EJA

OPEN

Eur J Anaesthesiol 2022; **39:**549–557

ORIGINAL ARTICLE

Dexamethasone for the treatment of established postoperative nausea and vomiting

A randomised dose finding trial

Christoph Czarnetzki, Eric Albrecht, Jules Desmeules, Christian Kern, Jean-Baptiste Corpataux, Sylvain Gander, Sander M.J. van Kuijk and Martin R. Tramèr

BACKGROUND Dexamethasone is widely used for the prevention of postoperative nausea and vomiting (PONV) but little is known about its efficacy for the treatment of established PONV.

OBJECTIVE To test the antiemetic efficacy of intravenous dexamethasone for the treatment of established PONV in adults undergoing surgery under general anaesthesia and to determine whether there is dose-responsiveness.

DESIGN The DexPonv trial is a multicentre, placebo-controlled, randomised, double-blind, dose-finding study. Inclusion of patients was between September 2012 and November 2017. Follow-up for PONV symptoms was for 24 h. Thirty days postoperatively, patients were contacted by study nurses for any information on postoperative bleeding and infection.

SETTING Four public hospitals in Switzerland.

PATIENTS A total of 803 adults scheduled for elective surgery without any antiemetic prophylaxis signed the consent form; 714 were included. Among those, 319 had PONV and 281 patients were eventually randomised (intention to treat population and safety set). The per protocol set consisted of 260 patients.

INTERVENTIONS Patients with PONV symptoms (including retching) were randomised to a single intravenous dose of dexamethasone 3, 6 or 12 mg or matching placebo.

MAIN OUTCOME MEASURES The primary endpoint was the absence of further nausea or vomiting (including retching), within 24 h after administration of the study drug.

RESULTS Dexamethasone was ineffective during the first 24 h, whatever the dosage, compared to placebo, even when the model was adjusted for known risk factors ($P = 0.170$). There were no differences in the time to treatment failure or the quality of sleep during the first night. There was a positive correlation between the dose of dexamethasone and blood glucose concentrations ($P < 0.001$), but not with bleeding risk, wound infections or other adverse effects.

CONCLUSION This randomised trial failed to show antiemetic efficacy of any of the tested intravenous regimens of dexamethasone for the treatment of established PONV in adults undergoing surgery under general anaesthesia.

TRIAL REGISTRATION clinicaltrials.gov (NCT01975727).

Published online 1 November 2021

Introduction

Postoperative nausea and vomiting (PONV) is a frequent adverse effect of surgery and anaesthesia. Even when using propofol and antiemetic agents, up to 45% of patients may experience PONV within the first 24 h.[1] Some surgical patients would rather have pain than PONV symptoms.[2] Among the best documented and the most efficacious, antiemetic drugs that are used for PONV prophylaxis today are 'setrons' (5-HT_3 receptor

From the Division of Anaesthesiology, Department of Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals, Geneva (CC, MRT), Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Emergency Medicine, Ospedale Regionale di Lugano, EOC, Lugano, Switzerland (CC), Division of Clinical Pharmacology and Toxicology, Department of Anaesthesiology, Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals (JD), Division of Anaesthesiology, University Hospitals of Lausanne (EA, CK), Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands (SMJvK), Division of Anaesthesiology, Réseau Hospitalier Neuchatelois, Neuchatel (J-BC), Division of Anaesthesiology, Etablissements Hospitaliers du Nord Vaudois, Yverdon les Bains et Saint Loup (SG), Faculty of Medicine, University of Geneva, Geneva (CC, JD, MRT) and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland (EA, CK)

Correspondence to Christoph Czarnetzki, MD, Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Emergency Medicine, Ospedale Regionale di Lugano, Via Tesserete 46, 6900 Lugano, Switzerland
Tel: +41 91 811 66 64; fax: +41 91 811 66 60; e-mail: chNstoph.czarnetzki@eoc.ch

DOI:10.1097/EJA.0000000000001636

antagonists), NK1 antagonists, glucocorticosteroids such as dexamethasone, and antidopaminergic agents like droperidol (D2 antagonists).[3] Dexamethasone remains one of the most popular antiemetic drugs at induction of general anaesthesia in the surgical setting and has proven its prophylactic efficacy especially when combined with 5-HT_3 antagonists.[4] The recent consensus guidelines of international PONV experts regarded dexamethasone as a cornerstone of antiemetic prophylaxis in surgical patients.[3] Curiously, relatively little is known about the antiemetic efficacy of dexamethasone for the treatment of established PONV symptoms. So far, only the setrons have been adequately tested and have proven efficacy in the treatment setting.[5] There is no adequately powered randomised trial available that formally tested the efficacy of dexamethasone for the treatment of established PONV symptoms. As a consequence, the real therapeutic antiemetic efficacy of dexamethasone remains unknown. Furthermore, corticosteroids have a wide range of adverse effects that are dose- and often time-dependent. The primary aim of this randomised study was to test the antiemetic efficacy of intravenous dexamethasone for the treatment of established PONV in adults undergoing surgery under general anaesthesia and to determine whether there is dose-responsiveness. The secondary objective was to evaluate the potential adverse effect profile of dexamethasone when administered as a single intravenous bolus dose in surgical patients undergoing general anaesthesia, including its effect on blood glucose, infection and quality of sleep.

