

A survey of corticosteroid use for the management of septic shock

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Abstract

Background: Critical illness is associated with pituitary-adrenal axis dysfunction, and may cause adrenal insufficiency that manifests as septic shock that is poorly responsive to fluid or inotropic therapy. Administering a low-dose corticosteroid to these patients results in faster shock resolution, but there is controversy regarding its effect on patient mortality. This survey aimed to describe how survey respondents are interpreting the current literature and using corticosteroids in patient management.

Method: A survey was conducted during the 2011 annual congress of the South African Society of Anaesthesiologists.

Results: Of the 65 respondents who completed the survey, all (except one specialist) had a background in anaesthesia or critical care. The majority of respondents agreed with the Surviving Sepsis Campaign definitions for sepsis and septic shock. A “typical” respondent would administer a total daily dose of 200 mg hydrocortisone, in boluses, to septic shock patients requiring inotropic support, or who were poorly responsive to inotropes. They would not use an adrenocorticotropic hormone stimulation test to identify these patients. Once shock resolved, or inotropes were no longer required, they would wean the hydrocortisone. More than 40% of respondents would use corticosteroids in clinical scenarios in which no patient benefit has been shown, and which might cause patient harm.

Conclusion: Respondents use corticosteroids as recommended by the Surviving Sepsis Campaign guidelines, but would extend this use to other clinical scenarios, i.e. sepsis without hypotension and for non-septic shock, which might cause patient harm. When making clinical decisions, more emphasis should be placed on patient-important outcomes than on surrogate outcomes.

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Introduction

Critical illness, and in particular severe sepsis and septic shock, is associated with hypothalamic-pituitary-adrenal axis dysfunction. Also termed critical illness-related corticosteroid insufficiency (CIRCI),¹ it may lead to adrenal insufficiency, manifesting as septic shock that is poorly responsive to fluid or inotropic therapy.^{2,3} Clinical trials have shown that administering low-dose steroids to these patients results in faster shock resolution, and has been incorporated into the Surviving Sepsis Campaign Guidelines.^{1,4,5} This beneficial haemodynamic effect has not translated into mortality reductions,⁶⁻⁸ and corticosteroid

use has been associated with side-effects such as hypernatraemia, hyperglycaemia and super-infection.⁹

Despite its inclusion into the guidelines, many questions regarding steroid use in this population remain unanswered. These include how patients with CIRCI should be identified; how steroids should be administered (bolus or infusion); should they be administered for a fixed duration; and should they be tapered, rather than abruptly discontinued? In the light of this uncertainty, our survey aimed to describe how survey respondents are interpreting the current literature and using corticosteroids for the management of critically ill patients.

Method

The study protocol was approved by the Postgraduate Education Committee, University of KwaZulu-Natal, and the Biomedical Research Ethics Committee (BE230/010). During the 2011 annual congress of the South African Society of Anaesthesiologists, the study questionnaire was distributed to all congress delegates. Informed consent was obtained from all survey participants.

Statistical analyses

Categorical data were analysed using descriptive statistics, and are presented as percentages. Categorical data were analysed using the Fisher's exact test or Pearson's chi-square test where appropriate. All continuous data were analysed using descriptive statistics and presented as mean [standard deviation (SD)] when the distribution was normal, and median [interquartile range (IQR)] with a non-Gaussian distribution, and compared using independent samples t-test, or Mann-Whitney U test, respectively. We considered a two-sided p-value of 0.05 to be significant for all test results.

Results

Table I describes the characteristics of the 65 survey respondents, who comprised specialists (54%) and non-specialists (46%). Of the 65 respondents who completed the survey, all except one specialist had a background in anaesthesia or critical care. Most of the respondents managed intensive care unit (ICU) patients. However, only 17% spent more than 50% of their time in an ICU.

Sepsis and septic shock definitions

The overwhelming majority of respondents (98%) agreed with the Surviving Sepsis Campaign definition of sepsis and septic shock,¹⁰ and all respondents would consider administering steroids to patients in at least one of the clinical scenarios of septic shock that were described.

Corticosteroid choice, dose, and administration

The majority of respondents (94%) would administer a steroid as a bolus, rather than as an infusion. Hydrocortisone was chosen by 92% of respondents, with the total daily dose ranging from 50-600 mg per day (median 200 mg, IQR 150 mg). Two respondents indicated they would give a dose of 600 mg. Methyl-prednisone was chosen by 7.7% of respondents, and fludrocortisone was chosen by 4.6% of respondents.

Table I: Characteristics of survey respondents

Job description	Total number of respondents n = 65 (100%)	Working in the public sector* n = 46 (71%)	> 50% working time spent in ICU n = 11 (17%)
Medical officer or registrar	30 (46%)	27 (59%)	3 (27%)
Specialist	27 (42%)	11 (24%)	1 (1%)
Sub-specialist (critical care or trauma)	8 (12%)	8 (17%)	7 (64%)

* Includes respondents who indicated that they worked in both the public and private sectors

Termination of corticosteroid administration

Sixty-eight per cent of respondents would terminate corticosteroid supplementation when shock resolved, or when patients no longer required inotropes; 19% when sepsis resolved; 12% once the patient was discharged from ICU; and 8% would administer the corticosteroid for a fixed duration. Lastly, 72% of respondents would make use of a weaning protocol when terminating administration.

