Author’s response to reviews

Title: Transabdominal laparoscopic retroperitoneal neurectomy for chronic pain after inguinal hernia repair and appendicectomy - a matched-pair study.

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Author’s response to reviews:
Dear Editors,

we would firstly like to thank you for the review of our study and for the opportunity to resubmit the manuscript including modifications made according to the reviewer comments.

Please find below the point-to-point answer to the reviewer comments. Modifications in the manuscript have been highlighted with yellow color and can be found in the corresponding sections.

Professor Harris raised the issue of eliminating the matched-pair setting in the trial. This fact is a major revision of the way we planned the trial and we consider the data raised during the matching process to be of scientific relevance even if another control group would have been more appropriate. We would be pleased if you could take our response to Professor Harris into consideration and discuss this issue with the other reviewers. If all reviewers agree that the matching is irrelevant we would remove it from the manuscript.
Yours sincerely,
Florian Herrle

Revisions according to the 1st reviewer’s comments:

Thank you for reviewing our work again, we are very happy you found our revision satisfactory.

Revisions according to the 2nd reviewer’s comments:

Dear Professor Harris,

thank you very much for the review of our manuscript and for your experienced opinion in the field of repair of complex hernias.

Concerning the comparison between patients with chronic postoperative pain and patients without chronic pain we fully agree with you. It is clear that the first group would have worse values in the QoL and Pain questionnaires and this fact would lead to a statistical significance. We had considered not creating a control group when we planned this trial. The reason why we eventually formed the control group (except from the slightly better level of evidence that a controlled study offers) was that we would not be able to explain the results of the findings of the QoL and Pain questionnaires.

Before beginning the trial, we performed a literature research and did not find relevant baseline values in order to compare with the results of our specific patient population. There are QoL and Pain data after mastectomies or thoracotomies but at the time we did not find sufficient data in this domain. We expected to find low values in the SF-36 and high values in the Pain detect but our question was how much do those patients really suffer. That was the reason that we used the questionnaire which was suggested by Loos. It was the only one offering a plausible chronological presentation of the change in the patient’s symptoms.

An interesting part in the evaluation of the results was that not all patients of the control group scored the expected high quality of life levels in the addressed questionnaires. As we described, this group was conceived as matched population with uncomplicated hernia surgery according to
our documentation and these patients were subsequently surveyed by our pain and QoL questionnaires. Therefore, we considered that the ‘matched’ setting may have offered relevant information for our planned comparisons. Indeed, we found that patients after an uncomplicated operation are not always free of symptoms and that seems to be a continuum of pain related problems in this uncomplicated surgery population except from the patients who actually fulfill the criteria for chronic pain. We had initially planned a bigger control group (matching of 1:5) but we could not reach the numbers in the control group. As we contacted the patients of the control group there were actually some who complained about pain (the patient who was eventually included in the control group when we had more than one matching candidates was randomly chosen in order to avoid a further selection bias).

We fully agree with your comment, that the most suitable control group would be one with patients receiving conservative or interventional treatment of chronic pain. Even better would be a prospective randomized setting. However, to our knowledge, there are only a few hernia centers (Milan, Leuven, Lichtenstein Center-LA, etc.) which are able to conduct such a trial. We would not be able to perform a trial with a reasonable power to answer this question.

Eliminating the control group from the study would mean a complete revision of the way we thought and planned the trial. We have addressed this issue and your comment to the editor in order to get feedback about this critical point from several perspectives. We propose that if the other reviewers agree that the control group is irrelevant and redundant then we remove the control group. We hope that this meets your expectation-

Concerning the decision which nerves to resect, we performed a meticulous clinical examination before operating each patient. EMG or nerve mapping were not used. We performed additional examinations such as sonography, computer tomography or interactive MRI scans (if needed) in order to sort out recurrent hernia or other confusing pathologies but we guided the resection according to the patient’s symptoms. Patients with pain in the proximal/lateral thigh received a neurectomy of the lateral femoral cutaneous nerve. The ilioinguinal nerve was resected in case of pain near-or-at the scar of the primary operation and the genitofemoral nerve was resected in case of pain in the genital region. We have changed the text in the manuscript and underlined it.

Revisions according to the 3rd reviewer’s comments:
Dear Professor Uen,

thank you very much for the review of our manuscript and for your experienced opinion.