Methods

Study design

This was a randomised, double-blind, placebo-controlled trial, testing three different intravenous single-dose regimens of dexamethasone, conducted in four public Swiss hospitals (Geneva and Lausanne University Hospitals, Etablissements Hospitaliers du Nord Vaudois (eHnv) and Réseau Hospitalier Neuchatelois (RHNe). The study protocol was approved on April 17th, 2012 by the Geneva *commission centrale d'éthique de la recherche sur l'etre humain* (president Prof. O. Huber, address: rue Adrien-Lachenal 8, 1207 Geneva, Switzerland, protocol CER 11–213/ NAC 11–076) and on the July 10th, 2012 by Swissmedic, the Swiss agency of therapeutic products (medical reviewer J. Abegglen, address: Hallerstrasse 7, 3000 Bern 9, Switzerland, protocol SM2012DR2118). Written informed consent was obtained from all patients before taking part. The study was registered at ClinicalTrials.gov (NCT01975727).

Inclusion and exclusion criteria

The anaesthesia teams of the four participating centres screened and recruited eligible patients during the preanaesthesia consultation. Both male and female patients, $\geq$ 18 years American Society of Anesthesiology (ASA) status I to III, scheduled for elective surgery, were eligible for inclusion. They had to be able to read and understand the information sheet and have signed and dated the consent form. If the patient was female and of childbearing potential, she should have a negative pregnancy test. Potential subjects who met any of the following criteria were not included: patients who underwent a surgical procedure that required mandatory prophylaxis of PONV according to the treating anaesthetist, needing postoperative intubation or a gastric tube postoperatively, receiving antiemetic drugs (butyrophenones, 5-HT_3 receptor antagonists) within 24 h before surgery, or those having to undergo specific types of surgery such as tonsillectomy (increased risk of postoperative bleeding). Further noninclusion criteria were administration of any investigational drug within 7 days of screening or enrolment in any clinical trial within 30 days. Pregnant, or intending to become pregnant women and breastfeeding women were also excluded from the study, as were those who had a history of allergy or hypersensitivity to dexamethasone, hepatic dysfunction (i.e. bilirubin >1.5 upper limit normal (ULN), alanine aminotransferase >2.5 x ULN, aspartate aminotransferase >2.5 x ULN), renal insufficiency (i.e. creatinine >1.5 x ULN, creatinine clearance >30 ml min^{-1}), active gastrointestinal ulcer, overt psychosis or administration of antipsychotic treatment (for instance, antidopaminergic drugs), those who received drugs with known emetogenic potency (for instance, L-Dopa, catechol-o-methyl-transferase inhibitors) and patients with local infections, except hepatitis A, B and C. Laboratory testing that takes into account type of surgery and patient factors was done according to institutional guidelines.

Study drug preparation, randomisation and blinding

The hospital pharmacy of Geneva University Hospitals was responsible for study drug preparation, randomisation and blinding in accordance with good manufacturing practice and good clinical practice. Patients were randomised into one of four groups: intravenous dexamethasone 3, 6 or 12 mg or intravenous placebo. Randomisation was applied after stratification for each centre and was done with a computer-generated random sequence into four groups of equal size and by blocks of 20 (i.e. 4×5 per block). Identical, numbered 10 ml syringes containing one of the three doses of dexamethasone or matching placebo were prepared and randomised in advance and delivered in sealed plastic bags. A numbered syringe ('study treatment') in its bag was assigned to each consenting patient preoperatively and followed the patient until discharge for ambulatory patients and up to 24 h postoperatively for inpatients. Patients who vomited at least once, or who showed symptoms of retching (i.e. vomiting reflex without production of stomach contents), or who had nausea symptoms (patients answering 'yes' to the question: Do you feel nauseous?) during the observation period, received their assigned 'study treatment' intravenously over 30 s by a nurse in the recovery room or on the ward.

The observation period was defined as the moment either from waking up until 1 h before scheduled discharge for outpatients or from waking up until 24 h postoperatively for inpatients and corresponded to the time window for treatment administration. We assumed that in Switzerland, the most widely used prophylactic antiemetic dose of dexamethasone in an adult undergoing surgery was between 4 and 6 mg intravenously at induction. As we aimed to test a large dose-range to increase the likelihood of identifying a dose-response, if one existed, we chose to test 3, 6 and 12 mg.

Interventions

Preoperative investigations, premedication, conduct of anaesthesia (volatiles, nitrous oxide, propofol, thiopental, ketamine, clonidine, opioids, neuromuscular blocking agents including succinylcholine) and postoperative analgesia (acetaminophen, nonsteroidal anti-inflammatory drugs, weak or strong opioids [including patient-controlled analgesia with morphine or fentanyl], or buprenorphine, methadone, tramadol) were at the discretion of the anaesthesiologist in charge. For those included, no prophylactic antiemetics (droperidol, $5HT_3$ receptor antagonists, dexamethasone) were allowed. Patients undergoing general anaesthesia and receiving an additional epidural or peripheral nerve block intra- and/or postoperatively were not excluded. As perioperative dexamethasone administration can cause an elevation in blood glucose,[6,7] a venous or capillary blood sample was taken to measure the postoperative blood glucose concentration. This was done at discharge in outpatients or in the morning after surgery in hospitalised patients. Randomised patients who had received their assigned study treatment and who continued to experience nausea or vomiting (including retching), received antiemetic rescue treatment. The minimum delay between administration of the study drug and administration of the rescue antiemetic was 30 min, which was thought to ensure that dexamethasone had the scope to show anti-emetic efficacy. First-line rescue treatment was intravenous ondansetron 4 mg. If the patient continued to suffer from PONV symptoms, second-line rescue treatment was decided by the physician in charge of the patient.

