Author's response to reviews

Title:A Collagen-Fibrin Patch (Tachosil(R)) for the Prevention of Symptomatic Lymphoceles after Pelvic Lymphadenectomy in Women with Gynecologic Malignancies: a Randomized Clinical Trial

Authors:

Christoph Grimm (christoph.grimm@meduniwien.ac.at)
Stephan Polterauer (stephan.polterauer@meduniwien.ac.at)
Samir Helmy (samir.helmy@meduniwien.ac.at)
David Cibula (d_cibula@yahoo.com)
Michal Zikan (michal.zikan@1f1.cuni.cz)
Alexander Reinthaller (alexander.reinthaller@meduniwien.ac.at)
Clemens Tempfer (clemens.tempfer@marienhospital-herne.de)

Version:5**Date:**12 August 2014

Author's response to reviews: see over

Christoph Grimm, M.D.
Comprehensive Cancer Center, Medical University of Vienna
Department of General Gynecology and Gynecologic Oncology
A-1090 Vienna/Austria, Waehringer Guertel 18-20
(+43 1 40400 2962, FAX +43 1 40400 2911
e-mail: christoph.grimm@meduniwien.ac.at

To the

Editor-in-Chief

July 27th, 2014

Re: *Manuscript revisions*

Dear Dr. Solera,

please find enclosed our revised manuscript **"A Collagen-Fibrin Patch (Tachosil®) for the Prevention of Symptomatic Lymphoceles after Pelvic Lymphadenectomy in Women with Gynecologic Malignancies: a Randomized Clinical Trial"**, which we submit for publication in Your *Journal*.

Thank you for the possibility to address the comments of the reviewers. I hope that the following responses address the comments adequately.

Referee #1

Comment #1: Implement discussion section, since it is of 76 words….

Response #1: As requested by the referee we extended the discussion section (Discussion, para1).

Comment #2: Add conclusions section

Response #2: As requested by the referee we added a conclusion section (Conclusion, para 1).

Comment #3: Insert few surgical images on TachoSil application into the paper, to better clarify TachoSil use during surgery.

Response #3: We now provide three surgical images showing the application of Tachosil® during surgery (Figures1-3, Figure legend).

Referee #2

Comment #1: Select an homogenous population (cervical and endometrial cancer imply different lymphadenectomies and LPS and LPT are too different approaches and may affect the results).

Response #1: We thank the referee for suggesting a more homogenous population. We also thought about restricting the population only to endometrial cancer cases. Nonetheless we decided to include endometrial as well as cervical cancer patients as there is no prospective study indicating a different prevalence of lymphoceles or lymphedema in endometrial compared to cervical cancer patients. We included the type of malignancy as a secondary outcome and aim to describe the prevalence of observed lymphoceles in these two groups.
With respect to the surgical approach (laparoscopy versus laparotomy) we had the same dilemma. To the best of our knowledge there is only very poor retrospective data (for example: Ghezzi F, Uccella S, Cromi A, Bogani G, Robba C, Serati M, Bolis P: Lymphoceles, lymphorrhea, and lymphedema after laparoscopic and open endometrial cancer staging. Ann Surg Oncol 2012,19:259-267.) indicating a difference in the rate of lymphoceles typically biased by historical control cohorts, small sample sizes and/or retrospective analyses. Thus, we aim to prospectively describe the differences observed between the laparotomy and laparoscopy approach in our prospective trial. This has been added to the methods/design and the discussion section (Methods/Design, para 2; Discussion, para 2, line 1).

Comment #2: The number of harvested lymph nodes should be described.

Response #2: As mentioned by the referee, the number of removed as well as the number of positive lymph nodes might possibly influence the risk of lymphocele development. Thus, these two parameters will be prospectively collected in our trial.

Comment #3: Although very well planned the study lacks of originality.

Response #3: Although there are two reports describing the use of Tachosil® in the prevention of lymphoceles in women after pelvic lymphadenectomy, we think that our study provides substantial information. The first study (Tinelli A, Mynbaev OA, Tsin DA, Giorda G, Malvasi A, Guido M, Nezhat FR: Lymphocele prevention after pelvic laparoscopic lymphadenectomy by a collagen patch coated with human coagulation factors: a matched case-control study. Int J Gynecol Cancer 2013,23:956-963.) is a retrospective matched case-control study with a historical control cohort and a total number of 55 patients. The sample size and the study design limit the clinical implication significantly. The second study (Tinelli A, Giorda G, Manca C, Pellegrino M, Prudenzano R, Guido M, Dell'Edera D, Malvasi A: Prevention of lymphocele in female pelvic lymphadenectomy by a collagen patch coated with the human coagulation factors: a pilot study. J Surg Oncol 2012,105:835-840.) is a prospective study that included also only 58 patients. This study observed a significant difference in the total rate of lymphoceles. Although the rate of symptomatic lymphoceles varied considerably between the Tachosil® and the control group, the difference was not significant (Tachosil® group: n=3/30, 10% vs. control group: n=9/28, 32.1%, p=0.053). Most likely, the lack in significance is caused by the limited number of patients. Thus, we designed a larger multicenter trial to evaluate the efficacy of Tachosil® in preventing symptomatic lymphoceles in women with gynecological malignancies after pelvic lymphadenectomy, as this is a clinical relevant endpoint. This is now discussed in the Discussion section (Discussion, para 3, line 1).