Indications for corticosteroid use

Table II describes the scenarios in which respondents would make use of a low-dose corticosteroid for the management of patients with sepsis. Table III describes scenarios in which respondents would make use of a low-dose corticosteroid for the management of shock patients without sepsis. Despite 39% of respondents having laboratory facilities to carry out an adrenocorticotrophic hormone (ACTH) stimulation test, only 9.2% would use the test to direct corticosteroid administration. The trigger to initiate therapy would be either a low baseline cortisol level or a lack of response to an ACTH stimulation test.

Table II: Clinical scenarios in which respondents would consider using a low-dose corticosteroid in septic patients

Clinical scenario	Percentage who would use a low-dose corticosteroid
Sepsis suspected, no hypotension	3.1%
Sepsis confirmed, no hypotension	9.2%
Septic shock	33.8%
Septic shock, requiring inotropic support	50.8%
Septic shock, poorly responsive or resistant to inotropic support	67.7%

Table III: Clinical scenarios in which respondents would consider using a low-dose corticosteroid in shock patients without sepsis

Clinical scenario	Percentage who would use a low-dose corticosteroid
Shock	10.8%
Shock, requiring inotropic support	21.5%
Shock, poorly responsive or resistant to inotropic support	43.1%

Discussion

Based on these findings, “typical” respondents would administer a total daily dose of 200 mg hydrocortisone, in boluses, to septic shock patients requiring inotropic support, or who are poorly responsive to inotropes. They would not make use of an ACTH stimulation test to identify these patients. Once the shock had resolved, or inotropes were no longer required, they would wean the hydrocortisone. This pattern of practice is in keeping with the Surviving Sepsis Campaign guideline recommendations.¹¹

Sepsis and septic shock definitions

There was almost complete agreement among survey respondents with regard to the “sepsis” and “septic shock” definitions that were used in this survey. These definitions are consistent with those presented at the International Sepsis Definitions Conference.¹⁰ It would appear that these definitions, proposed in 2001, have been successful in creating a shared understanding of what the terms “sepsis” and “septic shock” refer to. This is a vital step in ensuring the successful development of critical care research.

Choice of corticosteroid

Hydrocortisone is recommended as the corticosteroid of choice in the Surviving Sepsis Guidelines,⁴ and in this survey, the majority of respondents chose to use hydrocortisone. Two respondents indicated they would use fludrocortisone in addition to hydrocortisone. In a single trial, fludrocortisone was added to a hydrocortisone treatment regimen to maximise mineralocorticoid activity. This was carried out despite hydrocortisone having its own mineralocorticoid activity.⁶ Guidelines have since recommended the use of fludrocortisone only when a corticosteroid with no mineralocorticoid activity is used, and its use is considered optional when hydrocortisone is used.⁴ More recently, fludrocortisone was found to be associated with no mortality benefit, and an increased risk of infection.¹² Three respondents in this survey chose to use methylprednisone alone, a corticosteroid with half the mineralocorticoid activity of hydrocortisone.

Dose of corticosteroid

High-dose corticosteroid administration in severe sepsis or septic shock has been shown to cause harm,¹³⁻¹⁵ and in the Corticosteroid Therapy of Septic Shock (CORTICUS) study,⁹ which used low-dose hydrocortisone, patients receiving additional corticosteroid had more cases of super-infection, new sepsis, septic shock, hyperglycaemia and hypernatraemia.⁹ The Surviving Sepsis Campaign Guidelines recommend that doses less than 300 mg per day are used.⁴ In this survey, 12.4% of respondents indicated that they would use a hydrocortisone dose greater than 300 mg, with some using as much as 600 mg daily. Using such high corticosteroid doses for the management of CIRCI does not seem to be appropriate and is likely to cause harm to patients.

Administration of corticosteroid

Little literature has examined the optimal method of administering supplemental corticosteroid. Hydrocortisone may be dosed at 100 mg 8 hourly, 50 mg 6-8 hourly, or may be given as a continuous infusion. Continuous infusions are associated with less blood-sugar elevations, but may cause greater rebound effects.¹⁶ This survey found that most respondents used a bolus technique, perhaps reflecting the ease with which such a prescription can be incorporated into day-to-day patient management.