Assessments and outcomes

The primary endpoint was complete control of established PONV symptoms, i.e. absence of further nausea or vomiting (including retching), within 24 h after administration of the study drug, in a patient who had undergone surgery under general anaesthesia and who was suffering from PONV symptoms. Recurrence of nausea or vomiting symptoms within 30 min after study drug administration was not regarded as a failure. Secondary endpoints were 'short-term' efficacy, i.e. absence of any nausea and/or vomiting (including retching) in a nauseated or vomiting patient within 6 h after administration of the study treatment; the time to treatment failure; quality of sleep during the first night after administration of the study drug (assessed via a numerical rating scale ranging from 0 = no sleep at all to 10 = excellent sleep); raised postoperative blood glucose and any minor or major adverse effects during 24 h after administration of the study drug. As there is some evidence that dexamethasone may increase the bleeding risk through inhibition of wound healing,[8] any case of reoperation due to bleeding, rehospitalisation due to bleeding or need for blood transfusion within 30 days postoperatively was recorded. Finally, signs of infection (culture of surgical site, antibiotic treatment, surgical intervention due to infection) within 30 days postoperatively were documented. We measured total opioid administration during anaesthesia and total opioid consumption since extubation until study drug administration. Established factors that are associated with the development of PONV symptoms were also collected.

Sample size

Based on data from placebo-controlled randomised trials testing a variety of $5\text{-}HT_3$ receptor antagonists for the treatment of established PONV, we assumed that between 70% and 90% of patients who suffered from PONV symptoms during the first 6 h postoperatively would continue to suffer from these symptoms during the next 24 h if they were given a placebo and no rescue medication.[5] The degree of efficacy of $5\text{-}HT_3$ receptor antagonists for the successful treatment of established PONV symptoms (i.e. no further symptoms in a previously nauseous or vomiting patient during 24 h after treatment) corresponded to an absolute risk reduction of 20 to 30% (number needed to treat [NNT] 3 to 5).[5] We expected the same degree of efficacy with dexamethasone. To obtain a 90% power to detect a similar degree of antiemetic efficacy (absolute risk reduction, 20%), if it existed, in a population with a 'placebo response' of 30% and using an alpha level of 5% and a one-sided test, we would need 111 nauseous and/or vomiting patients per group (444 in total).

Interim analysis

Due to recruitment problems, we performed an interim analysis, after having received approval of the ethics committee. At this timepoint, 246 nauseous and/or vomiting patients had been randomised and treated. This corresponded to 55% of the planned study sample. The analysis was conducted for efficacy and futility assessment by an independent Data Monitoring Committee. Stopping boundaries were chosen based on Pocock approach[9] and suggested by Pampallona and Tsatis.[10] With a power of 85% and an alpha threshold equal to 3.4%, the study was declared futile and was stopped.

Statistical analysis

Baseline characteristics of patients were summarised separately for each group of treatment. Continuous variables

were described as mean ± standard deviation or as median [1st and 3rd quartile]. Categorical variables were described as count and percentage. The primary endpoint was analysed as 'intention to treat' (ITT) and 'per protocol'. We developed two scenarios for the ITT analysis for patients with missing information for the primary endpoint: (a) all patients with missing information had a treatment success ('best case scenario'); (b) all were treatment failures ('worst case scenario'). Secondary endpoints other than adverse events and serious adverse events were analysed 'per protocol'. Adverse events and serious adverse events were analysed in the safety set.

The primary endpoint, the proportion of complete control of PONV symptoms in each dexamethasone group was compared with the proportion in the placebo group. Odds ratios (OR) with 95% confidence intervals (CI) comparing each dose of dexamethasone (3, 6, 12 mg) with placebo were computed for the two scenarios in case of missing outcome data. Risk factors for persistence of nausea or vomiting following dexamethasone treatment are unknown. However, as even a small imbalance of strong predictors among study groups might affect the results, we inferred that risk factors for PONV were also risk factors for resistance to treatment. Therefore, established risk factors for PONV, such as female gender, history of PONV, motion sickness or migraine, nonsmoking status, opioid use and type of surgery, were included into a logistic regression model to estimate adjusted effects.

For binary outcomes crude risk difference and crude OR with 95% CI comparing each dose of dexamethasone (3, 6, 12 mg) with placebo were computed. We used the same methodology described above for the primary endpoint. For continuous outcomes (i.e. quality of sleep during the first postoperative night and blood glucose (mmol l an extension of a nonparametric Wilcoxon rank-sum test for trend across ordered groups[11] was used to compare the values of these continuous variables across the four groups. Time to event was defined as the duration between the time of entry as 30 min after study drug administration and the time of treatment failure (in hours). Time of censoring for all patients was defined as 24 h following drug administration. The Kaplan-Meier method was used to calculate survival rate. We used survival curves to describe survival probabilities over the follow-up period and compared groups using a logrank test. Median [interquartile range] time to vomiting and/or nausea considered as a treatment failure was provided for each group. The percentages of patients presenting adverse effects during the 30 days postoperatively, for cases of bleeding and infection, and during the first 24 h for all other events, were reported in each group of treatment and were compared using the chi-square test. Statistical analyses were performed using R version 3.6.1. Statistical significance was set at $P < 0.05$ for each analysis.

