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REVIEW

Corticosteroids for cardiac surgery: a summary of two large randomised trials

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Abstract

The postoperative systemic inflammatory response syndrome that is associated with cardiac surgery and the use of cardiopulmonary bypass may contribute to postoperative organ dysfunction and complications. Two recent multicentre randomised clinical trials evaluated the prophylactic use of high-dose corticosteroids to suppress the postoperative inflammatory response in a total of 12,001 cardiac surgery patients. The studies were negative on their primary endpoint, and showed a blend of benefit and harm on secondary endpoints. For dexamethasone, its overall pulmonary benefit was probably the most marked effect, which was demonstrable at multiple levels. There also appeared to be an age-dependent effect of corticosteroids with younger patients (<65 years) with a lower risk of mortality and older patients (>80 years) with an increased risk of mortality when receiving steroids. The differential effects of corticosteroids on patient outcomes between the different age groups may be based on a decreasing intensity of the systemic inflammatory response with advancing age. Future studies should be designed to identify those individual patients who are more susceptible to developing an excessive inflammatory response, and who may receive benefit from anti-inflammatory treatment.

Steroids in cardiac surgery: an eminence-based routine

The postoperative systemic inflammatory response syndrome (SIRS) that is associated with cardiac surgery and the use of cardiopulmonary bypass may contribute to postoperative organ dysfunction and complications.[1-4] In the Netherlands and some other countries, high-dose corticosteroids are often routinely administered during cardiac surgery to reduce inflammatory activation, and thus improve outcomes. The use of high-dose corticosteroid drugs for prophylaxis of postoperative systemic inflammation, however, is a topic of increasing controversy. Over the last decades, the design of cardiopulmonary bypass machines has improved remarkably, with membrane oxygenators instead of bubble oxygenators, centrifugal pumps instead of roller

Table 1. Principal outcomes of the DECS and SIRS trial

	DECS trial			SIRS trial		
	Dexamethasone (n=2239)	Placebo (n=2255)	P	Methylprednisolone (n=3755)	Placebo (n=3752)	P
Primary (combined) endpoint	7%	9%	0.07	24%	24%	0.53
Mortality	1%	2%	0.73	4%	5%	0.19
Q-wave myocardial infarction	2%	2%	0.65			
Enzymatic myocardial injury				13%	11%	<0.01
Stroke	1%	1%	0.71	2%	2%	0.51
Renal failure	1%	2%	0.15	4%	4%	0.21
Respiratory failure	3%	4%	0.02	9%	10%	0.21
Other endpoints						
Any infection	10%	15%	<0.01	12%	13%	0.33
Any transfusion	39%	42%	0.03	49%	50%	0.43
Atrial fibrillation	33%	35%	0.14	22%	23%	0.48
Delirium	14%	15%	0.79	8%	8%	0.80
Length of hospital stay (days)	8	9	<0.01	9	9	0.06

DECS trial =Dexamethasone for Cardiac Surgery trial.[5] SIRS trial = Steroids In caRdiac Surgery trial.[6] The primary endpoint of the two trials consisted of five components: mortality, myocardial infarction or myocardial injury (DECS trial and SIRS trial, respectively), stroke, renal failure and respiratory failure. Length of hospital stay is expressed as medians.

pumps, and heparin-coated tubing. With severe SIRS gradually becoming less of an issue for the everyday care of cardiac surgical patients, it is increasingly recognised that the scientific evidence necessary to justify the routine use of perioperative high-dose steroids was – until recently – largely lacking.[1-4]

Five years ago, four independent meta-analyses were published about corticosteroids in cardiac surgery.[1-4] They were based on the same around 50 small randomised studies, including 3000 patients in total. Most of these small studies had a primary focus on intermediate endpoints rather than on relevant patient effects. The available studies were very heterogeneous, spanning a 35-year period of improvements in the quality of surgical techniques, cardiopulmonary bypass and perioperative care, and a subsequent decreased perioperative risk. The pooled analysis of these data was dominated by results from the earlier studies with the highest incidence of adverse outcomes, but which were least relevant for current clinical practice.

With this evidence gap, local experience and subjective belief became the driving forces that determined the practice of corticosteroid prophylaxis in most places, resulting in large global variation.

This practice variability formed the basis for two recent large multicentre randomised clinical trials. The first one, the DExamethasone for Cardiac Surgery (DECS) trial, recruited 4500 cardiac surgery patients in the Netherlands and was published in 2012.[5] The second study, the Steroids In caRdiac Surgery (SIRS) trial, randomised 7500 patients and was published in 2015.[6] We will now briefly discuss the principal results of these two large trials, which are also summarised in *table 1*.

