Author’s response to reviews

Title: The influence of dexamethasone on postoperative swelling and neurosensory disturbances after orthognathic surgery: A randomized controlled clinical trial.

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Author’s response to reviews:

Dear Prof. Stamm,

We were delighted to receive your e-mail of October 2, 2017 in which you indicated that our manuscript might be of potential interest for publication in your journal once we address the concerns raised by the reviewers. We would like to thank you and the reviewers for identifying areas of our manuscript that needed corrections or modification. We believe that the changes have improved the manuscript.

Our response to each of the comments of the reviewers are documented below. All contributors certify that they are aware of and are in agreement with the revisions.

We hope that the revised manuscript is adequate for publication in your journal.

Sincerely,

Wiebke Semper-Hogg

Reviewer #1: The study "The influence of dexamethasone on postoperative swelling and neurosensory disturbances after orthognathic surgery: A randomized controlled clinical trial" depicts the postoperative swelling after three different surgical procedures in orthognathic surgery. The three groups are sub-divided into a study (medication) and control group.
Overall, the study design and statistic analysis are appropriate. Study population and inclusion/exclusion criteria are reasonable. Technical description of methods is thorough and comprehensive. Results are clear and to the point. Discussion is detailed and in length.

Many thanks for the positive valuation of our study. We thank the reviewer for the time spent on our manuscript.

Thus I recommend acceptance of the article. Yet I would like to address three minor comments:

1. In the abstract please clearly state that you have three surgical groups which you divide into a study and control group. Currently, at first you think you only have a study and control group.

Comment:
We amended the abstract for more clarity.

New text: Thirty-eight patients (27 male and 11 female) patients, all with the indication for an orthognathic surgery, were enrolled in this study (mean age: 27.63 years, range: 16-61 years) and randomly divided into two groups (study group/ control group). Both groups underwent either maxillary and/or mandibular osteotomies, resulting in three subgroups according to surgical technique (A: LeFort I osteotomy, B: bilateral sagittal split osteotomy, C: bimaxillary osteotomy).

2. Figures: Please include in FIG 5 (bimaxillary osteotomy) also day 1 like in the other two groups.

Comment:
Many thanks for this idea. Unfortunately, we have no data for those patients from day 1, since patients after a bimaxillary osteotomy cannot be investigated with the 3D scanning device due to physical impairment. In order to give most possible information to the readership, we decided to give information for subgroups A and B as from day 1 and for subgroup C as from day 2 after intervention. For more clarity, we added some information to the Methods section.

New text: 3D surface scans were generated at five different time points: D1 (first postoperative day, only for subgroups A and B, in subgroup C not possible due to physical impairment after intervention)…

3. Methods: Perhaps the authors could include also the time duration of surgeries. This could perhaps also explain the high significant statistical results (p < 0.001) of using dexamethasone for bimaxillary osteotomy.

Comment:
Many thanks, this is a good idea. We added the information to the Methods and Results section.

New texts:

Methods: Surgery duration was documented in all cases.

Results: Mean surgery duration was 97.16 (±41.29) minutes in subgroup A, 142.56 (±29.24) minutes in subgroup B, and 285 (±63.56) minutes in subgroup C.

Reviewer #2: Thank you for submitting this well written paper on the use of dexamethasone for reduction of facial swelling following mandibular and maxillary surgery.

Many thanks for the very helpful comments on our manuscript. We very much appreciate the time the reviewer spent on our manuscript.

I have the following comments:

Abstract

line 7 replace the word psychic (= wizardry or magic) with psychological

Comment:

Please accept our apology for this flaw. We have replaced the word as suggested.

New text: “Serious swelling can lead to great physical and psychological strain.”

Introduction

Page 4 line 21 what do you mean by 'technical difficulties'

Comment:

We are sorry, however, we not fully understand what the reviewer means with this comment, since we haven’t used the term “technical difficulties” in the text. If the reviewer means the technical capabilities on page 3 line 9, this means that other research groups do not have access to 3D scanner systems or does not use such systems as a standard. For more clarity we amended the sentence.

New text: All these clinical trials were not able to measure the swelling three-dimensionally due to a lack of technical capabilities, such as 3D scanning facilities.