Results

Patients and recruitment

Two hundred and eighty-one patients (148 in centre A, 101 in centre B, 26 in centre C, 6 in centre D) were randomised into one of four groups: intravenous dexamethasone 3 ($N = 68$), 6 ($N = 71$) or 12 mg ($N = 72$) or intravenous placebo ($N = 70$), between September 3rd 2012 and November 8th 2017 (Fig. 1). The ITT set and the safety set consisted of 281 patients and the per protocol set consisted of 260 patients. Baseline characteristics were similar in each group (Table 1).

Risk of complete control (no PONV) during the first 24 h following treatment

After study drug administration, complete control within 24 h was observed in a total of 87 patients. Intravenous dexamethasone at any dosage did not result in a different proportion of patients experiencing cessation of PONV compared to those receiving placebo ($P = 0.170$) (Table 2). Similar results were observed in the per protocol set ($P = 0.131$).

Risk of complete control (no PONV) during the first 6 h following treatment

The treatment success was evaluated in the per protocol set during the first 6 h following treatment (supplemental Table 1, http://links.lww.com/EJA/A652). No effect of dexamethasone (whatever the dosage) compared with placebo was observed.

Risk of no nausea or no vomiting during the first 24 h following treatment

No significant effects were observed for the effect of dexamethasone on either nausea exclusively or vomiting exclusively at 24 h for a best and a worst-case scenario (supplemental Table 2, http://links.lww.com/EJA/A653).

Time to treatment failure

Time to treatment failure was represented by a Kaplan-Meier survival curve for each treatment group (Fig. 2). The median time to the first new episode of nausea and/or vomiting after treatment for the placebo and the 3, 6 and 12 mg groups was 1.8 h (95% CI, 1.5 to 3.8), 1.9 h (1.7 to 2.6), 2.4 h (1.5 to undefined) and 1.7 h (1.2 to 4.7), respectively. A log-rank test showed that there was no statistically significant difference between groups in time to treatment failure ($P = 0.500$).

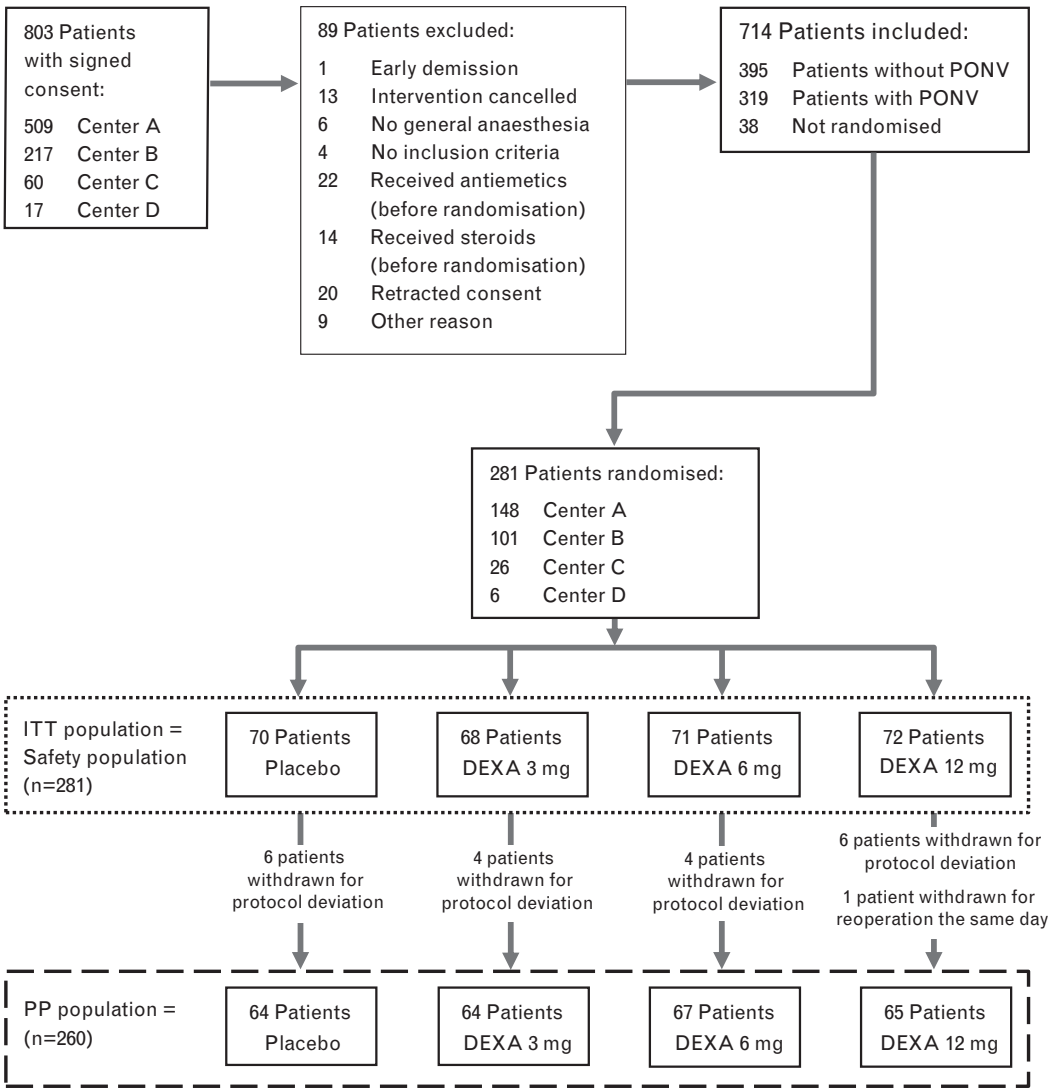
Evolution of hyperglycaemia and quality of sleep

