BJA

British Journal of Anaesthesia, 118 (2): 190–9 (2017)

doi: 10.1093/bja/aew446
Clinical Practice

Intraoperative dexamethasone does not increase the risk of postoperative wound infection: a propensity score-matched *post hoc* analysis of the ENIGMA-II trial (EnDEX)

T. Corcoran[1,2,3,4,*], J. Kasza[4], T. G. Short[5], E. O'Loughlin[2,6], M. T. V. Chan[7], K. Leslie[4,8,9], A. Forbes[4], M. Paech[1,2] and P. Myles[4,10], for the ENIGMA-II investigators[†]

[1]Department of Anaesthesia and Pain Medicine, Royal Perth Hospital, Perth, Western Australia, Australia, [2]School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia, [3]Western Australia Health Department, Perth, Western Australia, Australia, [4]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia, [5]Department of Anaesthesia, Auckland City Hospital, Park Road, Grafton, Auckland, New Zealand, [6]Department of Anaesthesia and Pain Medicine, Fiona Stanley Hospital, Perth, Western Australia, Australia, [7]Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China, [8]Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, Victoria, Australia, [9]Anaesthesia, Perioperative and Pain Medicine Unit, and Department of Pharmacology and Therapeutics, University of Melbourne, Melbourne, Victoria, Australia and [10]Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Melbourne, Victoria, Australia

*Corresponding author. E-mail: mascor@bigpond.net.au
[†]Investigators in the ENIGMA-II trial are listed in Appendix.

Abstract

Background. In a *post hoc* analysis of the ENIGMA-II trial, we sought to determine whether intraoperative dexamethasone was associated with adverse safety outcomes.
Methods. Inverse probability weighting with estimated propensity scores was used to determine the association of dexamethasone administration with postoperative infection, quality of recovery, and adverse safety outcomes for 5499 of the 7112 non-cardiac surgery subjects enrolled in ENIGMA-II.
Results. Dexamethasone was administered to 2178 (40%) of the 5499 subjects included in this analysis and was not associated with wound infection [189 (8.7%) *vs* 275 (8.3%); propensity score-adjusted relative risk (RR) 1.10; 95% confidence interval (CI) 0.89–1.34; $P=0.38$], severe postoperative nausea and vomiting on day 1 [242 (7.3%) *vs* 189 (8.7%); propensity score-adjusted RR 1.06; 95% CI 0.86–1.30; $P=0.59$], quality of recovery score [median 14, interquartile range (IQR) 12–15, *vs* median 14, IQR 12–16, $P=0.10$), length of stay in the postanaesthesia care unit [propensity score-adjusted median (IQR) 2.0 (1.3, 2.9) *vs* 1.9 (1.3, 3.1), $P=0.60$], or the primary outcome of the main trial. Dexamethasone administration was associated with a decrease in fever on days 1–3 [182 (8.4%) *vs* 488 (14.7%); RR 0.61; 95% CI 0.5–0.74; $P<0.001$] and shorter lengths of stay in

Editorial decision: December 5, 2016; **Accepted:** December 10, 2016

hospital [propensity score-adjusted median (IQR) 5.0 (2.9, 8.2) *vs* 5.3 (3.1, 9.1), $P<0.001$]. Neither diabetes mellitus nor surgical wound contamination status altered these outcomes.

Conclusion. Dexamethasone administration to high-risk non-cardiac surgical patients did not increase the risk of postoperative wound infection or other adverse events up to day 30, and appears to be safe in patients either with or without diabetes mellitus.

Clinical trial registration. NCT00430989.

Key words: dexamethasone; nitrous oxide; postoperative nausea and vomiting; surgical wound infection

Editor's key points

- Dexamethasone is widely used to prevent and treat postoperative nausea and vomiting.
- The association of intraoperative dexamethasone with postoperative infection, quality of recovery, and adverse safety events was tested in a *post hoc* subgroup analysis of the ENIGMA-II trial.
- Dexamethasone was not associated with postoperative infection or adverse events in a group of high-risk non-cardiac surgical patients.