The DECS trial

The DECS trial was performed in patients aged 18 years or older undergoing cardiac surgery at eight cardiac surgical centres in the Netherlands.[5] Patients were randomised to a single intraoperative dose of 1 mg/kg dexamethasone (n=2239) or placebo (n=2255). The primary endpoint was a composite of death, myocardial infarction, stroke, renal failure, or respiratory failure, at one-month follow-up. Of the patients in the dexamethasone group, 7.0% reached the primary study endpoint, compared with 8.5% of the patients in the placebo group (p=0.07). In the dexamethasone group, more patients remained free of transfusion of blood products (58% vs 61%, p=0.03), but concurrently more patients had a rethoracotomy (9.7% vs 7.3%, p=0.005). Dexamethasone was associated with a lower risk of respiratory failure (3.0% vs 4.3%, p= 0.02) and a reduction in postoperative infections (9.5% vs 14.8%, p<0.001). Also, duration of postoperative mechanical ventilation (p<0.001), intensive care unit stay (p<0.001) and hospital stay (p=0.009) was shorter in the dexamethasone group. As a result, treatment with dexamethasone reduced costs per patient by €1084.

The SIRS trial

The SIRS trial was another double-blinded, randomised, controlled trial in adult patients undergoing cardiac surgery.[6] Patients were only eligible if they had a European System for Cardiac Operative Risk Evaluation (Euroscore) of at least six points. Patients were recruited at 80 cardiac surgery centres in 18 countries and they were randomised to an intraoperative dose of 500 mg methylprednisolone (n=3755) or placebo (n=3752). The two co-primary outcomes were mortality, and a composite of death, myocardial injury, stroke, renal failure, or respiratory failure, within one month. The incidence of death was 4% in the methylprednisolone group and 5% in the placebo group (p=0.19). The composite endpoint occurred in 24% vs 24% of the patients (p=0.52). The beneficial effects of steroids on respiratory failure, infection rate, and duration of hospitalisation that were found in the DECS trial were not confirmed in the SIRS trial. The rethoracotomy rate was not reported.

Neuropsychiatric substudies

The SIRS that is associated with cardiac surgery and many other categories of intensive care patients is thought to cause an increased blood-brain barrier permeability and neuroinflammation.[7-9] This could be a source of delirium, cognitive decline and even cerebral oedema. The DECS trial investigators hypothesised that the use of dexamethasone could reduce the risk of postoperative cerebral oedema, delirium and cognitive decline, and therefore performed three substudies. In 768 participants of the DECS trial, the incidence of delirium was assessed during the first four postoperative days using the Confusion Assessment Method (CAM), accompanied by chart review. The incidence of delirium was similar between the dexamethasone (14.2%) and placebo (14.9%) groups (p=0.79).[7] In the SIRS trial, delirium was assessed on the third postoperative day in all participants, and was found in 8% of the patients in both groups.[6]

In 291 participants of the DECS trial, cognitive performance was assessed with a battery of neuropsychological tests before surgery and at one-month and one-year follow-up.[8] At one-month follow-up, 13.6% of the dexamethasone patients and 7.2% of the placebo patients had cognitive decline (p=0.09). At 12-month follow-up, the incidence of cognitive decline was 7.0% and 3.5%, respectively (p=0.24).

Finally, in 18 participants of the DECS trial, a CT scan of the brain was performed immediately after surgery.[9] Whereas two older studies published in 1993[10] and 1998[11] showed transient cerebral oedema in 11 out of 13 cardiac surgery patients, only one of the 18 patients in the present study had slight cerebral oedema.

A mix of benefit and harm

The DECS and SIRS trials did not demonstrate a statistically significant difference on the primary composite endpoint between the two treatment arms. As a consequence, there is no

evidence to suggest that cardiac surgery patients have an overall benefit from corticosteroids and should therefore receive routine corticosteroid prophylaxis. However, the analysis of secondary endpoints did show some substantial treatment effects, which formed an interesting but complex blend of potential benefit, absence of anticipated clinical effects, and also possible harm.

