

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effect of perioperative intravenous lidocaine on postoperative outcomes in patients undergoing resection of colorectal cancer: a protocol for systematic review and meta-analysis
<b>AUTHORS</b>	Wentao, Ji; Xiaoting, ZHANG; Guolin, SUN; Xiandong, WANG; Jia, LIU; Jinjun, BIAN; Bo, Lulong

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Liu, Hengrui University of Cambridge, Department of Biochemistry
<b>REVIEW RETURNED</b>	19-Mar-2021

<b>GENERAL COMMENTS</b>	<p>The meta-analysis protocol is systematic and complete. Generally speaking, this protocol is good for acceptance. However, one thing I would like to point out is the targeting outcomes are limiting the value of this meta-analysis for clinicians. The effect of lidocaine, as well as other LA on multiple cancer, has been studied a lot in a preclinical study, lidocaine is potentially affecting cancer recurrence and metastasis after surgery, the primary outcomes evaluating in this protocol should also include cancer recurrence and metastasis, if not, the author should indicate somewhere and maybe change the title into a more specific one excluding cancer recurrence and metastasis, because cancer recurrence and metastasis are part of postoperative outcomes. Nevertheless, the author should mention the potential of lidocaine directly affecting cancer cells in the discussion, here are some recommended references that can be cited.</p> <p>Anticancer Res. 2017 Apr;37(4):1941-1945. doi: 10.21873/anticancerres.11534.</p> <p>Cancers (Basel). 2021 Jan 10;13(2):234. doi: 10.3390/cancers13020234.</p> <p>BMC Cancer (2018) 18:666 <a href="https://doi.org/10.1186/s12885-018-4576-2">https://doi.org/10.1186/s12885-018-4576-2</a></p> <p>Bratisl Lek Listy. 2019;120(3):212-217. doi: 10.4149/BLL_2019_036.</p> <p>Artif Cells Nanomed Biotechnol. 2019 Dec;47(1):2866-2874. doi:10.1080/21691401.2019.1636807.</p> <p>Pharmacol Ther. 2020 Aug;212:107558. doi: 10.1016/j.pharmthera.2020.107558. Epub 2020 Apr 25.</p>
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<b>REVIEWER</b>	Paterson, Hugh University of Edinburgh
<b>REVIEW RETURNED</b>	24-Mar-2021

<b>GENERAL COMMENTS</b>	The literature contains few publications on IV lidocaine in colorectal surgery and the number containing data specifically for
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	<p>colorectal cancer will be fewer still. There may also be heterogeneity of the definition used for the primary endpoint of return of gut function in studies- time to first flatus, time to first defecation, time to GI-3 (composite of time to first flatus AND tolerating oral intake), time to GI-2 (composite of time to first defecation AND tolerating oral intake). How will the authors deal with this?</p>
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**VERSION 1 – AUTHOR RESPONSE**

Comment from Reviewer 1

Dr. Hengrui Liu, University of Cambridge

The meta-analysis protocol is systematic and complete. Generally speaking, this protocol is good for acceptance. However, one thing I would like to point out is the targeting outcomes are limiting the value of this meta-analysis for clinicians. The effect of lidocaine, as well as other LA on multiple cancer, has been studied a lot in a preclinical study, lidocaine is potentially affecting cancer recurrence and metastasis after surgery, the primary outcomes evaluating in this protocol should also include cancer recurrence and metastasis, if not, the author should indicate somewhere and maybe change the title into a more specific one excluding cancer recurrence and metastasis, because cancer recurrence and metastasis are part of postoperative outcomes. Nevertheless, the author should mention the potential of lidocaine directly affecting cancer cells in the discussion, here are some recommended references that can be cited.

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Pharmacol Ther. 2020 Aug;212:107558. doi: 10.1016/j.pharmthera.2020.107558. Epub 2020 Apr 25.

Re: We appreciate the valuable comments and advices from Dr. Liu. We strongly agree with Dr. Liu's opinion that the postoperative survival rate and tumor recurrence and metastasis are important components of the postoperative outcome of patients with colorectal cancer. In view of this, we added the long-term survival outcome, and tumor recurrence and metastasis rate into the main outcomes, hoping to respond to the current clinical concerns about whether intravenous lidocaine can improve the outcome of patients with colorectal cancer under surgical resection. We also revised the section of discussion. We have added the potential mechanism of lidocaine directly affecting cancer cells, and the references you provided were read and added into the manuscript.

Thanks again to Dr. Liu for his sincere comments on our manuscript.

Comment from Reviewer 2

Dr. Hugh Paterson, University of Edinburgh

The literature contains few publications on IV lidocaine in colorectal surgery and the number containing data specifically for colorectal cancer will be fewer still. There may also be heterogeneity of the definition used for the primary endpoint of return of gut function in studies- time to first flatus, time to first defecation, time to GI-3 (composite of time to first flatus AND tolerating oral intake), time to GI-2 (composite of time to first defecation AND tolerating oral intake). How will the authors deal with this?

Re: We appreciate the valuable comments and advices from Dr. Paterson. We do have the same questions on the subject as raised by Dr. Paterson. Although there are few publicatons on IV lidocine

in colorectal surgeries, more clinical trials are on the way including yours. Thus, we would like to put forward the topic and conduct a meta-analysis, while the current protocol is a prelude. We also read your several publications on the topic. We agree with Dr. Paterson that heterogeneity exists in terms of the primary endpoint selected in studies, and interpretation of the existing literature is challenging. In order to minimize heterogeneity as much as possible, we intend to select a more reliable and easily observable indicator as a reference for recovery of intestinal function, namely, time to first defecation or flatus. Since defecation and flatus can be easily observed as indicators of bowel movement with small errors, we will not consider other types of intestinal activity, such as intestinal peristalsis and bowel sounds. We have revised accordingly in our manuscript. We wish our revision is much more acceptable. Thanks again to Dr. Hugh Paterson for his critical comments on our manuscript and hope to have more communication.

Thanks a lot again for editors' attention. If you have any other queries, please don't hesitate to contact me. We would like to revise our manuscript at your any request.