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Clinical Investigation

CLINICAL INVESTIGATION

Intraoperative dexamethasone alters immune cell populations in patients undergoing elective laparoscopic gynaecological surgery

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Abstract

Background. Anaesthetists use dexamethasone principally for its anti-emetic effect. The purpose of this study was to characterize the effects of a single intraoperative dose of dexamethasone on cellular and metabolic components of the immune system in patients undergoing laparoscopic surgical procedures.

Methods. In this prospective double-blind trial, female patients undergoing elective major laparoscopic surgery were randomized to receive saline (Control group, n=16) or dexamethasone 4 mg (Dexamethasone group, n=16) i.v. after the induction of anaesthesia. Inflammatory markers and immune cell counts were examined at 24 and 48 h and 6 weeks after surgery. The changes from baseline preoperative values were compared between groups using a Mann–Whitney U-test, and linear mixed models were used to validate the findings.

Results. No differences in concentrations of serum glucose and interleukin-6 were observed between groups after surgery. The increase in C-reactive protein concentration at 24 h after surgery was greater in the control group [median (interquartile range), 33 (25–65) *vs* 17 (7–26) mg dl^{-1}; P=0.018]. Extensive changes in the counts of white cells, including most lymphocyte subsets, were observed 24 h after surgery, and dexamethasone appeared to attenuate most of these changes. Changes at 48 h and 6 weeks did not differ between groups.

Conclusions. In female patients undergoing elective laparoscopic gynaecological surgery, dexamethasone administration appears to attenuate inflammation and to alter immune cell counts at 24 h, with no effects identified after this time. The importance of these changes for postoperative immune function is unknown.

Trial registration. Australia and New Zealand Clinical Trials Registry (ACTRN12608000340336).

Key words: anaesthesia; dexamethasone; inflammation

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Editor's key points

- Anaesthetists commonly administer dexamethasone for its anti-emetic properties.
- Like other steroids, it can modulate immune responses and functions.
- The authors studied the effect of a single intraoperative dose on leucocyte subtype counts.
- Significant changes were found at 24 h but not at 48 h and 6 weeks.

Surgical trauma is characterized by a tightly integrated sequence of neurohumoral and immunological processes.[1] When this is marked, it can manifest as a clinical entity called the systemic inflammatory response syndrome.[2] This inflammation is a double-edged sword. It is essential to facilitate removal of dead tissue and to promote remodelling followed by healing. However, the processes involved can produce a degree of immunosuppression and, in severe instances, immunoparesis. Recent advances in our understanding of the immune responses to tissue injury,[2] coupled with an increased understanding of how genomic determinants may direct inflammatory responses,[3] has led to the theory that the inflammatory milieu in the postoperative period can be a harmful and potentially modifiable condition. The T-cell exhaustion and lymphocyte anergy that are often observed are believed to create an environment that renders the patient vulnerable to both infection and the recurrence of malignancy.[4 5] The importance of preoperative inflammation to outcome in patients undergoing surgery for malignancy is well established.[6 7] However, its role in altering healing and infective outcomes is less clear, but does appear to be important.[6 8 9] The role played by postoperative inflammation-related immune suppression in terms of postoperative infection risk and malignancy recurrence, and the role that anaesthesia techniques may play, are currently subjects of intense speculation and investigation.[5 10–12]

Glucocorticoids are compounds with protean effects upon the human immune system,[13] being widely used in the perioperative period for multiple benefits, including an improvement in analgesia in surgical patients,[14] and decreased swelling in dental and maxillofacial surgery.[15] The principal anaesthesia indication for their use is in the prevention of postoperative nausea and vomiting,[16] and the synthetic glucocorticoid dexamethasone is both effective and recommended by international consensus for this indication.[17] Glucocorticoids, however, have both genomic and non-genomic actions, which lead to complex effects upon cellular components of the immune system.[18] They are, for example, pro-apoptotic in the treatment of haematological malignancy,[19] but prolong neutrophil survival through an anti-apoptotic effect.[20] Although concern has been expressed that such effects in the perioperative period might increase the risk of postoperative infections, and wound infections in particular,[21] the effect of intraoperative anti-emetic doses of dexamethasone on postoperative cellular immunity has not been elucidated.

The purpose of this study was to examine the effect of a single intraoperative dose of dexamethasone, in patients undergoing laparoscopic surgery, on the cellular components of the immune system in terms of the changes in peripheral cell counts up to 6 week after surgery. Gender appears to influence the pattern of inflammatory responses observed, and in order to limit this confounding we performed this study in female patients only.[22] Our hypothesis was that dexamethasone would alter immune cell populations in the postoperative period.

Methods

This prospective, double-blinded randomized controlled trial received approval from the Human Research Ethics Committee of King Edward Memorial Hospital for Women (1554/EW). The trial was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12608000340336). Women were recruited at pre-assessment clinics and from preoperative wards. Patients eligible for selection comprised adult females, ASA I or II, of age 18–60 yr, and undergoing elective major laparoscopic gynaecological surgery expected to require at least 90 min of operative time, requiring a hospital stay to include at least the first postoperative night. Patients were excluded if they were currently or recently taking immunosuppressive agents, had known or suspected malignancy, hypertension, diabetes mellitus, a history of peptic ulceration, chronic pain syndrome requiring regular opioid consumption, a predicted requirement for i.v. patient-controlled analgesia, or known hypersensitivity to dexamethasone or granisetron. Patients were randomized before surgery, in a 1:1 ratio using a computer-generated random number sequence, and allocated to one of two groups using sealed opaque envelopes. A standardized anaesthetic technique was used for all participants. This comprised fentanyl 1 μg kg^{-1} i.v. and midazolam 2 mg i.v. before induction, with target-controlled propofol infusion commenced at an effect site concentration of 6–8 μg ml^{-1}, and titrated thereafter to maintain anaesthesia. Entropy monitoring (Datex Ohmeda, GE Healthcare, Giles, UK) was used to ensure comparable and appropriate depth of anaesthesia, with propofol infusions targeted to state entropy of 40–55. Intraoperative opioids were administered at the attending anaesthetist's discretion.

Airway management comprised tracheal intubation after the administration of a non-depolarizing neuromuscular blocking agent and pressure-controlled ventilation with an air–oxygen mix. An inspired oxygen concentration of 60% was targeted unless there was a clinical imperative to target a different concentration. Tracheal extubation occurred at the end of surgery after antagonism of neuromuscular block using neostigmine and glycopyrrolate. All patients received parecoxib 40 mg i.v., and postoperative analgesia comprised titration of i.v. fentanyl in the recovery room and thereafter paracetamol 1 g every 6 h, ibuprofen 400 mg orally every 8 h, and oxycodone 5–15 mg orally for breakthrough pain.

Each patient received granisetron 1 mg and an assigned study drug (saline or dexamethasone 4 mg; Control and Dexamethasone groups, respectively) i.v. after the induction of anaesthesia. The study drug was prepared by an observer who was not connected to the study and diluted to a total volume of 4 ml with 0.9% sodium chloride in an unmarked syringe. The patient, the patient's anaesthetist, and all investigators were blinded to the study drug identity.

Interventions

After an overnight fast from solids but unrestricted water consumption, a baseline blood sample was obtained (T_0) upon insertion of a 20-gauge cannula for the induction of anaesthesia. Further blood samples were obtained at 24 h (T_1), 48 h (T_2), and 6 weeks after surgery (T_3). At each time point, 4 ml of blood in EDTA and a 4 ml clotted serum sample were collected. The serum samples were immediately centrifuged at 2500*g* for