Of the 'secondary' effects of dexamethasone, its overall pulmonary benefit was probably the most marked effect, which was demonstrable on multiple levels.[5] The most prominent effect was a 31% reduction of the incidence of respiratory failure, associated with a reduced duration of postoperative mechanical ventilation, and a reduced length of postoperative stay in the ICU and the hospital. The observed pulmonary benefits in the DECS trial may be the result of an improved pulmonary condition due to less inflammatory effects on the lung tissue, and are consistent with results from previous smaller studies.[12,13] Also, the incidence of postoperative pneumonia was reduced in the dexamethasone group. This effect was contrary to expectations, since the potential for an increased risk of infections as a result of immunosuppression was one of the major safety concerns associated with the use of high-dose corticosteroids.[14] Interestingly, similar effects of steroids on infectious complications have been observed in several recent studies in ICU patients with trauma or sepsis.[15,16]

The DECS and SIRS trials also generated data that indicate the potential for harm from corticosteroid treatment. Increased postoperative hyperglycaemia, with markedly higher insulin requirements,[5,6,17] confirmed the well-known side effect of corticosteroids of increased insulin resistance. In the SIRS trial, perioperative methylprednisolone increased the release of cardiac enzymes (CK-MB)[6] and in the DECS trial, dexamethasone was associated with higher postoperative lactate levels.[17] In observational studies higher glucose, CK-MB, and lactate levels are usually associated with worse outcomes.[6,17] In the randomised DECS and SIRS studies, corticosteroids increased the levels of these three biomarkers, but apparently without a negative effect on clinical outcomes.[5,6] However, it has been suggested that increased postoperative hyperglycaemia following dexamethasone administration may have contributed to a possible negative effect on postoperative cognitive function, which was observed in one of the substudies of the DECS trial.[8] Moreover, in the report on the results of the large international Corticosteroid Randomization after Significant Head Injury (CRASH) trial,[18] the authors hypothesise that steroid-associated hyperglycaemia was the driving mechanism behind the negative effect of methylprednisolone on neurological outcomes in their study.

An unanticipated finding in the DECS trial was the increased rate of late surgical re-interventions in patients randomised to dexamethasone.[19] Although the mechanisms of this effect are not clear, it is possible that suppression of the inflammatory response resulted in a delayed resolution of the sterile pericarditis that is present in many cardiac surgical patients, resulting in increased pericardial fluid accumulation. As such, steroid prophylaxis may have the potential to impair postoperative recovery in otherwise uncomplicated cases.

The DECS trial showed more effects (both positive and harmful) than the SIRS trial. An important difference between the two studies is the corticosteroid drug that has been used. Although the glucocorticoid effect of 100 mg dexamethasone and 500 mg methylprednisolone is comparable, dexamethasone does not have a mineralocorticoid effect, whereas methylprednisolone does. However, this difference between the two drugs does not straightforwardly explain the effects that were found in the DECS trial but not confirmed in the SIRS trial.

Variation across patient groups

Pre-planned subgroup analyses were carried out in both the DECS trial and the SIRS trial.[5,6] Although it was anticipated that patients undergoing prolonged procedures would have more benefit from corticosteroids, this was not the case. Surprisingly, there appeared to be an age-dependent effect of corticosteroids on mortality. This age effect was most convincingly observed in de DECS trial (*figure 1*), but the SIRS trial also showed that younger patients (<65 years) have a lower risk of mortality when receiving corticosteroids. In older patients (>80 years), steroids do not reduce mortality but appear to increase the risk.

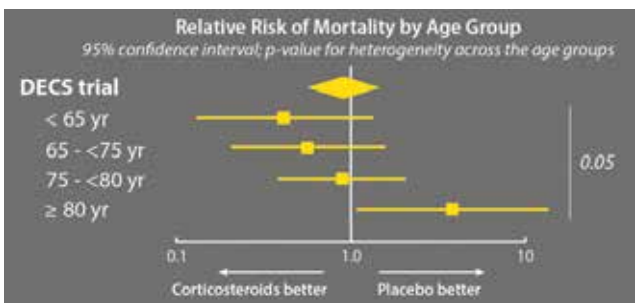

Figure 1. Effects of dexamethasone on one-month survival in different age groups

Discussion

Personalised treatment for a variable systemic inflammatory response

The differential effects of corticosteroids on patient outcomes between the different age groups of the DECS and SIRS trials may be based on a decreasing magnitude of the systemic inflammatory response phenotype with advancing age. In other words, this variability may result from age-related, a priori differences in the susceptibility of individual patients to develop a severe systemic inflammatory response, when exposed to the stimuli associated with cardiac surgery.