A significant, positive dose effect relationship was shown between the dose of dexamethasone and the level of raised blood glucose ($P < 0.001$) (Table 3). No statistically significant difference was shown in quality of sleep between the four treatment groups (Table 3).

Adverse events

A total of 28 nonserious adverse events occurred in 24 patients (8.5%) (Table 4) and a total of 11 serious adverse

Fig. 1 Study Flowchart



ITT, Intention to treat; PP, Per protocol.

events occurred in 9 patients (3.2%) (Table 4). There were no significant differences between groups ($P = 0.187$).

Discussion

Our study failed to show any antiemetic efficacy for the three different doses of intravenous dexamethasone compared with placebo when considering the proportion of nauseous or vomiting surgical patients without further nausea or vomiting within 24 h after drug administration. There was neither antiemetic efficacy within the first 6 postoperative hours, nor was there any effect on nausea or vomiting when analysed separately within 24 h after study drug administration or on the time to treatment failure. However, with increasing dexamethasone doses, postoperative blood glucose values increased proportionally and significantly. Strengths of our study are its design as a large, multicentre randomised placebo-controlled trial with the enrolment of a large number of patients. We used a standardised method to evaluate PONV outcome. The main limitations of our study are that it was not conducted in a selected study population with a particularly high risk of nausea and vomiting. Between-groups effects may therefore have been much smaller compared to patient populations with a high underlying risk of PONV. Furthermore, we stopped the study prematurely as the risk reduction was much lower than anticipated, rendering the study futile. Although it is unlikely that conclusions would have changed in case of attaining the intended sample size, results would have been estimated with more statistical precision. However, we considered it unethical to continue randomisation after concluding that patients were unlikely to benefit from the

Table 1 Baseline characteristics in the intention to treat population and by treatment group (*N* = 281)

	Missing data	Total *N* = 281	Placebo IV (0.9% saline) N = 70	Dexamethasone IV 3 mg N = 68	6 mg N = 71	12 mg N = 72
Age	0	45.3 ± 14.4	47.4 ± 13.0	44.3 ± 15.5	44.7 ± 15.4	44.7 ± 13.8
BMI	0	26.3 ± 5.1	25.9 ± 5.0	26.4 ± 5.3	26.6 ± 5.4	26.4 ± 4.9
Female	0	204 (72.6)	47 (67.1)	50 (73.5)	50 (70.4)	57 (79.2)
Type of intervention	2					
Gynaecology		40 (14.3)	11 (15.7)	12 (17.9)	7 (10.0)	10 (13.9)
Orthopaedics including back surgery		49 (17.6)	16 (22.9)	8 (11.9)	15 (21.4)	10 (13.9)
Abdominal surgery		63 (22.6)	18 (25.7)	16 (23.9)	17 (24.3)	12 (16.7)
Ear, Nose and Throat surgery		39 (14.0)	8 (11.4)	9 (13.4)	10 (14.3)	12 (16.7)
Neurosurgery		21 (7.5)	3 (4.3)	6 (9.0)	4 (5.7)	8 (11.1)
Plastic surgery		67 (24.0)	14 (20.0)	16 (23.9)	17 (24.3)	20 (27.8)
Smoking status	0					
Non smoker		141 (50.2)	41 (58.6)	35 (51.5)	33 (46.5)	32 (44.4)
Ex-smoker		62 (22.1)	16 (22.9)	14 (20.6)	12 (16.9)	20 (27.8)
Smoker		78 (27.8)	13 (18.6)	19 (27.9)	26 (36.6)	20 (27.8)
Volatile anaesthesia	0	255 (90.7)	60 (85.7)	62 (91.2)	66 (93.0)	67 (93.1)
Combined anaesthesia	1	61 (21.8)	17 (24.3)	16 (23.5)	15 (21.1)	13 (18.3)
History of PONV after general anaesthesia	14					
Yes		100 (37.6)	27 (40.9)	25 (39.1)	29 (42.0)	19 (27.9)
No		116 (43.2)	27 (40.9)	27 (42.2)	28 (40.6)	34 (50.0)
Never had general anaesthesia		51 (19.2)	12 (18.2)	12 (18.8)	12 (17.4)	15 (22.1)
Suffers from motion sickness	1	96 (34.3)	22 (31.4)	27 (39.7)	24 (33.8)	23 (32.4)
Suffers from migraine	3	91 (32.7)	18 (25.7)	22 (32.4)	30 (42.9)	21 (30.0)
Total opiate administration during anaesthesia in IV morphine equivalents (mg)	1	30 [25 to 40]	30 [23 to 45]	30 [25 to 40]	30 [20 to 40]	35 [25 to 45]
Total opiate consumption since extubation to study drug administration in IV morphine equivalents	35	4.0 [0 to 10.0]	5.0 [0 to 12.0]	3.5 [0 to 10.8]	4.0 [0 to 10.0]	3.3 [0 to 10.0]

Data are mean ± SD, number (%), median [IQR]; BMI, body mass index; ITT, intention to treat; SD, standard deviation; PONV, postoperative nausea and vomiting; IV, intravenous

intervention. Lastly, to reflect normal clinical practice as closely as possible, we did not standardise anaesthesia and analgesia techniques and medications; these were left to the discretion of the physicians. Therefore, no conclusions may be made for specific strata of patients, only for the average patient as observed in our study. The study was too small for extensive subgroup analyses.

