Painful to describe, painful to diagnose: opioid-induced hyperalgesia

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Editor—We thank Fletcher and Martinez1 for bringing renewed attention to the important topic of opioid-induced hyperalgesia (OIH) with their systematic review and meta-analysis. Whilst we applaud them for their work, we would like to highlight what we feel to be a considerable shortcoming in OIH research and its subsequent translation into clinical practice.

First, scientists and clinicians need to understand and use the correct terminology. As comprehensively reviewed by Sandkühler,1 the term ‘allodynia’ in clinical and experimental pain medicine is reserved to describe a specific condition, namely ‘pain in response to a non-nociceptive stimulus’. He further clarifies that the only established method of eliciting this phenomenon is with ‘brushing of the skin’, a test which avoids stimulation of nociceptors.2 ‘Hyperalgesia’, in contrast, Sandkühler suggests viewing as an umbrella term that can be employed to describe all conditions where increased pain sensitivity is present. These include allodynia, decreased pain thresholds, or increased responses to suprathreshold stimulation. Furthermore, given that it is often unclear whether a stimulus activates nociceptors or not, ‘hyperalgesia’ should be the preferred term.2

Considering these distinctions, the use of the term ‘allodynia’ in preclinical animal research is often questionable, because current experimental models cannot exclude nociceptor activation reliably.3 4 In this regard, research with human participants should be relatively straightforward, providing studies are designed to test specifically for hyperalgesia or allodynia, or both. Establishing hyperalgesia should be a minimal criterion when investigating OIH.5 6

Second, a widely accepted clinical definition of OIH and its diagnostic criteria that incorporates the above considerations does not yet exist. We believe that Velayudhan and colleagues5 provide the clearest and most comprehensive description of OIH to date in the accompanying issue of Continuing Education in Anaesthesia, Critical Care & Pain of the British Journal of Anaesthesia. They describe OIH to be ‘characterized by a paradoxical increase in pain associated with allodynia and hyperalguesia’.

Application of these criteria in order to diagnose OIH clinically has been recognized to be challenging, especially in the perioperative setting.7 8 In an attempt to overcome this obstacle, studies have often used postoperative increased pain intensity scores and opioid consumption as surrogate markers to identify the presence of OIH. Considering the definitions provided by Sandkühler,1 a condition based on these surrogate cannot be termed ‘hyperalguesia’ or even ‘hypersensitivity’ but must be ‘pain’ or ‘something else’. This difficulty in diagnosing OIH experimentally and clinically has also created a dilemma for authors of review articles and is likely to contribute to the continuing discussion on whether OIH indeed exists or is a clinically relevant phenomenon.5 For example, in their review, Fishbain and colleagues7 were keen to include only studies that used an ‘acceptable measure of hyperalguesia’. In the end, however, they also had to use articles in which OIH was diagnosed based on pain severity and opioid consumption.

Fletcher and Martinez1 were faced with a similar dilemma. Only seven of the 27 (26%) articles included in their analysis clinically assessed specifically for symptoms of hyperalgesia, allodynia, or both. Most studies (n=20/27; 74%), however, relied on postoperative pain scores and opioid consumption to diagnose OIH. We are concerned that the employed surrogate outcomes do not reliably differentiate OIH from other conditions that are associated with increased pain and opioid consumption. Lee and colleagues8 have highlighted the importance of distinguishing OIH from opioid tolerance, disease progression, or increased pain, because all these conditions require a completely different therapeutic approach.

Finally, to complicate matters further, even if allodynia and hyperalgesia have been assessed in a study, no consensus currently exists regarding the best method for this purpose.5 7 Different modalities, such as thermal (heat or cold) or mechanical (pressure or pin-prick) pain thresholds, have been used.9 10 All seven studies included in the analysis by Fletcher and Martinez1 employed different methods of assessment. Six assessed mechanical thresholds using von Frey filaments.11–15 Pressure pain thresholds were investigated in two of the studies.15 16 From our point of view, all these different approaches and confusing terminology make it difficult to appraise the current evidence appropriately. We feel that a consensus is urgently needed on the basic diagnostic criteria for OIH. Once these criteria have been established, more research is required to develop easily applicable paradigms for both the experimental and the clinical setting.

Declaration of interest

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Reply from the authors

Clinical outcomes to evaluate opioid-induced hyperalgesia

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We thank Dr Bantel and colleagues for their interesting comments on our article.1

These comments are mainly on the considerable shortcomings in opioid-induced hyperalgesia (OIH) research and its subsequent translation into clinical practice. Dr Bantel and colleagues also highlight the various techniques used to evaluate pain thresholds in patients. We agree with their remainder of the definition of allodynia and hyperalgesia. We also agree that establishing hyperalgesia should be an important criterion when investigating OIH.

However, the reality of clinical research in this area is quite different. As mentioned by Dr Bantel and colleagues, in our review only seven of the 27 (26%) articles included in our analysis used specific assessments for symptoms of hyperalgesia, allodynia, or both. The purpose of our review was neither to clarify the definition of OIH nor the modalities used to evaluate it in surgical patients; rather, we tried to discuss the clinical significance of OIH. From this perspective, the important issue was to compare the impact of variation of intraoperative dose of opioid on pain-related clinical outcomes (i.e. pain intensity and opioid use). Although we agree that these clinical outcomes are surrogates for OIH evaluation, they are in fact the only ones that matter from our clinical perspective. In addition, we observed that in the remifentanil subgroup, standard mean difference for both primary hyperalgesia and secondary hyperalgesia were substantially different depending on the intraoperative dose of remifentanil.

In conclusion, we share the concerns of Bantel and colleagues about methodology in clinical studies on OIH. However, we think our review, despite these helpful critiques, offers a more precise picture of the clinical impact of high intraoperative doses of opioid.

Declaration of interest

None declared.

Reference