The synthetic glucocorticoid dexamethasone is widely used as an antiemetic in the perioperative period.[1] It is inexpensive, effective, and long-acting and is recommended as a first-line antiemetic in recent international guidelines.[2] However, in common with other glucocorticoids, it has significant metabolic and immunological side-effects.[3] Immune suppression and hyperglycaemia[4] are the cardinal concerns in the perioperative period, because both may contribute to an increased risk of infection. Despite widespread use of dexamethasone amongst surgical patients, there remains uncertainty as to whether this is associated with increased risk of postoperative infection.[5 6]

The ENIGMA-II trial was a large international randomized controlled trial examining the postoperative cardiac events after 70% nitrous oxide in high-risk adults undergoing non-cardiac surgery; the primary end point was a composite outcome of death and major non-fatal cardiovascular events up to 30 days after surgery.[7] A substantial proportion of patients recruited to the ENIGMA-II trial received intraoperative dexamethasone as a part of their routine perioperative care. The ENIGMA-II data set, therefore, provides an opportunity for further evaluation of the association of dexamethasone administration and postoperative infection in a prospectively collected data set with robust outcome methodology. The primary aim of this *post hoc* subanalysis was to explore the association between intraoperative administration of dexamethasone and wound infection. Our *a priori* hypothesis was that patients receiving dexamethasone were at higher risk of postoperative wound infection, and the subgroups at greatest risk would be patients with diabetes mellitus or a contaminated surgical field. We also sought to explore the association of dexamethasone with fever on days 1–3 after surgery, severe postoperative nausea and vomiting (PONV) on day 1, length of hospital stay, quality of recovery (QoR), and the composite primary end point of the main trial.

Methods

The design and rationale of the ENIGMA-II trial has been published (ClinicalTrials.gov identifier NCT00430989).[8] In summary, patients were eligible for inclusion if they were ≥45 yr old, undergoing elective non-cardiac surgery for 2 h or longer, and were considered to be at high risk of cardiac events. Patients were excluded in the following circumstances: (i) if they were having cardiac surgery; (ii) if they had marked impairment of gaseous exchange requiring an inspired oxygen fraction (FIO_2) >0.5 during surgery; (iii) in a specific circumstance where nitrous oxide use is contraindicated (volvulus, bowel obstruction, or elevated intracranial pressure); or (iv) where nitrous oxide is not available for clinical use. The primary end point was a composite outcome of death and major non-fatal cardiovascular events up to 30 days after surgery. We also collected data regarding wound infection, duration of stay in the intensive care unit (ICU) and hospital, and severe PONV. Severe PONV was defined as two or more episodes of nausea, vomiting, or both at least 6 h apart, or requiring three or more doses of rescue antiemetics of two or more different classes in any 24 h during the first 3 days after surgery. Quality of recovery (QoR) score was recorded on day 1. Body temperature was measure from day 1 to 3. Fever was defined as core temperature ≥38 °C.

All centres obtained institutional review board approval, and all patients provided written informed consent for enrolment in the original trial. This substudy and analysis was not planned at the time of initiation of the trial. It followed a predefined analysis plan, which was approved by the steering committee of the main trial. Patients were randomly assigned to receive a general anaesthetic either with or without nitrous oxide in the gas mixture. Treatment assignment was stratified by site with permuted blocks. Attending anaesthetists were aware of the group assignments, but subjects, the operating team, research coordinators who conducted the postoperative interviews, and end point adjudicators were unaware of treatment group. For subjects assigned to receive nitrous oxide, anaesthetists were advised to give nitrous oxide at an inspired concentration of 70% in 30% oxygen, and for patients assigned not to receive nitrous oxide, anaesthetists were advised to give an air–oxygen gas mixture with $FIO_2=0.3$ for maintenance of anaesthesia and tracheal intubation or laryngeal mask insertion. The allocated gas concentrations were then continued until the completion of surgery. Prophylactic antibiotics were administered according to local practice, and usual efforts to avoid intraoperative hypothermia were made. Standard anaesthetic and other perioperative care was given. There was no restriction on the use of neuraxial or other regional anaesthetic techniques. Anaesthetic depth was adjusted according to clinical judgement, with guidance from monitoring. Subjects were reviewed daily while in