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AN OPEN ACCESS JOURNAL COVERING NEW FINDINGS IN LAPAROSCOPIC SURGERY

Peer Review File

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Reviewer A

Thank you for asking me to review this 'mini-review' on low pressure pneumoperitoneum. I appreciate that this is a mini-review and does not require a strict format, however I feel that this review struggles between personal opinion and an actual review without any mention of methodology for this review. The paper was also difficult to read with overly long sentences, some simplistic English, and some grammatical errors.

In reply: Thank you for this comment. The article format for this paper is that of a classic narrative review. This means that the reviewer is absolutely correct in pointing out that it is a mixture of personal opinion and an actual review, as this constitutes the structure of a narrative review, where a formal literature search mechanism has not been used. Otherwise, it would be a systematic review implying a different methodology (and reporting). As a narrative review it is unusual to describe the methodology as the methodology is in fact not systematic for such a review. We have therefore chosen not to correct the paper on this point. The reviewer mentions that there are some slight language problems. We have carefully read the paper and corrected a few obvious errors in spelling and grammar.

Some other points to consider for improving this paper:

1. It was difficult to follow which meta-analysis or RCT you were describing, and whether you thought that was a seminal paper in the field

   In reply: Since we submitted the paper a new meta-analysis has been published (ref. 15). This has now been included in the manuscript.

2. The paper appears to collate all literature regarding penumoperitoneum, regardless of the type of laparoscopic surgery being performed - hence I'm not sure if some of the conclusions are fair or valid, eg the discussion about positioning.
   In reply: We have included a recent meta-analysis about positioning (ref. 23). It is our opinion that the pathophysiological implications of positioning is less dependent on the type of surgery performed (as long as it is not cardiopulmonary). The paragraph, however, lacked information on anti-Trendelenburg and we have therefore added a sentence about this: To our knowledge there are not data to suggest that steep anti-Trendelenburg position has any negative effects on postoperative clinical complications either.

3. The presentation of data around increased intracranial and intraocular pressure is extremely rare and flimsy at best. Yet there is no presentation of the more relevant data regarding reduced perfusion of the liver and kidneys.

In reply: Thank you for this comment. We added the following to the manuscript:

Hepato-renal problems

Similar to the cardiovascular changes an increase in pneumoperitoneal pressure can also led to hepato-renal modifications. It may decrease hepatic arterial and portal venous blood flow and can reduce splanchnic perfusion. Vena cava compression may decrease venous return and pooling of venous blood in the lower extremities (13). Finally, pneumoperitoneum has important effects on renal physiology. Direct compression of the renal vasculature can lead to a reduction in renal blood flow, glomerular filtration rate, and oliguria (13). Although uncommon, laparoscopy poses an increased risk of acute kidney injury in patients with preexisting kidney disease (14).

How

Thus, several lines of evidence, and summarized in a newly published meta-analysis, suggest that low pressure peritoneum significantly reduces the incidence of mild to moderate postoperative complications, reduces early postoperative pain scores, reduces PONV scores and reduces the mean length of hospital stay (15). However, it remains to be determined how peritoneal pressure can be reduced without compromising surgical conditions and patient safety.

Reviewer B

This is a well-done literature review.
I would ask the authors to clarify that this was a narrative review rather than a systematic review. If it was a systematic review please define the search terms used.
The authors mention in their opening statements that "Furthermore, there also seemS (remove S) to be differences within and between specialties.
In reply:the "S" has been removed as requested.

However, in most institutions there seems to be a consensus that 12 mmHg is the chosen standard pressure for laparoscopy." I would ask the authors to elaborate on this in the manuscript and compare some papers from different fields where the amount of pneumoperitoneum is mentioned. They say "seem" more than once - let's see the data.

In reply: We have rephrased the sentence, deleting "seems" and written "may" instead. In this way we don't say too much about the issue. It is the experience from both authors that there are differences between specialties and countries for routine levels of pneumoperitoneum. We have both travelled extensively around the world and gained this

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insight, but we are not able to document it by recent publications. We have therefore chosen the "soft way" in the manuscript using the term "may" instead of underlining the statement with literature references.

Reviewer C

Thank you for giving me the opportunity to review the manuscript entitled:

Low pressure pneumoperitoneum - why and how.

I think this is a stimulating and instructive report worthy of publication in LS.

I have one concern that I would like to address:

Jacob Rosenberg and Thomas Fuchs-Buder, after a careful review of the studies on the effects of low intrapneumoperitoneal pressure in laparoscopic surgery, give a mini-review and mention that the RECOVER trial proved that the quality of recovery after this type of surgery is better, thanks to the use of low intra-abdominal CO_2 pressure during surgery, but without giving a simple definition of the quality of recovery and the distinction between early and late recovery criteria. So it would be very useful if they would include this in this review page 3, line 84.

Best regards.

In reply: We referred to the RECOVER trial (ref. 3) in the paragraph about immune function. We actually in this paragraph did not discuss the term "recovery", but only discussed immune function and cellular effects. We have therefore, thanks to the insightful comment by the reviewer, chosen to rephrase the paragraph heading to "Immune function and cellular effects" thereby deleting the term "recovery" from the heading. This gives much better sense.

