Author's response to reviews

Title: Stimulation of the autonomic nervous system in colorectal surgery: a randomized, placebo-controlled trial

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Author's response to reviews: see over
Dear Editor,

Thank you for giving us the opportunity to resubmit a revised version of our manuscript entitled: “Stimulation of the autonomic nervous system in colorectal surgery: a randomised, placebo-controlled trial”.

The manuscript has been changed based on the valuable comments of the reviewer. All changes are marked in the text and a point by point reply has been given below to the reviewers report.

We hope the Editorial Board will reconsider this revised manuscript for publication.

Yours sincerely,

Tim Berghmans
Reply to the reviewer

Reviewer 1
We would like to thank the reviewer for the constructive comments and we would like to address the points made as follows:

1. Concerning the high-fat enteral nutrition. Enteral high-fat nutrition has been shown to stimulate the autonomic nervous system in experimental studies. This high fat enteral nutrition is not given in daily clinical practice. In this trial none of the individuals receives high fat enteral nutrition. The experimental nature of this nutrition is clarified in the text (page 4, line 1-6, marked in yellow).

2. In line with the previous comment, it is stated more clearly that the beneficial effects of high fat nutrition are only proven in rats and further clinical research is needed (page 4, line 1-6, marked in yellow).

3. Fast-track surgical programs are generally accepted and implemented at both hospitals. Length of stay is shortened by enhanced recovery and we aim to add to this the effect of gum chewing. This is why both the chewing gum group as the dermal patch group will receive the same fast-track surgical program. Gum chewing is thought to stimulate the autonomic nervous system during the period of fasting both preoperatively and postoperatively. This is explained in the text now (page 6, line 20-21, marked in yellow).

4. The reviewer questions why colorectal surgery is chosen and whether this theory might be extrapolated to other surgical contexts. Colorectal surgery was chosen since this is a rather homogenous patient group, in which we know from other studies we have performed that a postoperative inflammatory response can be measured and postoperative ileus occurs. Indeed, in theory, this principal may apply to other kinds of surgery.

5. The reviewer states that the rationale for the control group (dermal patch) must be explained more carefully. This has been done and indicated in the text in yellow (pages 5 last line to page 6, line 1-6). The dermal patch does not contain an active ingredient, neither does the chewing gum. The chewing itself (sham feeding) is the investigated intervention; thereby any similar intervention would somehow involve chewing and thus sham feeding. The choice of the dermal patch is because of the ease of use, comfort and feasibility. A study of (J Am Coll Surg. 2006 May;202(5):773-8,) used a bracelet as a placebo with a similar intention. The reviewer states that the rationale for the control group (dermal patch) must be explained more carefully. This has been done and indicated in the text in yellow (pages 5 last line to page 6, line 1-6).

6. Encouraged is indeed the better description. No expected duration of chewing has been predefined. Patients are encouraged to chew chewing-gum as often and as much as they prefer. They have been informed about the expected effects and advantages of this chewing of the chewing gum. There
only is one type of chewing gum used (Freedent Frozen Mint). In the manuscript stimulated has been replaced by encouraged. (page 6, line 16)

7. To our knowledge there are no safety issues for chewing gum. No literature has been reported. During our current experience of 58 patients there have been no safety issues due to chewing of chewing gum whatsoever.

8. Concerning the potential crossover effect: On admission the patient either receives a dermal patch or a chewing gum. When the patient is allocated in the dermal patch group patients are instructed not to chew any chewing-gum during their admission. At admission this is being explained carefully to all patients within the dermal patch group (page 6, lines 18-19, marked in yellow).

9. The reviewer questions what to do with habitual gum chewers: The study and the objectives are explained at the outpatient clinic and additional information is given. When the patient is a habitual gum chewer and is randomized to the control group, the patient is instructed to cease gum chewing at the time of fasting, until normal diet is resumed. In this way unwanted crossover is avoided. During admission the patient is again clearly instructed as is mentioned at point 8. A patient can withdraw from the study at any moment. This information is also in the text (page 6, lines 18-19, marked in yellow).

10. The reviewer states the sample size calculation is not easy to follow. Clinically, several outcome parameters are important such as postoperative ileus. The incidence of postoperative ileus is related to length of stay which in the literature is regarded as valuable. Power analysis was calculated with postoperative ileus as primary outcome parameter and length of stay. For length of stay we assumed that a decrease of the mean of 1 day would be relevant. In our center we experienced a hospital stay in the control group with a mean of 5 days. The effect-size of chewing gum on postoperative ileus as described in the literature is substantial and slightly less patients would be required when using POI as primary outcome parameter. Therefore, we used length of stay as the primary outcome parameter for the Power calculation so both parameters are adequately powered. To clarify this information has been added to our manuscript (page 8, lines 4-12 marked in yellow).

11. In the current design of the study subjects already chew gum both before and after surgery. This is explained in the text (page 6 lines 15-17, marked in yellow) When patients are admitted and randomized within the chewing gum group they are encouraged/instructed to start chewing gum, at least from the moment of fastening preoperatively. This chewing is continued until postoperatively at least until the moment at which normal solid food intake is being tolerated.

12. As requested by the editorial board the approval of the Medical Ethics Committee has been added. (page 6, line 8-10)