

The use of a perioperative supra-physiological dose of glucocorticoid is not supported by evidence – a systematic review

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ABSTRACT

INTRODUCTION: A supra-physiological dose of glucocorticoid (SDS) is administered routinely in the perioperative management of patients on long-term regular glucocorticoid therapy. The dose of glucocorticoid used in these regimens varies. The current treatment is based on two 60-year-old case reports. No data exist to document the required dose of glucocorticoid to prevent perioperative hypotension or the category of patients needing this dose. Having in mind that high doses of glucocorticoids have several potential side effects, this practice ought to be re-evaluated in the light of available evidence.

METHODS: We searched MEDLINE, Embase and the Cochrane Library for data about perioperative stress dose. The search was conducted by the two authors and repeated by a research librarian to ensure inclusion of all related studies. All original articles and reviews relating to the perioperative use of SDS in chronic glucocorticoid-treated patients were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were applied.

RESULTS: A total of 21 studies met the inclusion criteria of which five were prospective studies, five retrospective studies, three randomised controlled trials and eight reviews (three systematic reviews, one Cochrane review, three treatment guidelines, and one meta-analysis). No data supported routine use of SDS. Patients who continued their normal glucocorticoid treatment throughout the perioperative period had no need for SDS.

CONCLUSION: No evidence supports the preoperative use of SDS in patients receiving chronic glucocorticoid therapy.

Glucocorticoids have a wide range of uses, especially in autoimmune and inflammatory diseases such as chronic obstructive pulmonary disease, rheumatoid arthritis, asthma, systemic lupus erythematosus and patients who receive an organ transplant. Treatment with glucocorticoids is associated with a number of side effects that depend on the duration of treatment, the dose, and each patient's response. The most common side effects are osteoporosis, diabetes mellitus and an increased risk of infection. A serious side effect to long-term and/or high-dose of glucocorticoids is secondary adrenal insufficiency.

Exogenous glucocorticoid causes negative feedback on the hypothalamus-pituitary-adrenal axis and thus reduced stimulation of cortisol production by the adrenal cortex. The result is atrophy of the adrenal cortex and hence secondary adrenal insufficiency.

Cortisol is important for the regulation of systemic blood pressure, response to catecholamines, electrolyte imbalance and the metabolism of carbohydrates and lipids. Under normal circumstances, the production of cortisol is 5-10 mg of per square meter surface area corresponding to a 24-hour production of approximately 10-20 mg for a healthy man with a height of 1.8 metres and weighing 75 kg. In response to physiological stress such as surgery, trauma or infection, the production of cortisol will increase up to six times the basal value. In humans with a normal adrenal function, the cortisol production will increase by about 50 mg/day during minor surgery and 100 mg/day during major surgery [1].

The time from discontinuation of glucocorticoid treatment to full recovery of adrenal gland function varies from person to person from four days to nine months [2]. During secondary adrenal insufficiency, sudden ending of treatment or lack of supplement upon exposure to surgical stress, acute adrenal insufficiency and hypovolemic shock may arise. The fear of such event led many hospitals in the world, including those in Denmark, to routinely use supra-physiological dose of glucocorticoid (SDS) as a supplement dose in patients on long-term glucocorticoid therapy. When and how high a dose of glucocorticoids should be given in this context is disputed and may vary from hospital to hospital. In general, the use of a high dose of glucocorticoid is widespread,

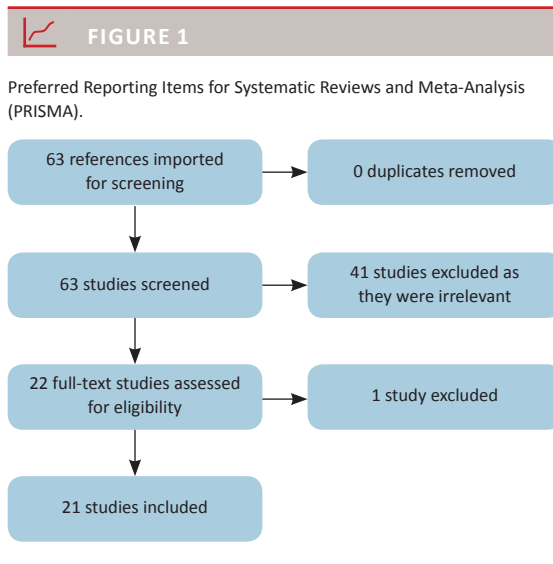
SYSTEMATIC REVIEW

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! KEY POINTS

- Patients on chronic glucocorticoid therapy receive high doses of glucocorticoids perioperatively to avoid development of acute adrenal insufficiency.
- A perioperative supra-physiological dose of glucocorticoids is not required. Continuation of the usual glucocorticoids dose during surgery is sufficient to avoid acute adrenal insufficiency.
- Avoid unnecessary overdoses and post-operative complications. Improve the post-operative outcome.



well above the usual preoperative dose. The purpose of this review was to examine any evidence relating to the use of SDS in patients receiving glucocorticoid therapy on a regular basis due to chronic disease.

