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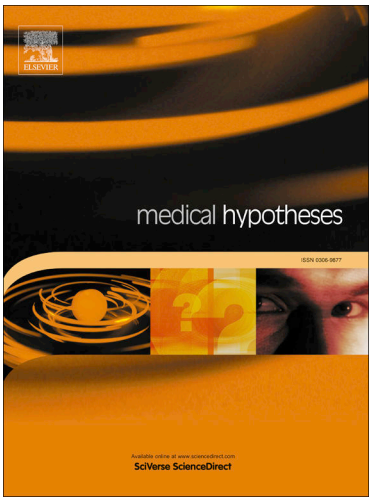

Dexamethasone induced hyperglycaemia and adverse outcomes – are we there yet?

Ketan K Dhatariya

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Title:
Dexamethasone induced hyperglycaemia and adverse outcomes – are we there yet?

Authors:
Ketan K Dhatariya MBBS MSc MD MS FRCP PhD[1,2]

Affiliations:
1. Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospitals NHS Foundation Trust, Colney Lane, Norwich, Norfolk, UK NR4 7UY
2. Norwich Medicine School, University of East Anglia, Norwich, Norfolk, UK

Corresponding author:
Prof. Ketan K Dhatariya
Consultant in Diabetes and Endocrinology
Honorary Professor of Medicine, Norwich Medical School
Elsie Bertram Diabetes Centre,
Norfolk and Norwich University Hospitals NHS Foundation Trust,
Colney Lane,
Norwich, Norfolk, UK
NR4 7UY

Tel: +44 (0)1603 288170
Email: ketan.dhatariya@nnuh.nhs.uk

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Introduction

There are numerous studies suggesting that poor peri-operative glycaemic control – measured either as plasma glucose, or as glycated haemoglobin (HbA_{1c}) – is associated with adverse post-operative outcomes, including surgical site infections across a number of specialities (1-3). Furthermore, outcomes were worse when

glucose concentrations were highest in those not known to have diabetes or hyperglycaemia prior to their operation (4). Previous work has also shown that raised glucose levels or HbA_{1c} *within the reference range* are associated with harm, with one study of 989 people with diabetes showing that for each 1.0 mmol/l increase in blood glucose 30 day mortality rose by 1.19 (CI 1.1 - 1.3) (5). Thus, even small rises in glucose may not be benign. Frisch et al showed that if glucose concentrations were high (i.e. >16.6mmol/l [300mg/dl]) pre-operatively in people not known to have diabetes then the risk of dying at 30 days after surgery was over 12 times higher than those who had a normal pre-operative glucose, and this increased to over 40 times higher if the post-operative glucose was high i.e. (>16.6mmol/l [300mg/dl]) (4). Mortality was double in those known to have diabetes if their glucose concentrations were >16.6mmol/l (300mg/dl) compared to those with mean glucose concentrations of 5.5mmol/l (100mg/dl). Rates of other complications, including acute myocardial infarction, acute kidney injury, wound infections, and other infections were also significantly higher in those known to have diabetes prior to surgery (4). These trends in higher morbidity and mortality in those not known to have diabetes but with peri-operative hyperglycaemia have been confirmed in larger observational datasets (6; 7).

There has been speculation as to why morbidity and mortality is lower in those known to have diabetes, even when glucose concentrations are high. It may be that because people known to have diabetes frequently have bedside capillary glucose measurements, they need to be attended to more often that those who do not have diabetes – the simple act of visiting the bedside, may allow staff to pick up on changes in status more quickly and intervene to prevent further deterioration.

Indeed, data have suggested that those people who had a higher pre-operative HbA_{1c} were more likely to go onto insulin post-operatively, particularly if their glucose was high, and also had more frequent post-operative glucose checks (11).

To address the issue of peri-operative glycaemic control, in 2011 the Joint British Diabetes Societies for Inpatient Care produced a guideline to try to formulate a series of recommendations to help improve outcomes (8). This was later adapted by the Royal College of Anaesthetists in the UK (9), and most recently the issue has been championed by the Centre for Perioperative Care, who have once again further updated the guidance (1). These guidelines suggest that for elective surgery, pre-operative HbA_{1c} concentrations should ideally be ≤69mmol/mol (8.5%) where it can be safely achieved and that glucose concentrations should be maintained at 6.0 – 10.0 mmol/l (with up to 12.0 mmol/l being acceptable).

The effects of glucocorticoids on blood glucose

Glucocorticoids raise blood glucose concentrations by a variety of mechanisms including increasing insulin resistance, and promoting hepatic gluconeogenesis (10). Even a single dose of dexamethasone can raise transiently glucose concentrations, particularly when added to the physiological stress of acute illness or surgery, transient hyperglycaemia often results – so called stress hyperglycaemia (11; 12).

