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Benefits *versus* harm of intraoperative glucocorticoid for postoperative nausea and vomiting prophylaxis

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Summary

Intraoperative use of glucocorticoids is effective for postoperative nausea and vomiting prophylaxis and can also provide early postoperative analgesic effects, but the consequences for chronic post-surgical pain are debatable. In a secondary analysis of the large pragmatic Perioperative Administration of Dexamethasone and Infection trial (n=8478), the primary outcome of pain at the surgical wound at 6 months after surgery was increased in subjects receiving dexamethasone 8 mg i.v. for postoperative nausea and vomiting prophylaxis, a dose not associated with the detrimental effect of surgical

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site infection in the original study. In contrast, a more detailed assessment of chronic post-surgical pain after exclusion of patients with preoperative pain at the surgical site showed no differences with or without intraoperative dexamethasone regarding chronic post-surgical pain characteristics (intensity and neuropathic features). Because of several confounding factors especially regarding surgical details, these unexpected findings call for more well-designed studies about the potential risk of intraoperative treatments, such as glucocorticoids, on late post-surgical pain.

Keywords: chronic post-surgical pain; dexamethasone; glucocorticoids; PADDI trial; postoperative pain; postoperative recovery; wound pain

There is firm evidence for the value of small doses of dexamethasone (4–8 mg i.v.) given intraoperatively for postoperative nausea and vomiting (PONV) prophylaxis.[1] This evidence has been accepted worldwide and incorporated into clinical practice. In addition to reducing PONV, dexamethasone also provides early postoperative analgesic effects in several procedures.[2]

So far, so good, but one of the major challenges in perioperative care is a better assessment of potential harms, including the well-known risk of chronic post-surgical pain (CPSP), which can occur in 2–20% of surgeries at 3 months[3] depending on patient and procedure characteristics. One of the risk factors for developing CPSP is early postoperative pain, especially when not well treated. However, the evidence is debatable regarding the relationship between acute postoperative pain severity and the development of CPSP.[4] Further, the preventive effect of perioperative pharmacological interventions to reduce early and late postoperative pain is questioned.[4–6]

Results of the large pragmatic international non-inferiority randomised controlled Perioperative Administration of Dexamethasone and Infection (PADDI) trial are therefore most welcome.[7] The PADDI trial included 8478 participants scheduled for elective noncardiac surgery and receiving intraoperative dexamethasone 8 mg (n=4258) or matched placebo (n=4220). The primary outcome of this large trial was surgical site infection within 30 days after surgery, which found that a single perioperative dose of dexamethasone 8 mg i.v. was not inferior to placebo with respect to surgical site infections within 30 days after surgery.[7] Other large-scale cohort studies have shown no risk of wound infections or healing problems after hip and knee arthroplasty, even with higher doses of glucocorticoids.[8] Furthermore, with dexamethasone doses up to 8 mg, there were no problems with glycaemic control either in non-diabetic or well-controlled diabetic patients.[9]

Consequently, existing data favour the balance between benefits and potential harms of perioperative use of dexamethasone 8 mg regarding the risk of wound infection. However, a secondary analysis of the large well-designed PADDI trial, where the primary outcome was 'pain at the surgical wound at 6 months after surgery', despite confirmation of an early analgesic effect, found that dexamethasone was associated with an increased risk of persistent wound pain.[10] At 6 months postoperatively, 491 patients (11.5%) receiving dexamethasone reported pain compared with 404 patients (9.6%) in the placebo group (relative risk 1.2; 95% confidence interval: 1.06–1.36).[10] Although unexpected, this finding could be clinically important in certain patients and certainly calls for further studies before changing current recommendations for dexamethasone use. Beyond prophylactic effects against PONV, intraoperative dexamethasone can also improve acute postoperative pain management, as supported by the PADDI trial findings showing reduced early postoperative pain.[10]