METHODS

Articles were identified by searching electronic databases and running through reference lists in relevant literature. We searched the MEDLINE, Embase and Cochrane Library databases from the date of inception to 11 September 2017 when the last search was conducted.

Inclusion criteria

Clinical trials, original articles and reviews about adult patients on glucocorticoid treatment who underwent surgical intervention and received perioperative SDS.

Exclusion criteria

Studies where the outcome was not clinical adrenal insufficiency. Articles in languages other than English, Danish, Swedish and Norwegian. Also, editorials, correspondence and studies not relating to humans were excluded.

Search strategy

The two authors conducted the search independently, and a research librarian at the Medical Library – Aalborg University Hospital – Denmark, then repeated the search to ensure that all relevant studies were included.

The search was conducted by selecting relevant Medical Subject Heading (MeSH) terms so that we only included topic-specific articles. Next, we used advanced free text search and search words like “surgery”, “stress dose”, “steriod”. These words’ synonyms were com-

bined with “or” to expand the search. All synonyms were then merged using “AND” to include all relevant articles. The used keywords were as follows:

Adrenal Insufficiency [MeSH] or adrenal insufficienc* [text word (tw)] or adrenal gland hypofunction* [tw] or hypoadrenalism* [tw] AND Surgical Procedures, Operative [MeSH] or General Surgery [MeSH] or surgery [tw] or operation* [tw] or perioperat* [tw] AND Steroids [MeSH] or steroid* [tw] or Adrenal Cortex Hormones [Pharmacological Action] or Glucocorticoids [Pharmacological Action] or glucocorticoid* [tw] or corticosteriod* [tw] AND high dosage [tw] or high dose* [tw] or stress dosage [tw] or stress dose [tw].

Both authors scrutinised the articles using Covidence tools for systematic reviews (www.covidence.org). Relevant studies were identified by title, abstract and, in case of doubt, full text articles were retrieved before inclusion/exclusion. Disagreements were solved by discussion. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. PRISMA is an evidence-based method of searching systematic reviews and meta-analyses that ensure clarity with respect to inclusion/exclusion and reduces any bias.

Data extraction

Both authors participated in the data extraction.

RESULTS

A total of 41 articles were excluded by title/abstract screening, and one article was excluded after full-text screening. In all, 21 studies were included (**Figure 1**). **Table 1** describes 13 original studies, five prospective studies, five retrospective studies and three randomised controlled studies (RCT). **Table 2** shows eight reviews, of which four are systematic reviews, three treatment guidelines and one a meta-analysis. The following account describes some of the included studies to give an idea about the subject:

In the two prospective studies by Bromberg et al [4, 5] with a total of 84 glucocorticoid-treated renal transplant patients who received usual glucocorticoid dose perioperatively, fatal consequences or haemodynamic instability could not be detected. A prospective study by Friedman et al [6] of 28 glucocorticoid-treated patients who underwent orthopaedic surgery with their usual glucocorticoid dose showed no clinical or laboratory test signs of adrenal insufficiency. This was later confirmed by Glowniak & Loriaux [7] who published the results of a double-blinded study of 18 patients with secondary adrenal insufficiency. All patients were treated with a minimum of 7.5 mg prednisolone daily for a minimum of two months. The majority of patients underwent major surgery such as abdominal operations, hip replacements,



TABLE 1

Overview of included randomised controlled trials and original studies about the use of a supra-physiological dose of glucocorticoid in patients who are on regular glucocorticoid treatment.