Referee #3

Comment #1: …technical removement of the lymphatic tissue:…

Response #1: We thank the referee for pointing out a very interesting aspect of the trial. Although as a surgeon based on our clinical experience, we might think that there is a difference between the different surgical devices in the rate of lymphoceles, evidence is lacking. There is only very limited data, such as a study by *Ghezzi et al.* (Ghezzi F, Uccella S, Cromi A, Bogani G, Robba C, Serati M, Bolis P: Lymphoceles,

lymphorrhea, and lymphedema after laparoscopic and open endometrial cancer staging. Ann Surg Oncol 2012,19:259-267.) – a retrospective single center analysis indicating that new energy devices might reduce the rate of lymphoceles. As there is no prospective data in women with gynecological malignancies after pelvic lymphadenectomy, we decided to prospectively monitor the devices used and compare these groups in our trial (Methods/Design, para 2; Discussion, para 2, line 1).

Comment #2: Another important aspect seems to be the number of removed lymph nodes, which should be at least counted very thoroughly and the pathologists…..

Response #2: As mentioned by the referee, the number of resected as well as the number of positive lymph nodes might possibly influence the rate of lymphoceles. Thus, these two parameters will be prospectively collected and documented in the present trial (Methods/Design, para 2).

Comment #3: The problem seems to be that the surgeons, aware of the intervention group, might reduce radicality in patients designated to the TachoSil patches. This bias should be reduced as much as possible.

Response #3: This might be a misunderstanding, which now has been clarified. Patients have to sign the informed consent and agree to participate in the study at least one day before surgery. If patients are eligible and agreed to participate, they are included in consecutive order. Patients receive an envelope according to their inclusion number in which allocation is documented. This envelope accompanies the patient into the operating room. A nurse opens the envelope not before pelvic lymphadenectomy and hemostasis are completely finished. According to the treatment group the patient is allocated, the surgeon now has to apply either two Tachosil® patches in the intervention group or no Tachosil® in the control group. Therefore, the surgeon cannot influence the extent of the lymphadenectomy, as he is not aware of the patient's allocation until the end of the lymphadenectomy. This has now been clarified (Methods/Design, para 9, line 1).

Comment #4: What is the reasons for two licenses in Europe 2004 and 2007, please clarify.

Response #4: Unfortunately this has been a misspelling. This has now been clarified, as Tachosil has been licensed in the EU in 2004 (Background, para 3, line 1).

Comment #5: Are there Ethics committee approvals for the two other hospitals in Prague and Bochum?

Response #5: Approvals of the respective Ethics committees for all three hospitals have been obtained prior to study initiation. This has been clarified in the manuscript and ethics approvals are attached as supplemental data in the revised manuscript (Methods/Design, para 10, line 1; Supplemental data).

Comment #6: Thrombosis in the lower limb should be taken into account for secondary outcome variable, as it reflects quite often presentations of lymphocysts.

Response #6: As thrombosis typically presents with leg swelling after surgery it will closely be monitored and documented as lymphoceles with leg swelling are defined as symptomatic lymphoceles by the CTCAE 4.03 grading system – our primary outcome parameter. If thrombosis occurs without the presence of a lymphocele it will be documented as an adverse event.

Comment #7: How do the authors want to make sure, that symptomatic lymphoceles will be treated in their departments and not somewhere else?

Response #7: Patients receive an additional information leaflet describing typical symptoms after surgery in general and pelvic lymphadenectomy in particular in addition to their patient information. They receive a 24h hotline, which they can contact in case of postoperative problems. Moreover, they are asked to visit the respective hospital, where the surgical procedure within the clinical trial has taken place, as this is important for the clinical trial they are participating in.

Comment #8: At what time point will the anonymzation will take place? How do the authors want to link follow-up data of patients tp the surgical intervention, if patients

are anonymized?

Response #8: Patients will be pseudo-anonymized for protection of data privacy. At the time of inclusion, a code based on initial of given name and surname and their date of birth will be assigned to every patient. The code will only be used for data entry in the database, as the patient's full name is not documented in the same database, where clinical information is collected and stored. During the clinical routine and follow-up visits patient information is documented on study documents, where both, patient's full name and patient's code, have to be documented. This has now been clarified in the manuscript (Methods/Design, para 18, line 1).

We hope, that the revised manuscript is now suitable for publication in your Journal.

Yours sincerely,

Christoph Grimm, M.D., Ass. Prof.
Department of General Gynecology and Gynecologic Oncology, Gynecologic Cancer Center, Comprehensive Cancer Center, Medical University of Vienna, Austria
Waehringer Guertel 18-20
1090 Vienna
Austria