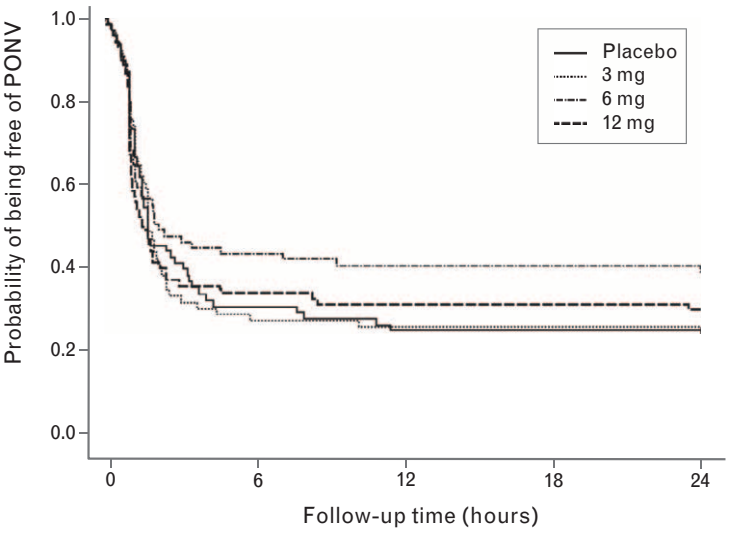
There is convincing empirical evidence that dexamethasone has preventive antiemetic efficacy in surgical patients[12] and also has antiemetic properties in patients undergoing emetogenic chemotherapy.[13] The complete lack of antiemetic efficacy of dexamethasone in the treatment of established PONV symptoms was therefore quite unexpected. We chose dexamethasone regimens that are widely used in daily clinical practice, and there was no reason to believe that these regimens were subtherapeutic. Also, postoperative hyperglycaemia increased in a dose-dependent fashion significantly confirming the nongenomic impact of glucocorticoid effects.

Table 2 Risk of no PONV at 24 h by group of treatment (primary outcome)

	Total	PONV	Unadjusted OR (95% CI)	*P*-value*	Adjusted OR (95% CI)**	*P*-value*
At 24 hours ITT				0.158		0.170
Placebo	70	18 (25.7)	reference		reference	
Dexamethasone IV 3 mg	68	17 (25.0)	0.96 (0.44 to 2.08)		1.02 (0.46 to 2.24)	
Dexamethasone IV 6 mg	71	29 (40.8)	1.99 (0.98 to 4.13)		2.09 (0.99 to 4.51)	
Dexamethasone IV 12 mg	72	23 (31.9)	1.36 (0.66 to 2.84)		1.48 (0.69 to 3.24)	
At 24 hours PP				0.115		0.131
Placebo	64	18 (28.1)	reference		reference	
Dexamethasone IV 3 mg	65	1 6 (25.0)	0.83 (0.38 to 1.83)		0.89 (0.39 to 2.00)	
Dexamethasone IV 6 mg	67	29 (43.3)	1.95 (0.95 to 4.09)		2.08 (0.97 to 4.57)	
Dexamethasone IV 12 mg	65	20 (30.8)	1.14 (0.53 to 2.44)		1.31 (0.59 to 2.93)	

Data are number, number (%), OR (95% CI, x toy). * Likelihood ratio test (global effect of treatment). ** Adjusted model on sex, type of surgery, smoking status, suffers from migraine, suffers from motion sickness, and total opiate administration during anaesthesia in IV morphine equivalents; CI, confidence interval; PONV, postoperative nausea and vomiting; ITT, intention to treat; PP, per protocol; OR, odds ratio; CI, confidence interval; IV, intravenous.

Fig. 2 Time to vomiting and/or nausea (treatment failure) for each study group of treatment using the Kaplan-Meier method



Number at risk					
70	23	19	19	19	Placebo
68	20	19	19	19	3 mg
71	32	30	30	30	6 mg
72	26	24	24	23	12 mg

Some antiemetics, for instance, 5-HT_3 receptor antagonists, block specific central receptor systems and this mechanism is likely to explain their antiemetic efficacy both for the prevention of PONV and the treatment of established PONV symptoms.[5] For dexamethasone, no specific receptor involved in the emetic pathway is known. Indeed, the biological basis of dexamethasone's antiemetic efficacy is still not fully understood.