As a secondary analysis of a large trial, the secondary analysis by Corcoran and colleagues[10] suffers certain limitations and potential biases. First, several parameters, such as perioperative anaesthesia and analgesic regimens, were not standardised, with potential implications for both acute pain and the development of chronic pain. Furthermore, it is possible that some subjects received repeated postoperative dexamethasone to control acute pain and local swelling. Second, the primary aim of the study was the presence of 'wound pain at 6 months after surgery', relying on a binary response (presence of wound pain, YES or NO on a telephone call interview without other detailed information). However, because ~25% of the subjects had pain preoperatively at the surgical site (probably leading to the indication for surgery, at least in orthopaedic procedures), it makes interpretation and conclusions about 'pain at the surgical wound' at 6 months postoperatively difficult. Also, pain at the wound differs greatly dependent on the procedure,[11] and few details are presented, hindering a detailed analysis and interpretation. Third, the secondary outcomes beyond the improved acute pain response included the presence of CPSP, which, according to the international definition, is pain persisting beyond the healing process (i.e. at least 3 months after surgery), whilst other causes of pain, including infection, malignancy recurrence, and pain continuing from a pre-existing pain problem, have been excluded.[3] Consequently, for the CPSP analysis, ~25% of the patients with preoperative surgical site pain had to be excluded, leading to only 7.7% (n=671) of chronic pain patients with CPSP features not being different between the dexamethasone and placebo groups. Pain intensity was reported as moderate to severe by 57% of subjects with CPSP, and the presence of neuropathic characteristics did not differ between the dexamethasone and placebo groups.[10] With regard to CPSP, the authors defined it as chronic wound pain, but the PADDI trial included a variety of surgical procedures (orthopaedic, digestive, urologic, and gynaecologic, including both open and minimally invasive surgeries) with limited specific information about the risk of nerve injury or other patient pain risk factors, such as 'high pain responders' (catastrophisers, chronic opioid users, etc.).[4,12]

Thus, the presence of CPSP associated with deep visceral pain might have been missed in some subjects. Finally, although the authors assessed the presence of neuropathic features in chronic wound pain, they chose a questionnaire (the neuropathic pain questionnaire) with the lowest sensitivity and specificity amongst all screening questionnaires for neuropathic pain.[13] This could explain why the reported incidence of 21.6% of neuropathic pain in the CPSP cohort was

different and lower than the incidence found in the literature, usually 60–80%.[3,11]

Consequently, the unexpected finding that intraoperative dexamethasone 8 mg was associated with a higher incidence of 'chronic pain in the wound' could be a 'chance finding', but, nevertheless, it is an observation that deserves attention and needs to be studied in relation to other studies of the impact of perioperative pain treatment on postoperative outcomes, such as pain resolution.[14]

The immune response, involving an acute inflammatory reaction, can condition patient outcomes to surgery.[15] Currently, the most used and most effective analgesics in acute pain conditions, such as anti-inflammatory drugs, such as NSAIDs and corticosteroids, interact with the immune system to reduce the inflammatory reaction.[16] Thus, intraoperative high-dose glucocorticoids can reduce the adaptive immune response for up to 48 h, with little or no effect on the innate immune system,[17] which is known to be important for pain recovery.[15] Recent findings in a non-surgical setting (i.e. acute musculoskeletal pain) suggest that acute pain treatments that modulate the inflammatory response, such as NSAIDs and corticosteroids, might interfere with natural recovery processes.[18] Patient data supported experimental observations in an animal model, showing that the acute inflammatory response involving neutrophil activation protects against development of chronic pain. Beyond early pain relief, treatment of inflammation at the onset of acute low back pain (or in the early postoperative period in animals) is potentially detrimental because it fosters transitioning to chronic pain.[18]

In conclusion, this secondary analysis of a standard PONV prophylactic dose of dexamethasone provides important information demonstrating the need not only to study long-term and potentially undesirable sequelae of this treatment, but also the need for improved design of interventional perioperative outcome studies depending on a specific outcome with multiple pathogenic factors.

Authors' contributions

P.L. and H.K. contributed equally to the preparation and redaction of the paper.

Declaration of interest

The authors declare no conflict of interest.

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