Concerning your first comment on quantitative data for the assessment of the intra- or intergroup differences in the surgical outcomes I am afraid we do not have further data on this field. Intergroup difference regarding the primary operation could not be quantitatively assessed because of the retrospective character of the trial. The only fact is that all patients of the control group were operated in our department, from or under the supervision of a specialized hernia surgeon, following the current trends and guidelines in hernia surgery. The patients of the LTRN- group received the primary hernia operation in other hospitals, some of them decades ago with operative techniques which are no longer (commonly) practiced. The main problem of our trial and of many other trials in this field is the high heterogeneity of patients and symptoms.

Regarding the intragroup difference, we carefully assessed the pain localization and the pain symptoms before operating the patient. Further quantitative parameters were not routinely evaluated. The operating surgeon critically evaluated the previous treatment of the patients, subjectively assessed the level of disability and the probability that the operation could offer pain relief, based on his experience. Quantitative sensory testing would have been an excellent idea, mainly in predicting the postoperative outcome and therefore, the probability of pain relief. This method has been implemented and in some way, validated, in the field of chronic back pain and has shown very promising results. However, the available data were (at the time when we conducted our study) and still are somehow confusing, since it is clear that QST can discriminate patients with pain from those who are pain free, but are not yet associated with the perspective of selecting the responders [1].

The only 2 trials addressing the use of QST in chronic postoperative inguinal pain were published by the group of Professor Amid a few months ago [2, 3]. The second actually presented very interesting results in a small group of patients where the preoperative and postoperative findings in the sensory mapping provide a sound explanation on how the neurectomy really works [2]. It is clearly a hot issue and a major field of research at the moment and we are fascinated to see the next steps.
Considering the second issue you raised about differences between responders and non-responders, there are many factors which can influence the response in the neurectomy and this is the cornerstone of selecting the right patients for surgery.

In our trial we had 2 patients who clearly not responded to the neurectomy. The first one had received a bilateral TEP and then the neurectomy about 4 years after the primary operation, having failed infiltrations and further conservative treatment in his history. In the follow up after the neurectomy he described numbness and persisting pain in the proximal thigh despite the resection of the genitofemoral and the lateral femoral cutaneous nerve which actually, perfectly corresponded to the area of symptoms. This patient had had prostate cancer in his history and a complicated postoperative course after da Vinci-surgery but he had clearly described that the pain had nothing to do with the urological complications and already existed at the time of the prostatectomy. That is why we proceeded with the neurectomy.

The second patient received the neurectomy about 12 years after the primary operation (anterior herniotomy). He was a severely ill hemodialysis-patient with chronic renal failure and permanent oxygen support because of a gold IV chronic obstructive pulmonary disease. He had undergone a bilateral hip replacement in the past but the pain character did not meet criteria for a possible orthopedic complication. The relevant question on this case is if the neurectomy came too late to defeat 12 years of strong pain. However, looking at the other patients of our trial shows 3 further patients who received the neurectomy more than 10 years after the primary operation, one actually almost 25 years later and still responded well.

There are several other issues which can be discussed on why those particular patients did not respond and the others did. The first one is if the symptom-guided neurectomy was adequate for treating those patients or if a triple/quadruple neurectomy would have been the right choice. The idea of resecting all groin nerves was pioneered from the group of Professor Amid about 15 years ago and has been showing very good results in treating chronic postoperative groin pain [4, 5]. On the other hand, there were 7 patients who responded to the treatment so it is not always easy to accept the morbidity associated with resection of all groin nerves. Limiting factor here is, of course, the small group of patients we treated compared to the big series of the Lichtenstein center.
A further important issue is the selection of the patients to receive the neurectomy. We based the selection on the clinical symptoms, examination-clinical experience and fail of response to conservative treatment. We did not consider infiltrations with local anesthetics or other agents as a mandatory prerequisite since there was no consensus at the time on how to perform them or when [6]. The first publication which clearly suggested performing preoperative infiltrations was published almost 2 years ago from an international group of hernia specialists proposing an algorithm for treating patients with chronic postoperative groin pain [7]. This algorithm has been now implicated in our clinical praxis.

It is really difficult to find a plausible explanation on why some patients respond and some not. The pathophysiology of pain development and chronification as well as patient related characteristics influence this pathway and make the treatment of this condition truly challenging, also for experienced surgeons. However, the issue you raised above with the sensory testing, combined with structured diagnostic approach and treatment of those patients will probably standardize and bring more perception and comprehension in this pathology and therefore make it simpler to treat in the next years.

Literature