Page 5 line 40 why do you use cooling? what is a 'standardised, cooling protocol'?
In our clinic, we usually use cooling with a standard protocol. All persons got an instruction in cooling for 14-16 h per day. All patients were supplied with a Hilotherm device. In the present study, cooling was performed in all patients to increase the homogeneity of the groups. For more clarity we amended the text.

New text: To homogenize the groups, all participants got a thorough instruction in cooling. This standardized postoperative cooling procedure was important to allow a direct comparison of the swellings. Therefore cooling was realized immediately after the operation for the time of hospitalization (for subgroups A and B 3-4 days, subgroup C 5-7 days). All participants used the same type of cooling device (Hilotherm GmbH, Argenbühl-Eisenharz, Germany) at a temperature between 17 and 19 °C for 14-16 hours/day.

how long do you keep patients in hospital? I would consider this a confounding issue.

Comment:

The reviewer is right and many thanks for this comment. The stay in hospital depends only on the type surgical intervention and might therefore be excluded as a confounder, as both interventions (injection/no injection) were performed in all subgroups. Patients normally stay in hospital in subgroups A and B for 3-4 days and in subgroup C for 5-7 days. We amended the text for more clarity.

New text: Therefore cooling was realized immediately after the operation for the time of hospitalization (for subgroups A and B 3-4 days, subgroup C 5-7 days).

Why not give dexamethasone without cooling?

Comment:

This is a good idea for a new study and it would be interesting whether we can dispense in the future the cooling procedure by such a single injection. However, in the present study, we just wanted to investigate the effect of dexamethasone under best boundary conditions. As we now know that the injection is helpful, we might plan now the next study.

How can you measure the reduction in swelling related only to the use of dexamethasone? These questions need to be addressed

Comment:

We closely controlled the patients and we standardized all procedures best possible (surgical experience, duration of surgery, cooling procedure, health condition of patient etc). Furthermore, we standardized the measurement procedure with the 3D system. The only difference in the iatrogenic treatment between the test and the control group was the application of the
dexamethasone. Therefore, the effects most like depend more or less only on the injection of the dexamethasone.

Methodology and results - all ok, especially if you can justify my questions above

Page 9 line 1 I am confused by your term 'regeneration' Was there something to that needed regeneration? Did the nerve degenerate? Are you saying that all the patients had some neurosensory deficit as a result of the surgery? Please explain.

Comment:

The term neuroregeneration might be a bit misleading. We replaced therefore this term by “reduction of neurosensory disturbances”.

Regarding the results found with our study: 78% showed neurosensory disturbances on day one after surgery. These values fit quite well with the results in the recent literature (e.g.: Antony PG et al.; J Oral Biol Craniofac Res. 2017)

I am not aware of any evidence for the use of steroids as an aid to sensoro-neural recovery

Comment:

Such effects have been demonstrated in some older studies (e.g.: Hall, Edward D. "The effects of glucocorticoid and nonglucocorticoid steroids on acute neuronal degeneration." Advances in neurology 59 (1992): 241-248.; Kiefer et al. "Effects of dexamethasone on microglial activation in vivo: selective downregulation of major histocompatibility complex class II expression in regenerating facial nucleus." Journal of neuroimmunology 34.2 (1991): 99-108). It was not the primary outcome of our study, however, as we always control the neurosensory disturbances in our patients after the surgery, it was a second target criterion of our study.

Page 9 line 44 'A preoperative scan would lead to wrong results, as the surgery changes the patient's facial profile' - but surely this would be an accurate reference/starting point, and the one to compare with day 90

Comment:

Many thanks for this comment. We know that the postoperative scan of day 90 has limitations, but since only swelling reduction was analyzed, we did not focus on the change of the patient’s facial profile in the present study.

Page 10 line 7 glucocorticoids are almost universally used in orthognathic surgery. Justify this statement. And nobody would consider long term use in this situation. These lines need modification, and the rest of the paragraph is really not relevant to the discussion

Comment:
Many thanks for this comment. Indeed it is not necessary to go in detail regarding the side effects of the glucocorticoids in case of long term use. We only listed the effects and condensed the section distinctly.

New text: Long-term glucocorticoid therapy can cause several side effects such as Cushing-Syndrome, adrenal insufficiency if administered with high doses and for more than five days, temporarily increase of blood sugar level psychological impairment or even decrease of wound healing. However, there…

We also restructured the following paragraph for more clarity.

