

Peer Review File

Article information: <http://dx.doi.org/10.21037/dmr-20-45>.

Reviewer 1's comments to the authors:

Overall well written – I have just made a few points for you to consider.

Abstract – Well written. Good summary.

Introduction

- Line 56 – “There may be inadvertent seeding of cancer cells perioperatively” is an isolated sentence that could flow better with re-wording.
- **Reply** – re-worded to flow better with the following sentence

Pathophysiology of cancer recurrence

- You could join distal and cavity spread bullet points together – both are the same mechanism of seeding during surgery.
- **Reply** – combined together

Surgery, pain and the stress response

- Would be nice to explain the actions of NK and CD8 T-cells in the first sentence ie: “particularly the anti-tumor activity of the natural killer (NK) cells and CD8 T-cells”
- **Reply** – “anti-tumor activity” added
- Line 83 – is it ‘closely related to’ or ‘caused by’
- **Reply** – changed to “is in part caused by” as there are then “other factors” discussed subsequently
- Line 84 - ?sympathetic immune system
- **Reply** – apologies, changed to sympathetic “nervous” system
- Line 89 – typo – CD8 T-cells
- **Reply** - corrected

Opioids

- As a general thought - throughout all the analgesic subheadings, the ‘effect’ section appears to be a more of an introduction to the evidence rather than a

separate section. I am not sure separating the section is necessary.

- **Reply** – You’re right, I think this was more to help us structure our article than anything! Sub-headings removed.
- Line 108 – you refer to Mu opioid receptor as MOP, later referring to it again as MOR.
- **Reply** – changed to MOR in the initial reference to it
- Lines 129 – 131 – what evidence? This might be better placed in the pathophysiology section.
- **Reply** – I think this was an introductory statement to the subsequent evidence but not explained well, we have adjusted as follows: “no detrimental effect in those who had *had* surgery, i.e. where the fentanyl’s analgesic effect would have been more important.”
- Line 136 – NSCLC – acronym not explained.
- **Reply** - added

NSAIDs

- Line 193 – RCT due for completion – would be interesting to have more details on how that may contribute to the evidence base
- **Reply** – unfortunately followed an old link here, was an RCT in China looking at perioperative steroids + NSAIDs in lung cancer but has now been terminated due to errors in following protocols. Other trials reviewed appear to be looking at long-term post op interventions or aspirin which we decided not to include. I have left the statement generalized that RCTs are required (even more so now!!)
- You conclude that the evidence is variable for NSAIDs but all studies that have been reviewed show positive or at least no negative results.
- **Reply** – The type of evidence was so variable we didn’t feel we could commit to it completely...have changed to “Overall the evidence suggests the use of perioperative NSAIDs may be beneficial in reducing cancer recurrence, however a recent review indicated the data was too heterogeneous for meta-analysis and concluded the effects were equivocal.”

Alpha-2 agonists

- Line 216 – ? “reverse alpha-2 agonist” – alpha-2 antagonist
- **Reply** - changed

Ketamine

LA agents

- Line 289 – discussed below rather than elsewhere would sound better.
- **Reply** - changed
- When discussing the effects of the LA agents – does the mode of administration make a difference to the immunomodulatory effects of each agent?
- **Reply** – It’s a good question...The sections were separated as the first bit is mainly talking about IV lidocaine, as the others can only be given as part of a regional technique in the clinical setting and so are discussed separately. The rest are in generally in vitro studies and therefore administered to the cells differently as far as I am aware...though this was not always clear from the studies.

LA regional

Conclusion

- “Given all of this” start of last paragraph – I would suggest rewording – ie Whilst awaiting the outcomes of these trials it is important that we aim to provide...etc
- **Reply** – agreed, changed

Reviewer 2’s comments to the authors

1. Line 131 is there a missing word “surgery-induced? decreases”

Reply 1. There isn’t a word missing but it reads slightly oddly – I have changed this to make it clearer

2. You have eluded to mitigating against stress response of morphine and fentanyl -what about very short acting drugs such as remifentanyl. This is commonly used as part of TIVA however no mention of consequences of the use of this - may complete the section on opiates.

Reply 2. We agree that with the growing use of Remifentanyl infusions it would be

interesting to see what its potential impact might be, whether it has immunosuppressive effects or is possibly beneficial by reducing the stress response. However, we struggled to find much in the way of evidence that looks specifically at Remi in this way. It generally seems to be studied as part of a TIVA vs Volatile debate rather than specifically as an analgesic or because of its properties as an opioid per se. We have mentioned this within the opioid section now for completeness.

3. Multiple mentions of NSCLC -However no full name given -would state this (1st mention on line 136) and then subsequently use the acronym through the rest of the text.

Reply 3. Added