Reviewer D

The review is very interesting and well written.
In the topic 'Why', i suggest to expand more the topic of post-operative adhesions. There are many preclinical studies showing that a lower pneumoperitoneal pressure induces less postoperative adhesion formation. Two groups were working on this topic for many years: the team of Professor Koninckx and of Professor Canis.

In reply: Thank you for this comment. The problems of adhesions after surgery and the possible effects of intraabdominal pressure have already been mentioned in the paragraph about immune function and cellular effects and supported by refs. 5 and 6 (where professor Canis is first author).

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Reviewer E

Good morning, I find this a very interesting topic. Perhaps one should go a bit deeper on deep and moderate NMB. There are published papers stating that deep neuromuscular blockade is not decisive in improving surgical conditions compared to moderate neuromuscular blockade.

In reply: We agree with the reviewers comment. Indeed, there is an ongoing discussion whether or not to apply routine deep neuromuscular blockade for abdominal laparoscopic surgery. Of interest in this context, the European Society of Anaesthesiology and Intensive Care recommends in their recently published guideline on peri-operative management of neuromuscular blockade (ref. 16), to switch from moderate to deep neuromuscular blockade only if surgical conditions really need to be improved, rather than opting for routine deep neuromuscular blockade for abdominal laparoscopy. This on-demand approach is further supported by observations that surgical conditions are often already good even at moderate neuromuscular blockade. This applies particularly during volatile anaesthesia. However, in the original version of the manuscript we already mentioned in the Abstract section (see Abstract second paragraph) "..;However, further studies are needed to validate its efficacy and determine the optimal level of neuromuscular blockade."
To avoid any misunderstanding, we have now added the following to the manuscript:
Accordingly, the recently published guideline on the peri-operative management of neuromuscular blockade from the European Society of Anaesthesiology and Intensive Care recommends deepening neuromuscular blockade if surgical conditions need to be improved (16).

Line 82: indeed, NMB does reduce the production of inflammatory cytokines, but it should also be mentioned, as in discussions in other articles, that this may be due to the anti-inflammatory effect of drugs used for that purpose, such as cisatracurium.

*In reply: In a lung injury rat-model it could be shown that both steroidal and benzylisoquinoline NMBA may improve pulmonary outcome, most probably via the nAChRα1 receptor. Two small randomized trials showed neuromuscular blockade with cisatracurium improved oxygenation (Gainnier M et al. Crit Care Med 2004)) and decreased inflammation (Forel JM et al. Crit Care Med 2006)) in **ARDS**. In 2010, finally a multicenter French trial (ACURASYS) tested cisatracurium for **48h** in 340 patients with ARDS and found improved adjusted 90 days survival (Papazian L et al. N Engl J Med 2010). Although intriguing, this approach has not been widely adopted (Bellani G et al. JAMA 2016). Reasons include*

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physician resistence to accept a single study, given lack of replicability of prior ICU trials, small sample size, unclear mechanism, and lack of long term-long follow-up for paresis and other outcomes. In addition, the ACURASYS control group received deep sedation, inconsistent with current clinical practice (Bellani G et al. JAMA 2016). As a result, a definitive phase III trial had been designed (Huang DT et al. Annals 2017; 14:124 - 133ATS) and had published after the enrollment of more than 1000 patients in the N Engl J Med in 2019 (Moss M et al. N Engl J Med 2019). Its conclusions were as follows: "Among patients with moderate-to-severe ARDS who were treated with a strategy involving a high PEEP, there was no significant difference in mortality at 90 days between patients who received an ***early and continuous*** *cisatracurium infusion and those who were treated with a usual-care approach with lighter sedation targets."*
Thus, there might eventually be (or has been) a controversy whether or not a continuous infusion of cisatracurium over 48h *in critically ill patients with ARDS may be beneficial; however, there is no evidence in the literature that a single bolus dose of cisatracurium has any clinical relevant anti-inflammatory effect in otherwise healthy patients undergoing elective surgery for laparoscopic cholecystectomy. That's why we feel that the observed effect are not due to the NMBA per se.*

Line 122: if you mention several animal and human studies, you should include several references (you only include one).

In reply: To support the statement in line 122 we used ref. no. 11 by Struthers & Cushieri. This paper is a review containing numerous references, and that is why we only had one reference to support the statement in line 122.

Line 153: I think pressure should be in the singular.

In reply: Absolutely correct. This has been changed in the revised manuscript.

Line 157: start the paragraph with a different sentence, such as: "In that same study...".

In reply: Thanks a lot for this comment. It has now been corrected.

Regarding cardiac problems, since this is a brief review, I think it should not be described how to proceed in a rare situation (cardiovascular collapse with decreased blood pressure that doesn´t respond to pharmacological treatment).

In reply: We see the point from the reviewer here, however, as the situation with partial cardiovascular collapse is exactly what is feared by the anaesthesiologist we felt that it would be appropriate to cover this issue with some quite simple advices implicating a close collaboration between surgeon and anaesthesiologist. This exactly underlines our aim of pointing at collaboration between the two specialities.

Finally, although it is a mini review, there are published papers (one with 90 patients) that state that deep neuromuscular blockade is not decisive in improving surgical conditions compared to moderate neuromuscular blockade. Perhaps they should be included in this work. These papers have been published recently (2017).

In reply: The data and findings of J. Barrio (J Clin Anesth 2017) are already included in the systematic review of ESAIC (ref. 16) and thus they are already considered in the manuscript.