Surgeons' view of the preoperative intravenous iron to treat anaemia before major abdominal surgery trial. Response to *Br J Anaesth* 2021; 126: e84–6

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Keywords: anaemia; colorectal surgery; intravenous iron; iron deficiency anaemia; postoperative complications

Editor—We read with interest the correspondence by Meyer and colleagues[1] regarding an editorial[2] on the preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT) trial.[3] We would like the opportunity to respond to the points raised. We welcome discussion on the mechanistic aspects of how anaemia could impact patient outcomes. PREVENTT was a pragmatic phase III clinical trial that did not look at mechanism.[4] There have been analyses of microvascular perfusion in surgery and the effects of anaemia and blood transfusion,[5] that suggest impaired sublingual microcirculation is associated with more frequent postoperative complications and increased length of hospital stay.[6] Tissue oxygen delivery is regulated by red blood cell oxygen content and the red blood cell flow regulation within the microcirculation but as alterations to microcirculatory flow are multifactorial, with direct effects of anaesthesia,[7] hormonal and metabolic stress responses to surgery, and haematological aspects of viscosity and flow, it would not be possible to run a large phase 3 clinical trial on tissue perfusion in this setting.

Similarly, the trial was not designed to look at the impact on platelet function or coagulation as neither of these is a routinely recommended clinical test before surgery unless patients are taking anticoagulants (which were reported by the trial).[4] In order to remove the confounding effect of difficult surgery and surgical haemorrhage, secondary outcomes included analyses of total number of units of blood given up to 30 days postoperatively and up to 6 months after operation, which excluded large blood transfusions (defined as four of more units of red blood cells).

PREVENTT was designed to assess, in patients with preoperative anaemia, the effect of the intervention of intravenous iron to increase haemoglobin levels compared to placebo. As hemoglobin levels are directly related (causal) to need for blood transfusion the trial was powered accordingly. As both preoperative anaemia and blood transfusion are related and both may be independently associated with adverse patient outcomes patient-related endpoints were listed as key secondary endpoints. Major complications defined as Clavien–Dindo grade 2 or above, included infection and surgical site infection, were not significantly different between the two study groups. We acknowledge that the importance of surgical site infection, and the overall incidence, in these predominantly clean operations was low.

In the setting of surgical practice, it was not routine to investigate the causality of preoperative anaemia until more widespread adoption of patient blood management principles.[8] Indeed, additional visits to hospital in addition to preoperative assessment were not acceptable to patients (necessitating protocol amendment, version 15, January 14, 2014). Therefore, to assess the efficacy and effectiveness of the interventions, serum ferritin and transferrin saturation were blindly assessed by the core laboratory at randomisation, with predefined endpoint analysis reported as per the statistical analysis plan.[9] Indeed, the majority of patients had either absolute or functional iron deficiency (76%), and analysis of the primary endpoint by baseline iron parameters showed near identical transfusion rates (see Appendix).

The novel findings in PREVENTT of increased haemoglobin concentration in the postoperative period and an association with a reduction in readmissions to hospital merit further assessment to test whether this association can be reproduced in a well-designed randomised controlled trial.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.02.014.

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doi: 10.1016/j.bja.2021.02.014
Advance Access Publication Date: 23 March 2021

Severe rebound pain after peripheral nerve block for ambulatory extremity surgery is an underappreciated problem. Comment on *Br J Anaesth* 2021; 126: 862–71

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Keywords: ambulatory surgery; anaesthesia; health outcomes; pain management; peripheral nerve block; rebound pain; upper extremity surgery

Editor—We read with great interest the article by Barry and colleagues[1] in which they identified factors associated with rebound pain after peripheral nerve block for ambulatory surgery as younger age, female sex, bone surgery, and absence of perioperative i.v. dexamethasone administration. We were surprised to learn that 482 of the 972 patients in their study who received a peripheral nerve block experienced *severe* rebound pain, with a mean rebound pain score of 8.24 out of 10. The prevalence of severe rebound pain after regional anaesthesia has otherwise been reported between 35% and 41%.[2,3] Therefore, Barry and colleagues[1] corroborate that rebound pain is a problem for a large portion of patients who receive a regional anaesthesia, a point that may be underappreciated by many anaesthetists and surgeons.

Rebound pain is not just a cause of patient dissatisfaction, but may also negatively affect patient outcomes. de Oliveira and colleagues[4] showed that inadequate postoperative analgesia in the first 24 h, in general, is associated with an increased incidence of cardiovascular complications, and Shea and colleagues[5] found that increased pain scores postoperatively can contribute to pulmonary complications. Fletcher and colleagues[6] showed that severe postoperative pain in the first 24 h after surgery (although not specifically rebound pain) is a risk factor for developing chronic postsurgical pain. Moreover, rebound pain after peripheral nerve block has even been shown to independently nearly double the odds of emergency department utilisation in the first few days after ambulatory upper extremity surgery.[7] Therefore, rebound pain is not just a burden for the patient, anaesthetist, and surgeon, but also for the healthcare system.

Identifying risk factors for severe rebound pain after regional anaesthesia allows targeting preventative strategies for those at greatest risk. An approach to prevent rebound pain should be multidisciplinary, especially for outpatient surgery, since in many centres postoperative pain management is transitioned to the surgical team upon discharge. Oral pain medications can start immediately after surgery, with the intent of achieving steady state before regional anaesthesia wears off. A multimodal oral pain medication regimen can include paracetamol, a non-steroidal anti-inflammatory medication, an opioid analgesic, and a gabapentinoid.[8] Our preferred regimen is presented in Table 1. Most patients are prescribed opioids at our institution since peripheral nerve block is reserved only for major extremity procedures. For minor procedures not requiring peripheral nerve block (e.g. carpal tunnel release, trigger finger release), opioids are not routinely prescribed. Adjuvants that decrease postoperative pain should also be used when possible. Dexamethasone, for example, prolongs the duration of the sensory block and reduces rebound pain[9]; accordingly, it was identified as a protective factor by Barry and colleagues.[1] Setting patient expectations with proper education about potential rebound pain will also help patients cope with the pain.[10]

DOI of original article: 10.1016/j.bja.2020.10.035.