New text: The present study used 40mg dexamethasone according to studies in traumatology. In these studies 40mg dexamethasone is administered as antiemetic and opioid-sparing medication after surgery. Also in oncologic studies a high single dose of dexamethasone shows beneficial effects versus prednisolone. Regarding side effects, the results are somewhat contradictory. While one study showed a slight increase of complications after perioperative corticoid administration, most studies showed no side-effects of a single high-dose dexamethasone therapy. Due to these very positive effects, we decided in favor to the relatively high single dose amount, even if in former studies in orthognatic and oral surgery, a single shot administration of only 8-16mg dexamethasone was used, which, however, shows some beneficial effects concerning swelling and edema.

Page 11 you return to the point about cooling. Massive swelling? You might cause it, I don't! Something to do with technique. I think you need to re-phrase these lines

Comment:

Swelling is a common condition after surgery. We removed the phrase massive in order to relativize it. We also rephrased the whole paragraph on this issue and pointed more out that the choice of surgical technique is relevant. Independent of the absolute amount of swelling we caused by the surgical intervention, which was standardized by including only cases treated by one surgeon, we have seen an effect of the single dose dexamethasone injection in both, in cases of severe swelling and in case of mild swelling, supporting the general effect of the injection.

New text: Regarding possible side effects of the glucocorticoids like decreased wound healing, increased infection rate hypotension, or even neurosensory disturbances, there was no difference between the control and the test group. However, the results confirm the assumption that glucocorticoids decrease postoperative edema after orthognathic surgery, which is a clear negative aspect of orthognathic surgery. The amount of swelling is inter-individually different and depends also on the surgical techniques. Differences in surgical techniques were excluded by including only cases treated by one surgeon. All in all, we were able to show that the single high dose of dexamethasone shows beneficial effects in reduction of postoperative edema, independent of the amount of swelling. Therefore, we can state that the single dose together with modern operation techniques can increase the patient’s comfort after such elective surgery.

Page 12 line 7 what is 'Semmes esthesiometer'?
The Semmes aesthesiometer sometimes also called Semmes-Weinstein aesthesiometer is a measuring device using nylon monofilaments to check the tactile sensitivity. For more clarity, we added some information to the text.

New text: …mechanical thresholds by Semmes aesthesiometer (measuring device for tactile sensitivity)…

Page 12 line 44 - you need a space between 'neuroregeneration' and 'Furthermore'

Comment:

The space has been included

I have, as may appreciate many concerns about this paper. As it is, I would not recommend publication but if you were to deal with the queries satisfactorily, then may be it could be. I hope you can!

We hope that we satisfactorily revised the manuscript and that the reviewer agrees with our changes.

Reviewer #3: The authors stress the importance of using 3D imaging technologies in gaining more information about a special therapy like orthognatic surgery. They present a method for reaching objective results.

Many thanks for your time you spent on our manuscript and the evaluation of our study.

For more information it would be interesting whether a different dose has a special impact on reduction of swelling. So further studies are recommended to quantify reduction of swelling according to dose and type of surgery.

Comment:

This is indeed a very interesting question, which should be investigated in further studies.

Unfortunately there is no discussion about postsurgery complication rates after administering corticosteroids.

Comment:

Many thanks for this comment. Indeed there is an increase in complication rate in case of long term administration of corticosteroids, in particular if further risk factors such as diabetes or smoking are present. Regarding the effects of a single dose administration, the results in the literature are somewhat contradictory. Snall et al. showed that there is the risk of occurrence of
disturbance in surgical wound healing after administration of dexamethasone (Effects of perioperatively administered dexamethasone on surgical wound healing in patients undergoing surgery for zygomatic fracture: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 2014, 117:685-689). However, other studies showed no side effects. Therefore, the positive effect of reduction of swelling must be weighed against the enhanced risk of wound healing. Therefore, in patients with further risk factors such as diabetes or smoking, the administration of glucocorticoids should be done carefully. For more clarity, we amended the respective part in the discussion.

New text: Regarding side effects, the results are somewhat contradictory. While one study showed a slight increase of complications after perioperative corticoid administration, most studies showed no side-effects of a single high-dose dexamethasone therapy.