Reference	Study design	Patients, n	Intervention/controls: n	Type of surgery	Clinical outcome
Shapiro et al, 1990 [3]	Prospective	13	-	Allograft nephrectomy	No adrenal insufficiency
Bromberg et al, 1991 [4]	Prospective	40	-	Mixed surgical procedures	No adrenal insufficiency
Bromberg et al, 1995 [5]	Prospective	52	-	Mixed surgical procedures	No adrenal insufficiency
Friedman et al, 1995 [6]	Prospective	28	-	Orthopaedic surgery	No adrenal insufficiency
Glowniak & Loriaux, 1997 [7]	RCT	18	SDS: 6 Usual dose: 12	Mixed surgical procedures	No adrenal insufficiency 1 in each group developed hypotension, which were treated with intravenous fluid therapy
Thomason et al, 1999 [8]	RCT	20	Patients were their own controls At the 1st operation they only received their usual dose, while at the 2nd operation they received their usual dose and SDS	Gingivectomy	No adrenal insufficiency
Mathis et al, 2004 [9]	Retrospective	58	SDS: 20 Usual dose: 38	Lymphocele surgery	No adrenal insufficiency
Zaghiyan et al, 2011 [10]	Retrospective	49	SDS: 11 No glucocorticoid: 38	Major colorectal surgery	No adrenal insufficiency
Zaghiyan et al, 2012 [11]	Retrospective	97	SDS: 43 Usual dose: 54	Major colorectal surgery	No adrenal insufficiency
Zaghiyan et al, 2012 [12]	Prospective	32	Usual dose: 10 No glucocorticoid, discontinued 1 yr preoperatively: 22	Major colorectal surgery	No adrenal insufficiency Transient hypotension treated with fluid therapy No need for vasopressors or high dose of glucocorticoids
Aytac et al, 2013 [13]	Retrospective	235	SDS: 89 Controls: 146	Abdominal surgery, proctocolectomy in CU patients	SDS group: 1 adrenal insufficiency 1 died of anastomotic leakage 25 days post-operatively
Zaghiyan et al, 2014 [14]	RCT	92	Randomised to either SDS or usual dose	Major colorectal surgery	No increased risk of adrenal insufficiency
Lamore et al 2014 [15]	Retrospective	49	SDS: 38 Usual dose: 11	Major colorectal surgery	No adrenal insufficiency

CU = colitis ulcerosa; RCT = randomised controlled trial; SDS = supra-physiological dose of glucocorticoid.

etc. All the participating patients in this study received their usual prednisolone dose. Six patients were randomised to receive SDS and a saline solution, while the remainder received only saline solution perioperatively. One patient in each group developed hypotension. There was no significant difference in mean heart rate and blood pressure ratio between the two groups. This RCT was followed by another RCT by Thomason et al [8] who investigated the perioperative use of glucocorticoids of 20 previously transplanted patients who underwent gingivectomy. All patients were administered their usual prednisolone dose and allocated to receive either SDS or placebo. None of the patients in the study developed symptoms of adrenal insufficiency. The authors concluded that if patients continue their usual dose of glucocorticoid perioperatively, SDS will not be needed.

Mathis et al [9] performed a retrospective study of 58 patients who were undergoing lymphocele drainage. Twenty patients were treated with SDS preoperatively, whereas 38 patients only received their usual prednisolone dose. Neither patients in the SDS nor patients in the prednisolone group developed any signs of acute adrenal insufficiency. Another retrospective study by Aytac et al [13] examined 235 prednisolone-treated colitis ulcerosa patients who underwent restorative proctocolectomy. Eighty-nine of the patients received SDS perioperatively, whereas the remaining 146 continued their usual prednisolone dose. No patient in the prednisolone group developed acute adrenal insufficiency. On the other hand, there was one patient in the SDS group who developed acute adrenal insufficiency post-operatively. Another patient in the same group was re-admitted with

TABLE 2

Overview of included reviews about the use of supra-physiological dose of glucocorticoid in patients who are on regular glucocorticoid treatment.

Reference	Studies, n	Method	Conclusion
Brown & Buie, 2001 [16]	11	Systematic review	SDS is unnecessary Usual dose is sufficient to avoid a hypotensive crisis and the adverse side effects associated with a high dose of glucocorticoids
de Lange & Kars, 2008 [1]	7	Systematic review	Exogenously inhibited adrenal glands are able to produce cortisol to withstand physical stress associated with surgery No evidence for SDS Usual glucocorticoid dose is sufficient during surgery There is a need for randomised, blinded studies confirming that SDS is unnecessary
Marik & Varon, 2008 [17]	9	Systematic review	As long as patients take their usual glucocorticoid dose, SDS is not required during surgery Patients with primary adrenal insufficiency (Addison) are an exception HPA axis function test cannot predetermine adrenal crises
Yong et al, 2009 [2]	2	Meta-analysis	Cannot confirm or refute the use of SDS due to small population studies However, they point out that the majority of patients who received usual glucocorticoid dose have been free from complications; this may indicate that SDS is unnecessary
Kelly & Domajnko, 2013 [18]	-	Review	Adrenal insufficiency is a rare cause of disease or death after surgery Based on existing evidence it is recommended that patients receiving long-term glucocorticoid therapy should maintain their usual dose throughout the perioperative period Treatment with SDS only in case of irreversible or unexplained hypotension Larger randomised controlled studies are required
Jonmarker et al, 2015 [19]	9	Guidelines, Swedish	No SDS for patients receiving glucocorticoids < 7.5 mg prior to elective surgery The exception is those whose usual dose is > 7.5 mg and who are undergoing emergency surgery The conclusion is based on literature and clinical experience.
Hicks et al, 2015 [20]	-	Guidelines	Must reduce unnecessary exposure to SDS and the risk of glucocorticoids-associated morbidity
MacKenzie & Goodman, 2016 [21]	-	Guidelines	No need for SDS

HPA = hypothalamic-pituitary-adrenal; SDS = supra-physiological dose of glucocorticoid.



