in a porcine model and subsequently measured axial and radial pull-off forces by means of an in vitro testing device. Of interest, they found that for all analyzed clips the radial pull-off force was lower than the axial one. Moreover, the radial pull-off force for the novel double-shanked clip was significantly higher when compared to the controls, indicating a possible safety advantage during clinical application.

Taken together, the authors report several findings, which should be interesting for a broad range of practical surgeons. The manuscript is well written. Nonetheless, I have several comments, which should be addressed to further improve the quality of this work:

1. The experimental approach seems confusing to me. The study was performed in 8 pigs. However, the animals were killed before the experiment! Hence, the described protocol could have been performed without killing any additional animals by simply using fresh vessel specimens from the slaughterhouse. Why didn't the authors apply the clips in anesthetized living animals, which would have been much more realistic? Moreover, it is not clear why the animals received heparin. Finally, why was there such a long period between the death of the animals and the clip application (see Tab. 2)? All these points need further clarification.

2. Results:

- "The axial pull-off force for the M-size double-shanked clip...was higher than both single-shanked controls" - this statement is not correct. It was only higher when compared to S1.

- "The pull-off force of the ML-sized double-shanked clip lay between S1...and S2" - this statement is not correct. There was no statistical significant difference between DS and S2!

- Why do the authors specifically mention the variation coefficient of pull-forces in the radial pull-off setting for size M? The variation is even higher for size ML! I further do not agree that the variation in axial pull-off forces was comparable in both clip types. At least for size ML, differences are in parts comparable to the results of the radial pull-off measurements.

3. The significant differences between the control clips (S1 and S2) need more discussion.

4. Figure 1: The authors should provide additional images of the control clips. Furthermore, the dimensions of the clips should be clear on the images, e.g. by adding scale bars.

5. Figs. 3-6: Because the novel DS clip (most interesting results) was compared to two control clips (S1 and S2), it may improve the clarity of the figures by changing the color (gray or white) of the columns / circles for S1 and S2.

6. If available, it would be further interesting to mention possible cost differences between the different clip types.

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Reviewer 2: Daniel Vallböhmer

Apr 13, 2016

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	80

Custom Review Question(s)	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	3
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	5 - High/Yes
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	3
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:

The current paper compares a novel double shanked titamium clip with the established single shanked clip regarding axial and radial pull-off forces. In a porcine (8 animals) model the authors prepared for the clip application arteria saphena, arteria carotis, arteria axillaris and arteria femoralis. Twenty double-shanked clips of each two sizes and each pull-off direction were compared to an equal number of two state-of-the-art single shanked clip systems. The authors revealed that the axial pull-off force of the double-shanked clip was higher than one single shanked clip. In addition, the radial pull-off force of the double shanked clip was significantly higher than both single-shanked clips. Finally, the variation of the radial pull-off force was lower for the double-shanked clip. Based on these results the authors suggest that the double-shanked clip might decrease the dislocation rate compared to single-shanked clips.

In my opinion this is very interesting study with an important issue: the safety of laparoscopic clips. Therefore, I have no major criticism. However, the authors should mention in their paper which further studies are needed to implement this double-shanked clip in clinical practice and in which surgical procedures it should specifically be used.

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Author's Response to Reviewers Comments

Mar 16, 2016

Reviewer #1: The authors compared two standard single-shanked clips with respect to axial and radial pull-off forces to a novel double-shanked titanium clip from Aesculap. For this purpose, they clipped arteries of two defined size ranges in a porcine model and subsequently measured axial and radial pull-off forces by means of an in vitro testing device. Of interest, they found that for all analyzed clips the radial pull-off force was lower than the axial one. Moreover, the radial pull-off force for the novel double-shanked clip was significantly higher when compared to the controls, indicating a possible safety advantage during clinical application.

Taken together, the authors report several findings, which should be interesting for a broad range of practical surgeons. The manuscript is well written. Nonetheless, I have several comments, which should be addressed to further improve the quality of this work:

1. The experimental approach seems confusing to me. The study was performed in 8 pigs. However, the animals were killed before the experiment! Hence, the described protocol could have been performed without killing any additional animals by simply using fresh vessel specimens from the slaughterhouse.

We initially thought about that option. As an institution we are frequent "customers" in the local slaughterhouses retrieving blood for transfusions. However, we and many working groups in our environment stopped harvesting porcine organs from the slaughterhouse. The reasons are mainly based on the fact that there is no possibility to interfere with the slaughter process as well to avoid possible interferences due to the conservation during the transport. First, A. carotis is cut undefined and there is no way to manipulate the animal during the bleeding process. Secondly, the animal is scalded with hot water, negatively influencing the biological properties of superficial vessels like A. saphena and parts of A. axillaris. After mechanical removal of the superficial skin and cutting the animal into half there is the first possibility to get access to the animals' organs. Harvesting of peripheral vessels remains impossible because the halves of the pigs have to be delivered untouched to the butcher. Therefore we and other groups refrained from this way of organ supply and decided to sacrifice animals in a more controlled way in our institution. For professional organizations, it is possible to use a good number of organs for different working groups. This was the case in this study as well. Not to involve any other negative effects to the vessels, the vessels for this study have been removed initially and before providing organs to any other working group.

No changes in manuscript. It is not typical to mention multi-organ harvesting in a manuscript.

Why didn't the authors apply the clips in anesthetized living animals, which would have been much more realistic?