A variety of potential mechanisms have been discussed.[14] In addition to its genomic effect dexamethasone has specific receptor-mediated actions, such as the antagonism of 5-HT_{3A} receptors expressed in xenopus oocytes. Although, these experimental conditions are in the range of 1 mM, it is far from the clinical conditions (more than 3 log higher than the expected dexamethasone plasma concentrations of our study).[15] Our results contrast those observed after chemotherapy induced emesis where corticosteroids decreased cisplatin-induced 5-HT release from peripheral blood mononuclear cells in vitro.[16,17]

Other direct nonspecific, nongenomic steroid actions occur. For instance, it has been suggested that the usefulness of dexamethasone in the control of emesis may be caused by the release of endorphins, resulting in elevation of well being and mood and appetite stimulation.[18] Furthermore, other potential mechanisms are related to the anti-inflammatory effect, or to a direct central action at the solitary tract nucleus,[19] or prostaglandin antagonism.[20] Finally, and more convincingly, especially in surgical patients, there is large body of evidence that dexamethasone may reduce pain and may thus exert an opioid-sparing effect which potentially reduces opioid-related nausea and vomiting.[8,21] Overall, the evidence confirms that in patients undergoing surgery, prophylactic dexamethasone should be administered, when required, at the induction of anaesthesia.[3,22] This may reflect

Table 3 Secondary endpoints: descriptive of postoperative hyperglycaemia and quality of sleep by group of treatment in the per protocol set (*N* = 260)

	Placebo IV (0.9% saline)	Dexamethasone IV			
	total	3 mg	6 mg	12 mg	*P*-value*
Blood glucose (mmol l^1)	217	53 6.0 [5.2 to 6.6]	54 6.2 [5.5 to 7.2]	58 6.4 [5.6 to 7.4]	53 6.9 [6.4 to 8.0]	<0.001
Quality of sleep	247	60 5.0 [4.0 to 7.0]	61 5.0 [4.0 to 7.0]	63 5.0 [3.0 to 7.0]	62 5.0 [3.0 to 8.0])	0.564

Data are number, and median [IQR]. *Trend test IQR, interquartile range.

Table 4 Number of patients with nonserious and serious adverse events in the safety set (N = 281)

	Placebo IV (0.9% saline)	Dexamethasone IV 3 mg	6 mg	12 mg	Total
Total of patients (%) with NSAEs*	6 (8.6)	9 (13.2)	3 (4.2)	6 (8.3)	24 (8.5)
Infections					
Urinary tract infection		2		2	4
Infection of ENT sphere	1	1	1		3
Local wound infection	2				2
Bleeding					
Local bleeding of wound	1				1
Meniscus hematoma		1			1
Other					
Anaemia	1	1	1		3
Urinary retention	1	1			2
Chest tightness				2	2
Serous wound exudate	1	1			2
Wound swelling	1				1
Pain and redness on arm		1			1
Paraesthesia in the foot		1			1
Scar dehiscence			1		1
Sciatic neuropathy				1	1
Suprapubic pain				1	1
Allergic reaction (erythema)				1	1
Unknown (missing data)			1		1
Total of patients with SAE*	2 (2.9)	2 (2.9)	1 (1.4)	4 (5.6)	9 (3.2)
Infections					
Generalised fever				2	2
Perineal abscess				1	1
Bleeding					
Postoperative haemorrhage needing surgical revision	2				2
Other					
Scar dehiscence needing surgical revision (no signs of infection)		2	1	1	4

* Some patients had two nonserious AE, one patient had both a nonserious and a serious adverse event, *p*-value (Fischer's exact test) = 0.187; ENT, ear nose and throat; NSAE, nonserious adverse event; SAE, serious adverse event.

the perceived inability of dexamethasone to develop fast antiemetic efficacy and that, contrary to 'classic' antiemetics that block receptor systems, dexamethasone's antiemetic mechanisms, if there are any, may be 'indirect', and therefore, delayed. As previously described, dexamethasone administration caused an elevation in blood glucose in the postoperative period.[6,7] We confirmed these observations; the elevations were significant and dose dependent. Serious adverse events (bleeding, infection) were rare. As dexamethasone is a widely used drug in the perioperative setting, it may be worthwhile to further study the potential impact of perioperatively administered dexamethasone on infection. We tested dexamethasone as a single-drug regimen. The combination of dexamethasone with $5HT_3$ receptor antagonists has proven efficacy for the prevention of PONV.[23] It may be worthwhile and eventually promising to test that combination also for the treatment of established PONV. Ormel *et al.* tested in-patients suffering from PONV symptoms despite triple prophylaxis (ondansetron, droperidol, dexamethasone) a combination of ondansetron and droperidol with or without dexamethasone as a rescue treatment.[24] Adding dexamethasone to the ondansetron-droperidol combination proved to be more efficacious as a rescue treatment compared with ondansetron-droperidol alone.[24] In conclusion, our randomised trial failed to show antiemetic efficacy of a single intravenous dose of dexamethasone, 3 to 12 mg, for the treatment of established PONV in adults undergoing surgery under general anaesthesia. These results do not refute the hypothesis that dexamethasone may be potentially useful to prevent delayed vomiting after surgery, but indeed, there are a number of effective molecules that have a better and a proven therapeutic profile.