Induction of anaesthesia. The perioperative supra-physiological dose of glucocorticoid is usually administered at this stage despite lack of evidence to support any such practice.

anastomotic leak 25 days post-operatively and subsequently died. In retrospective research of data from 49 IBD patients who discontinued prednisolone treatment within one year prior to colorectal surgery, Zaghiyan et al [10] reported that 11 of the patients received SDS. Adrenal insufficiency-related complications were not observed in the remaining 38 patients without SDS. There was no obvious advantage of SDS treatment when comparing the two groups' haemodynamic instability. The same authors conducted a similar study of 97 patients of whom 43 received SDS and 54 received only their usual

prednisolone dose [11]. Once again, there were no haemodynamic differences between the two groups. This encouraged the same authors to conduct a prospective study [12] of 32 IBD patients who also underwent major colorectal surgery. Ten of the patients received hydrocortisone treatment corresponding to their usual preoperative oral prednisolone dose, whereas 22 patients – who discontinued glucocorticoid therapy within one year prior to surgery – did not receive glucocorticoid therapy perioperatively. There was no significant difference with respect to haemodynamics, need of vasopressors, intensive treatment or symptoms of adrenal insufficiency. The study concluded that the usual glucocorticoid dose in IBD patients undergoing colorectal surgery seems safe. The same authors then conducted a single-blinded RCT [14] study which included 92 glucocorticoid-treated IBD patients who underwent major colorectal surgery. Patients were randomised to SDS or intravenous hydrocortisone corresponding to their usual glucocorticoid dose. The incidence of adrenal insufficiency or postural hypotension was the same in both groups. The reviews by Brown & Buie [16], de Lange & Kars [1], Marik & Varon [17] and Kelly et al from 2001, 2008, 2008 and 2013, respectively, concluded that there is no evidence in support for perioperative SDS as long as patients continue their usual glucocorticoid dose.

In the Cochrane review [2], Glowniak & Loriaux [7] and Thomason et al [8] RCTs were the only two studies that met the inclusion criteria. The conclusion was that, with the small patient group (37 patients) and the high risk of bias, the authors could neither support nor refute any need for SDS.

DISCUSSION

In this review, we found no evidence to support the use of SDS during surgery in patients with chronic disease requiring regular glucocorticoid therapy, provided the patients receive their usual dose of glucocorticoid pre-operatively. The use of SDS or what is called a steroid umbrella for this category of patients is based on two 60-year-old case reports, which described two patients whose glucocorticoid treatment was suddenly interrupted before surgery [1, 18] (possibly) leading to adrenal insufficiency crises and death. The level of cortisol was not measured and the cause of death was not investigated properly. Moreover, a great development in anaesthesia and peri-operative management has taken place since then. This was evident by reviewing articles from the past three decades. The updated guidelines from the European Crohn Colitis Organization and the European Society of Colo-Proctology (ECCO-ESCP) emphasise the lack of evidence in support of SDS treatment [22].

Although adrenal glands in patients with chronic glucocorticoid therapy can be shown to be suppressed by the synacthen test, they are (to a lesser extent) capable of increasing endogenous cortisol production, especially when exposed to stress like surgery. A study from adrenalectomised monkeys showed that physiological cortisol levels are sufficient to withstand surgical stress [23]. Therefore, the increased endogenous cortisol production combined with an exogenous glucocorticoid dose must be sufficient to withstand stress associated with surgery [1, 6-8]. Thus, there is no indication to use SDS in the perioperative setting. In most studies that describe the perioperative use of SDS in patients with autoimmune or inflammatory disease on long-term glucocorticoid therapy, adrenal insufficiency is measured by laboratory tests such as plasma and urine cortisol. Few studies are based on clinical measurements as a primary outcome and even fewer on combined clinical and laboratory outcomes.

Surgical stress response is different in different types of surgery and so is the risk of adrenal insufficiency. It is not clear if all surgical interventions carry a risk of adrenal crises in patients who are on regular glucocorticoid treatment.

The questions about the use of SDS on what type of patients, what is the most appropriate dose, when it must be administered, and what side effects does it have ought to be investigated in a well-designed large, multi-centre RCT.

CONCLUSIONS

There is no evidence supporting the use of SDS peri-operatively in patients who are on chronic glucocorticoid therapy. A well-designed, large multi-centre RCT is warranted.

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