The phenotype of systemic inflammation embraces a broad,

clinically heterogeneous spectrum of responses, rather than a single disorder that complicates surgery, trauma or infection.[20] Most surgical patients develop a systemic inflammatory response that is in the milder range of the spectrum. Such a response serves as a supportive response for wound healing and recovery, and has a low probability of having a significant negative clinical impact.[21,22] As suggested by the results of the DECS trial and some of its substudies, suppression of the inflammatory response is harmful in certain patients.[5,8,19] However, at the more extreme end of this spectrum there are patients who develop a severe phenotype of systemic inflammation, which has the potential to complicate their postoperative course, and which puts them at an increased risk of postoperative morbidity, and possibly even mortality.[23]

When considering this inter-individual variability in the inflammatory response phenotype, it is not surprising that the effects of anti-inflammatory therapy could vary between patients too. Suppression of inflammation in subgroups of patients with an exaggerated inflammatory response may be beneficial, whereas suppression in patients with a much more controlled, or even senescent[24] inflammatory response could impair its purpose of recovery and contribute to adverse outcomes.

The concept of broad-spectrum inter-individual variability of immune responses is, of course, not unique for the perioperative setting, but is increasingly recognised in several other medical areas as well. For example, patients suffering from major trauma often develop an exaggerated systemic inflammatory response, but the severity is also very variable between individuals.[25] Several recent studies in this field have demonstrated that in those patients, a more excessive early inflammatory response is associated with an increased risk of organ failure and mortality.[26-28]

The phenotypic heterogeneity of the inflammatory response arises at multiple levels, and is formed by a complex interaction between the individual and external stimuli. Patient-associated factors that define individual susceptibility include predefined genetic make-up on the one hand, and acquired comorbidities, and associated medications, on the other. It has been generally accepted that genetic make-up has a significant role in determining the way in which we respond to our environment. However, the results of studies linking variations in 'fixed' genetic predisposition (single nucleotide polymorphisms) to inflammation severity have not been able to explain a large part of the variability in the perioperative inflammatory response phenotype so far.[29] Similarly, while genetic variation in many candidate genes has been implicated in sepsis susceptibility, it has thus far not been possible to establish predictive links to clinical outcomes.[30] Therefore, the variability of gene expression may be more important than genetic makeup per se. Gene expression is controlled by epigenetic mechanisms in a way that is stably propagated over multiple cell divisions, but that is also flexible enough to respond to environmental influences.[31] This intermediate position between stability and plasticity may explain how we interact with our environment at the genetic level, and is potentially of great importance in understanding the relationship between gene expression and complex diseases, including the perioperative inflammatory response. Differences between patients in methylation of genes involved in the inflammatory response are determined by multiple factors, such as age, comorbidities and environment.[32] These differences result in differential expression of an otherwise fixed genetic sequence, a subsequent variable transcription of inflammatory proteins that drive the innate and adaptive components of the immune response, and finally a clinically variable phenotype of systemic inflammation.[32]

The challenge in developing effective strategies for those individual patients who may suffer from harmful inflammation lies in achieving early characterisation of both the inflammatory response and the response to anti-inflammatory treatment that can be expected. Only in this way will it be possible to better define patient populations that receive benefit from anti-inflammatory treatment, and concurrently recognise other patient groups that should not receive treatment. This should allow more selective targeting of anti-inflammatory prophylaxis and treatment at the personalised level. Within the relatively controlled setting of elective surgery, the insults triggering an inflammatory response are usually short lasting (hours, rather than days), and timing is almost entirely predictable. These characteristics make the perioperative setting particularly suitable for investigating well-targeted treatment strategies. More specific for the systemic inflammatory response, the perioperative environment could potentially provide a good model for research into more precisely targeted treatment approaches for complex inflammatory conditions such as sepsis and severe trauma.

Conclusion

In the multicentre DECS and SIRS trials, the use of intraoperative corticosteroids did not reduce the overall incidence of major adverse events. However, multiple important effects were present in analyses of pre-planned secondary outcomes and subgroups. Effects were variable in terms of benefit and harm, and different between patient subgroups. These heterogeneous effects are likely based on substantial inter-individual variability in the severity of the systemic inflammatory response to cardiac surgery. As a result of this variability, benefit from corticosteroid treatment may only be present in subgroups of patients who develop an excessive, potentially harmful inflammatory response. We therefore need to aim at more precisely targeting anti-inflammatory therapy. Future studies may identify those individual patients who are more susceptible to develop an excessive inflammatory response, and who will as such receive benefit from an anti-inflammatory treatment. This

is not only relevant for cardiac surgery patients, but might also have implications for a more personalised treatment of non-cardiac surgery, trauma and sepsis patients.

Disclosures

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