Acknowledgements relating to this article

Assistance with the study: We are grateful to Prof Nadia Elia, MD, Division of Anaesthesiology, Geneva University Hospitals, for her valuable help in co-writing the study protocol, fundraising, as well as for contributing to the analyses that led to the early termination of the trial, to Beatrice Gil-Wey, Claudine Carera, and Patrick Huwiler, research assistants, Division of Anaesthesiology, Geneva University Hospitals, and Carine Marcucci and Melanie Boand, research assistants, Department of Anaesthesiology, Lausanne University Hospital, for their efforts in data collection, and to Cecile Delhumeau-Cartier, PhD, Division of Anaesthesiology, Geneva University Hospitals, for preliminary statistical analyses. We also thank the Clinical Research Centres of University of Geneva and Geneva University Hospitals and University of Lausanne and Lausanne University Hospital for study monitoring.

Financial support and sponsorship: This project received support from the Swiss National Research Foundation (SNF 32003B_140783), the Clinical Research Centre, Geneva University Hospitals, Geneva, Switzerland (130301-CD) and the Division of Anaesthesiology, Ospedale Regionale di Lugano, Lugano, Switzerland (108.99001).

Conflicts of interest: none.

Presentation: none.

References

1 Mauermann E, Clamer D, Ruppen W, *et al.* Association between intraoperative fentanyl dosing and postoperative nausea/vomiting and pain: A prospective cohort study. *Eur J Anaesthesiol* 2019; **36**:871–880.
2 van Wijk MGF, Smalhout B. A postoperative analysis of the patient's view of anaesthesia in a Netherlands' teaching hospital. *Anaesthesia* 1990;**45**:679–682.
3 Gan TJ, Belani KG, Bergese S, *et al.* Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. *Anesth Analg* 2020; **131**:411–448.
4 Apfel CC, Korttila K, Abdalla M, *et al.* A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**:; 2441-2451; +2534.
5 Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: A quantitative systematic review. *BMC Anesthesiol* 2001; **1**:I2.
6 Cowie B, Allen K, Said S, *et al.* Antiemetic doses of dexamethasone suppress cortisol response in laparoscopic cholecystectomy. *Anaesth Intensive Care* 2010; **38**:667–670.
7 Eberhart LHJ, Graf J, Morin AM, *et al.* Randomised controlled trial of the effect of oral premedication with dexamethasone on hyperglycaemic response to abdominal hysterectomy. *Eur J Anaesthesiol* 2011; **28**:195–201.
8 Czarnetzki C, Elia N, Lysakowski C, *et al.* Dexamethasone and risk of nausea and vomiting and postoperative bleeding after tonsillectomy in children: a randomized trial. *JAMA* 2008; **300**:2621–2630.
9 Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977; **64**:191–199.
10 Pampallona S, Tsiatis AA. Group sequential designs for one-sided and two-sided hypothesis testing with provision for early stopping in favor of the null hypothesis. *J Stat Plan and Inference* 1994;19–35.
11 Cuzick J. A wilcoxon-type test for trend. *Stat Med* 1985; **4**:87–90.
12 Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000; **90**:186–194.
13 Kris MG, Gralla RJ, Tyson LB, *et al.* Controlling delayed vomiting: doubleblind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. *J Clin Oncol* 1989;**7**:108–114.
14 Chu CC, Hsing CH, Shieh JP, *et al.* The cellular mechanisms of the antiemetic action of dexamethasone and related glucocorticoids against vomiting. *Eur J Pharmacol* 2014; **722**:48–54.
15 Suzuki T, Sugimoto M, Koyama H, *et al.* Inhibitory effect of glucocorticoids on human-cloned 5- hydroxytryptamine3A receptor expressed in xenopus oocytes. *Anesthesiology* 2004; **101**:660–665.
16 Mantovani G, Maccio A, Esu S, *et al.* Evidence that cisplatin induces serotonin release from human peripheral blood mononuclear cells and that methylprednisolone inhibits this effect. *Eur J Cancer* 1996; **32**:1983–1985.
17 Tanihata S, Oda S, Nakai S, *et al.* Antiemetic effect of dexamethasone on cisplatin-induced early and delayed emesis in the pigeon. *Eur J Pharmacol* 2004; **484**:311–321.
18 Harris AL. Cytotoxic therapy induced vomiting is mediated via enkaphalin pathways. *Lancet* 1982; **319**:714–716.
19 Ho CM, Ho ST, Wang JJ, *et al.* Dexamethasone has a central antiemetic mechanism in decerebrated cats. *Anesth Analg* 2004; **99**:734–739.
20 Rich WM, Abdulhayoglu G, DiSaia PJ. Methylprednisoloneas an antiemetic during cancer chemotherapy-a pilot study. *Gynecologic Oncol* 1980; **9**:193–198.
21 Diakos EA, Gallos ID, El-Shunnar S, *et al.* Dexamethasone reduces pain, vomiting and overall complications following tonsillectomy in adults: A systematic review and meta-analysis of randomised controlled trials. *Clin Otolaryngol* 2011; **36**:531–542.
22 DREAMS Trial Collaborators and West Midlands Research Collaborative. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* 2017; **357**:j1455.
23 Som A, Bhattacharjee S, Maitra S, *et al.* Combination of 5-HT3 antagonist and dexamethasone is superior to 5-HT3 antagonist alone for PONV prophylaxis after laparoscopic surgeries: a meta-analysis. *Anesthes Analg* 2016; **123**:1418–1426.
24 Ormel G, Romundstad L, Lambert-Jensen P, *et al.* Dexamethasone has additive effect when combined with ondansetron and droperidol for treatment of established PONV. *Acta Anaesthesiol Scand* 2011; **55**:1196–1205.