Termination of corticosteroid administration

The trigger for termination of corticosteroid therapy has varied between studies, with some using a fixed duration,^{6,9,17,18} while others have used clinical triggers, such as the resolution of shock.^{8,19} Interestingly, the minority of survey respondents would make use of a fixed duration regimen. Considering the potential for infection that is associated with low-dose corticosteroid use, and keeping in mind that the only consistent benefit that is seen with corticosteroid use is faster shock resolution within the first three days, a strong case can be made for using a fixed duration regimen.¹⁸ In line with guideline recommendations,^{1,4} the majority of respondents in this survey would taper corticosteroids before discontinuation. The evidence supporting this practice is weak, with a single study showing that abrupt discontinuation may cause a pro-inflammatory rebound,¹⁵ while another suggests that discontinuation may be associated with the recurrence of hypotension.^{20,21}

Indications for corticosteroid use

The majority of respondents would consider using corticosteroids for the management of patients with septic shock requiring inotropic support, or who are poorly responsive to inotropes. Interestingly, just over a third of respondents would use corticosteroids in septic patients who do not have shock, and up to 40% would use corticosteroids in non-septic patients with shock. Between specialists (including sub-specialists) and non-specialists, both the indications for and the pattern of corticosteroid use were not different, except for septic shock patients without haemodynamic compromise. In this patient group, specialists were more likely to administer corticosteroids than non-specialists (p-value = 0.03).

These findings suggest that in general, respondents view low-dose corticosteroid therapy as a largely beneficial intervention, and are comfortable to extend its use into fields in which there is little support for its efficacy, e.g. extended durations of administration, use in sepsis without hypotension, and use in non-septic shock.

Unfortunately, the literature has not demonstrated a clear benefit regarding steroid administration for septic shock. A high-quality meta-analysis of 17 trials, conducted by many

of the authors who have published on this topic, found that steroid use in patients with sepsis and related syndromes is not associated with a mortality benefit.²¹ A second meta-analysis reported that steroid use in less critically ill patients increased mortality risk,²² and the CORTICUS results highlighted the increased risk of super-infection, new sepsis episodes, hyperglycaemia and hypernatraemia in patients receiving steroids.⁹

The reasons why respondents have adopted a positive view of steroid use have not been explored, and are largely speculative. Firstly, many clinicians will have personally seen that patients who are started on corticosteroids have reduced inotrope requirements. Secondly, the initial mortality reductions reported by early studies and the enthusiastic guideline recommendations may have created a positive impression regarding corticosteroid use. Thirdly, trials have consistently shown that corticosteroid administration reduces inotrope requirements, an outcome that many clinicians deem to be desirable. Finally, the side-effects of corticosteroid administration, such as super-infection or repeat septic episodes, are less common, and are less closely linked in time to corticosteroid administration, making it harder for individual clinicians to draw conclusions regarding the potential harm that relates to corticosteroids.

There are no patient-important outcomes that support the use of a low-dose corticosteroid in patients without sepsis, patients with severe sepsis without shock, or in those with non-septic shock. The use of a low-dose corticosteroid in this population has the potential to cause harm.^{9,23} Depending on the clinical scenario, 30-40% of respondents would use corticosteroids inappropriately. This is in sharp contrast to a global study that reported inappropriate low-dose corticosteroid use in only 14.2% of respondents.²⁴ The medical literature is rife with examples in which using surrogate end-points to direct research and clinical decision-making has led to increases in patient morbidity and mortality,²⁵⁻²⁷ and the dangers have been highlighted extensively.²⁸ It is clear that patients care about outcomes that impact on their lives, e.g. death, infection or rehospitalisation, rather than surrogate outcomes on which clinicians often focus.²⁹ It is imperative that more emphasis is placed on patient-important outcomes when making clinical decisions.

Study limitations

The majority of survey respondents were employed in the public sector, and this, together with the small number of responses, makes it difficult to generalise these results to the larger critical care community. In addition, the sample was drawn from delegates at an anaesthesia congress, further limiting its external applicability. Importantly, it must be noted that there was no statistically significant difference between how critical care sub-specialists, specialists, and non-specialists would use steroids in any of the clinical

scenarios. Identifying this pattern of steroid use in all categories of respondents, including critical care specialists and anaesthesia trainees, suggests that this is a true signal. Also, anaesthetists arguably receive the largest amount of ICU-specific training during their training, making it more likely that these results reflect general South African ICU practice.

It is likely that respondents represent a more motivated and possibly more informed group than non-respondents. To the extent that this is true, the results are concerning. We would have expected a more balanced interpretation of the current literature from such a group. We did not record in which country respondents were practising, and it is possible that these results include the opinions of non-South African clinicians.

Recommendations and implications for clinical practice

To determine if these results truly reflect ICU practice in South Africa, further surveys may have to be conducted, with a greater focus on South African intensivists. These findings suggest that greater efforts are required to convey a more balanced interpretation of the current literature as it relates to steroid use in sepsis and septic shock. More attention should be given to the limitations and potential side-effects of steroid therapy. In addition, a key component of this process would be to make clinicians more aware of the limitations of surrogate outcomes, and the importance of basing clinical decision-making on patient-important outcomes.

Conclusion

Respondents use corticosteroids as recommended by the Surviving Sepsis Campaign guidelines, but would extend this use to clinical scenarios, i.e. sepsis without hypotension and non-septic shock, that might cause patient harm. When making clinical decisions, more emphasis should be placed on patient-important outcomes, rather than on surrogate outcomes.

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Appendix 1: Survey questionnaire is available online at www.sajaa.co.za