Dexamethasone use in surgery

However, the potential risk of transient hyperglycaemia needs to be offset against the benefits in terms of reducing post-operative nausea and vomiting, as well as reducing post-operative pain and swelling – all of which will help lead to earlier

discharge from hospital (13-15). It was noticeable however, that the 2008 Cochrane review on drugs for preventing postoperative nausea and vomiting reviewed dexamethasone and recommended it's use – however, no mention was made of glucose in the 785 page document (13). A more up to date Cochrane review published in 2018 showed that wound infections or problems with wound healing were not more common those given dexamethasone regardless of dose when compared to placebo (16). They did, however show that dexamethasone use significantly increased post-operative blood glucose concentrations (16). However, the same group showed that the numbers of people in the studies was very small (an average of 56 people in each of the 12 studies) with the level of evidence being rated as poor or very poor (16).

In 2013 I wrote an editorial suggesting that dexamethasone use may contribute to postoperative morbidity and mortality (17). Recently Corcoran et al published the results of a large pragmatic non-inferiority trial that suggested that dexamethasone use did not increase the number of surgical site infections when compared to placebo, raising the possibility that my initial argument was wrong (18). The authors of that study suggested that dexamethasone was non-inferior to placebo, with the incidence of surgical site infections amongst 8725 people being 8.1% in those assigned to dexamethasone, and 9.1% in those given placebo ($p<0.001$ for non-inferiority after adjustment for diabetes status). There was also a statistically significant benefit in post-operative nausea and vomiting (PONV) between the dexamethasone group and placebo (42.2% vs 53.9% respectively). However, there were numerically more people who developed post-operative hyperglycaemia in the

dexamethasone group (0.6% vs 0.2%), but the number of people this represented was small – 22 in the dexamethasone group and 6 in the placebo group (18). However, my hypothesis is that these data are flawed, and that the wrong analysis was done and that the use of dexamethasone should continue to remain contentious.

Most studies that were included in the 2018 Cochrane review looked at the effect of dexamethasone on glucose have often used the differences in mean concentration (Figure 1). They pool all the patients together and compare steroid vs placebo. Indeed, the Cochrane review suggested that the median glycaemic response – i.e. change from baseline to 2-12 hours postoperatively, showed a rise in median glucose of 0.7mmol/l (13mg/dl), and that for 10-24 hours post-surgery, the mean difference in glucose was a rise of 1.8mmol/l (32mg/dl) in those given dexamethasone compared to placebo (16). However, as with the Corcoran study, the vast majority of individuals will not develop hyperglycaemia, thus in the groups as a whole, outcomes are unlikely to be different to those not given dexamethasone. However, within the groups, a proportion of the individuals do develop hyperglycaemia – indeed, in the Corcoran study, 6 people not previously known to have diabetes developed hyperglycaemia (18). Thus, whilst the medians may not be statistically different, for those people who develop hyperglycemia, there may have been a consequence. Thus, to see whether dexamethasone induced hyperglycaemia is associated with harm, the sample size should be based on the proportion of people who develop hyperglycaemia in each group – likely to be too large for most funders. The issue of potentially incorrect analyses is discussed in more detail elsewhere (19).

This brings me back to the Corcoran study. Their cohort had a diabetes prevalence of 13.2%. However, their mean HbA_{1c} was 51mmol/mol (6.8%) in the group receiving dexamethasone and 49mmol/mol (6.6%) in the placebo cohort. Thus, their diabetes was already close to optimal and, when looking at the data from Frisch et al their risks of developing post-operative complications already very small (4). The diabetes cohort in the Corcoran study is thus unlikely to be representative of the general surgical population, where in the UK only 29.9% of those with type 1 diabetes and 65.8% of people with type 2 diabetes achieved an HbA_{1c} target of ≤58 mmol/mol (20). The authors do not say how many people were excluded due to poor glycaemic control.

In summary, dexamethasone use is common, and it works very well in the peri-operative period for post-operative nausea and vomiting and other post-operative considerations. However, it has the side effects of transiently raising blood glucose concentrations. It is well recognised what high post-operative glucose is associated with harm, but to date, the question as to whether the post-operative hyperglycaemia associated with dexamethasone use is associated with harm has yet to be conclusively answered.

Legend to Figure 1

In people who have normal glucose tolerance, the administration of dexamethasone may leave to a transient rise in blood glucose, but that stays within the reference range for the vast majority of people – (dotted line). In others, who may have a degree of insulin resistance or have well controlled diabetes, their glucose may also

rise, but the mean rise is slightly higher than those with normal glucose control. Most studies have compared the mean rise in glucose from both groups and concluded that the differences are not statistically significant. However, in those without diabetes, a very small number may develop significant hyperglycaemia, and those with insulin resistance or well controlled diabetes many more may develop significant hyperglycaemia with the administration of dexamethasone. Of those, a small number of each group who develop hyperglycaemia will develop complications (those who fall into the marked area on the right). Sample sizes should be calculated on the estimates of a) what proportion of those who are given dexamethasone will develop hyperglycaemia (which may now be estimated using the data from the Corcoran study (18)), and of those who are likely to develop complications – which can be estimated from previous work on complication rates in hyperglycaemia.