We used a block-randomized serial clipping strategy on one vessel to reduce the number of animals used for the large amount of clips tested. Clinically, after the first clip, which is placed on a perfused vessel the blood flow will stop and all other clips will be placed without inner perfusion as it is in our model. To balance the animal number required and the advantage of realism of that first clip we decided to place all clips in a non-perfused vessel.

Changes in manuscript: Adding a limitations' paragraph to the discussion section: "The usage of non-perfused vessels of dead animals as a limitation of the model may be regarded of only limited importance for two reasons. First, in all laparoscopic and open-surgical interventions the second and potential further clips are placed on non-perfused vessels as well and secondly, it is not likely that the stop of the blood flow will change the biological and physical properties of the vessel."

Moreover, it is not clear why the animals received heparin.

Heparin prevents the blood from clotting. The application of heparin is part of the standard protocol for organ harvesting. It is not likely to have any effect on the question addressed in this study.

No changes in manuscript.

Finally, why was there such a long period between the death of the animals and the clip application (see Tab. 2)? All these points need further clarification.

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In the study we addressed 8 vessels (4 vessels on both sides). The mean preparation time for the vessels with an adequate length was done by an experienced animal surgeon (MS) and took in mean 15 minutes per situs (shorter for A. carotis, longer for A. femoralis). The clipping was done exclusively by an experienced clinical surgeon (GM) in 10 minutes while the preparation of the next situs went on. This resulted in the first clip set after 15 minutes and the last clip after 130 minutes (8*15 minutes plus 10 minutes). Therefore the mean time for clipping is around 70 minutes. These times were given to demonstrate the efficiency of the block randomization.

No changes in manuscript.

2. Results:
- "The axial pull-off force for the M-size double-shanked clip...was higher than both single-shanked controls" - this statement is not correct. It was only higher when compared to S1.
- "The pull-off force of the ML-sized double-shanked clip lay between S1...and S2" - this statement is not correct. There was no statistical significant difference between DS and S2!
- Why do the authors specifically mention the variation coefficient of pull-forces in the radial pull-off setting for size M? The variation is even higher for size ML! I further do not agree that the variation in axial pull-off forces was comparable in both clip types. At least for size ML, differences are in parts comparable to the results of the radial pull-off measurements.

I have rewritten the results section based on the comments above and tried to add more adverbs to my description.

3. The significant differences between the control clips (S1 and S2) need more discussion.

These differences were referenced in the results and in the discussion section.

4. Figure 1: The authors should provide additional images of the control clips. Furthermore, the dimensions of the clips should be clear on the images, e.g. by adding scale bars.

A new figure 1 is added.

5. Figs. 3-6: Because the novel DS clip (most interesting results) was compared to two control clips (S1 and S2), it may improve the clarity of the figures by changing the color (gray or white) of the columns / circles for S1 and S2.

Figures 3-6 are changed.

6. If available, it would be further interesting to mention possible cost differences between the different clip types.

Unfortunately it is not possible to mention possible cost differences for the different clip types. According to experiences, market prices differ considerably within wide tolerances. This is due to different market price levels, influenced by factors like quantity-dependent purchase respectively project-related or day-to-day business.

No changes in manuscript.

Reviewer #2: The current paper compares a novel double shanked titamium clip with the established single shanked clip regarding axial and radial pull-off forces. In a porcine (8 animals) model the authors prepared for the clip application arteria saphena, arteria carotis, arteria axillaris and arteria femoralis. Twenty double-shanked clips of each two sizes and each pull-off direction were compared to an equal number of two state-of-the-art single shanked clip systems. The authors revealed that the axial pull-off force of the double-shanked clip was higher than one single shanked clip. In addition, the radial pull-off force of the double shanked clip was significantly higher than both single-shanked clips. Finally, the variation of the radial pull-off force was lower for the double-shanked clip. Based on these results the authors suggest that the double-shanked clip might decrease the dislocation rate compared to single-shanked clips.

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In my opinion this is very interesting study with an important issue: the safety of laparoscopic clips. Therefore, I have no major criticism. However, the authors should mention in their paper which further studies are needed to implement this double-shanked clip in clinical practice and in which surgical procedures it should specifically be used.

The DS-Clip Portfolio, consisting of 6 different clip sizes is already available in the market. The first clip size, commercially available, was the Appendectomy-Clip (clip size X-Large) beginning of 2012. It is referred to the References, no. 9 and 10.

Following the X-Large Clip the portfolio is meanwhile consisting of the clip sizes Small, Small-Medium, Medium, Medium-Large and Large.

Bottom-line, these different sizes are comparable to the competition, portfolio-related as well as regarding the indications to be used for.

No changes in manuscript.

Reviewers' Comments to Revision

Reviewer 1: anonymous

Apr 21, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	90

Custom Review Question(s)	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	4
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:

The authors have adequately addressed all the issues raised by the reviewers. Most comments have been answered in the Response to Reviewer form without changing the manuscript text. However, I feel that this is appropriate, because these comments will also be available for the readers of this article after publication.

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Reviewer 2: Daniel Vallböhmer

Apr 22, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	80

Custom Review Question(s)	Response
Is the subject area appropriate for you?	3
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	4
Is the number of cases adequate?	3
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:
In my opinion the authors addressed the reviewers comments sufficiently. Therefore, I would accept the paper in the current form.

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