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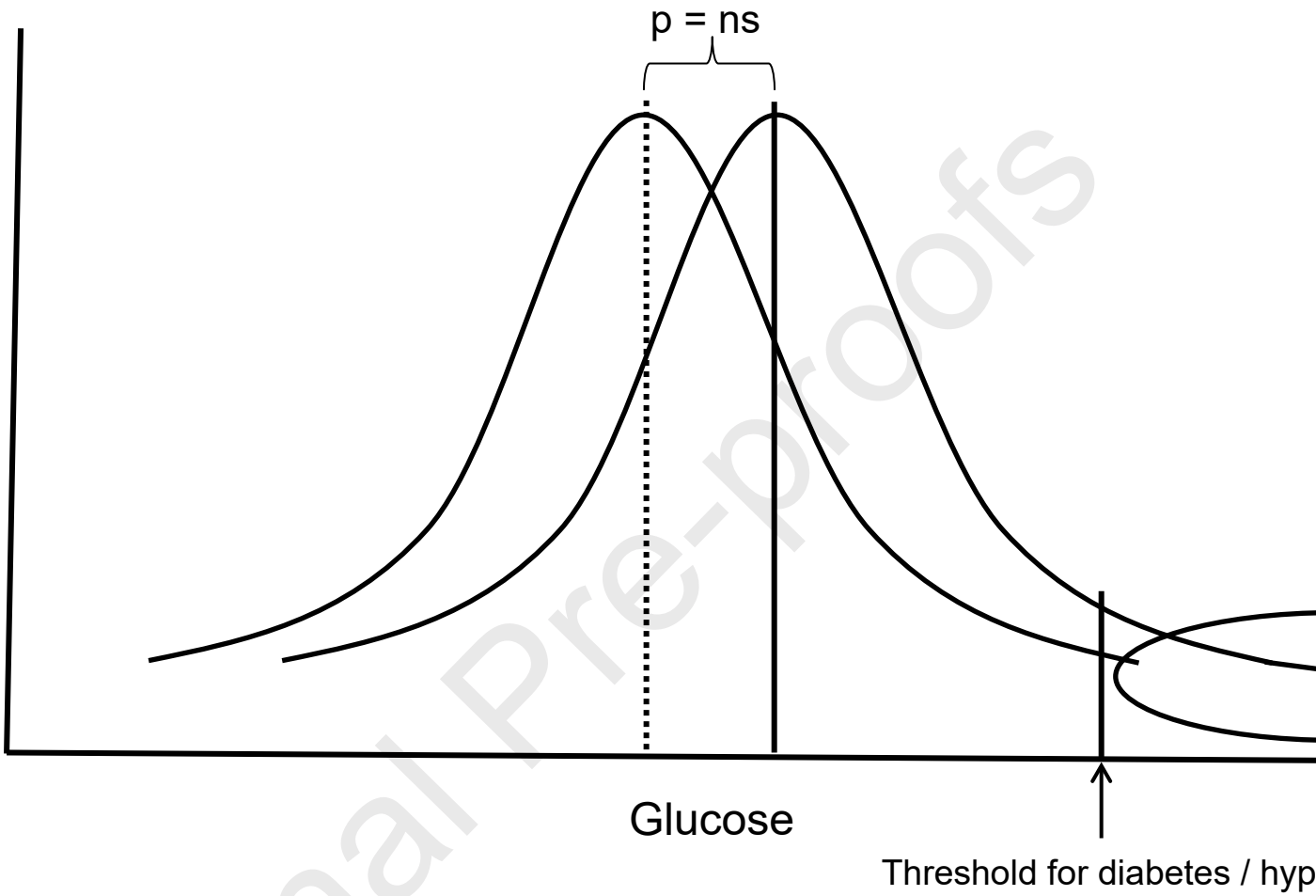
Figure 1



Abstract

Peri-operative hyperglycaemia is associated with poor post-operative outcomes in people with and without diabetes. Dexamethasone is a commonly used drug which works well to control post-operative nausea and vomiting. However, it is well recognised to cause transient hyperglycaemia. A 2018 Cochrane analysis and a recent large randomised controlled trial suggested that dexamethasone use was not

associated with an increased risk of surgical site infection in those with or without diabetes. I argue that the data used to generate the Cochrane data were weak and of very low quality. My hypothesis is that the recent large study on dexamethasone use and surgical site infections did the wrong analysis, meaning that the safety of dexamethasone has yet to be established.

Keywords:

Dexamethasone, harm, hyperglycaemia, anaesthesia, surgery

Duality of Interest The author declarse that there is no duality of interest associated with this manuscript.