Kidney360

Dexamethasone for Preventing Major Adverse Kidney Events following Cardiac Surgery: Post-Hoc Analysis to Identify Subgroups

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KIDNEY360 1: 530–533, 2020. doi: https://doi.org/10.34067/KID.0000812019

AKI is a serious and frequent complication of cardiac surgery, occurring in up to one third of patients (1). Despite years of investigation, therapies to prevent cardiac surgery-associated AKI (CSA-AKI) are lacking.

Glucocorticoids have been suggested as a potential therapy to prevent CSA-AKI, because inflammation induced by cardiac surgery could contribute to AKI in this setting. The Dexamethasone for Cardiac Surgery (DECS) study tested this hypothesis in a multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT00293592) in 4494 adults undergoing cardiac surgery with cardiopulmonary bypass (CPB) (2). Patients received a single intravenous dose of dexamethasone (1 mg/kg) or placebo before initiation of CPB (additional details are reported elsewhere) (2).

Although the DECS trial did not find an effect of dexamethasone on the incidence of AKI, the definition used for AKI—a tripling of serum creatinine (SCr) postoperatively—did not include the requirement for RRT. Thus, extracorporeal clearance of creatinine in patients who required RRT could have resulted in a discrepancy between actual AKI events and its protocol definition. Therefore, we previously conducted a *post hoc* analysis in which we defined AKI as the requirement for RRT. We found that the incidence of AKI requiring RRT was lower in dexamethasone- versus placebo-treated patients [relative risk, 0.44; 95% confidence interval (95% CI), 0.19 to 0.96]. In stratified analyses, the benefit of dexamethasone appeared greatest in patients with lower baseline eGFR (3).

Since it is unknown whether factors other than kidney function might modify the effect of dexamethasone on CSA-AKI, we investigated the treatment effect of dexamethasone on AKI across various subgroups of patient- and surgical characteristics. We reasoned that detection of heterogeneity across subgroups in the efficacy of dexamethasone could allow for more precise targeting of high-risk patients in future trials of glucocorticoid prophylaxis.

In the current analyses, we included 4465 (99.4%) of the 4494 patients enrolled in the original DECS trial (29 were excluded for reasons published previously) (3). We defined the baseline SCr as the value before and closest to cardiac surgery (in all cases at least one value was available within 30 days preceding surgery). The primary end point for the current analyses was Major Adverse Kidney Events within 30 days (MAKE30) of surgery, defined as an increase in SCr ≥50%, RRT, or death at any time within the first 30 days after surgery. Secondary end points were AKI stages 1, 2, and 3, defined according to the Kidney Disease: Improving Global Outcomes criteria (4). We performed subgroup analyses according to predetermined baseline patient and surgical variables (Figure 1B), and we assessed for effect modification by subgroup using logistic regression. P values <0.05 were considered significant.

The incidence of MAKE30, along with AKI stages 1, 2, and 3, was lower in dexamethasone- compared with placebo-treated patients (Figure 1A). Figure 1B shows the incidence of MAKE30 according to the following subgroups: age, EuroSCORE (European System for Cardiac Operative Risk Evaluation) (5), sex, body mass index, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, CKD, left ventricular function, type of surgery, duration of CPB, and use of a cell-saving device. The magnitude of the effect of dexamethasone on MAKE30 differed according to both age ($P=0.009$) and EuroSCORE ($P=0.03$). Specifically, we found a monotonic effect between both younger age and lower EuroSCORE and increasing benefit from dexamethasone. Because age is one of the components of the EuroSCORE, we also performed multivariable analyses in which we adjusted for age. The interaction between EuroSCORE and treatment group on MAKE30 remained significant even after adjusting for age (odds ratio, 0.41; 95% CI, 0.23 to 0.70; $P=0.02$ for interaction). Other subgroups did not demonstrate interaction with dexamethasone on the risk of MAKE30 (Figure 1B).

Intraoperative high-dose dexamethasone decreased the incidence of MAKE30 and all stages of AKI. Moreover, we report interactions between both age and EuroSCORE on the beneficial effect of dexamethasone, such that the benefit was greatest in younger patients and in those with lower EuroSCOREs, whereas older

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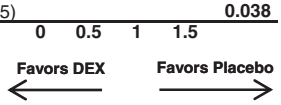
A

Outcome	DEX-group (n=2229)	Placebo-group (n=2236)	RR (95% CI)	P-Value
Primary Endpoint				
MAKE 30: ↑SCr ≥50%, RRT or death in the first 30 days	161 (7.2)	206 (9.2)	0.78 (0.64-0.96)	**0.016**
Secondary Endpoints				
KDIGO-AKI stage 1: ↑SCr ≥50% in the first 7 days	141 (6.3)	189 (8.5)	0.75 (0.61-0.92)	**0.007**
KDIGO-AKI stage 2: ↑SCr ≥100% in the first 7 days	65 (2.9)	90 (4.0)	0.72 (0.53-0.99)	**0.044**
KDIGO-AKI stage 3: ↑SCr ≥200% or RRT in the first 7 days	22 (1.0)	39 (1.7)	0.57 (0.34-0.95)	**0.038**



B

Subgroup	No. Pts	Event-rate n (%)	DEX-group n/n (%)	Placebo-group n/n (%)	RR (95% CI)	P-Value[1]
MAKE30: ↑SCr ≥50%, RRT or death in the first 30 days						
Age						**0.009**
<65 years	1869	92 (4.9)	28/909 (3.1)	64/960 (6.7)	0.46 (0.30-0.71)	
65-70 years	770	55 (7.1)	20/374 (5.3)	35/396 (8.8)	0.61 (0.36-1.03)	
>70 years	1824	220 (12.1)	113/944 (12.0)	107/880 (12.2)	0.98 (0.77-1.26)	
EuroSCORE[2]						**0.029**
<4	1564	55 (3.5)	15/779 (1.9)	40/785 (5.1)	0.38 (0.21-0.68)	
4-6	1606	105 (6.5)	47/807 (5.8)	58/799 (7.3)	0.80 (0.55-1.16)	
>6	1237	200 (16.2)	96/618 (15.5)	104/619 (16.8)	0.92 (0.72-1.19)	
Sex						0.59
Male	3234	238 (7.4)	102/1615 (6.3)	136/1619 (8.4)	0.75 (0.59-0.96)	
Female	1229	129 (10.5)	59/612 (9.6)	70/617 (11.3)	0.85 (0.61-1.18)	
BMI						0.80
<25	1415	104 (7.3)	48/702 (6.8)	56/713 (7.9)	0.87 (0.60-1.26)	
25-29	2013	155 (7.7)	66/1001 (6.6)	89/1012 (8.8)	0.75 (0.55-1.02)	
≥30	1017	107 (10.5)	47/518 (9.1)	60/499 (12.0)	0.75 (0.53-1.08)	
Hypertension						0.56
No	1941	140 (7.2)	65/973 (6.7)	75/968 (7.7)	0.86 (0.63-1.19)	
Yes	2348	210 (8.9)	91/1173 (7.8)	119/1175 (10.1)	0.77 (0.59-0.99)	
Diabetes Mellitus						0.96
No	3606	261 (7.2)	115/1809 (6.4)	146/1797 (8.1)	0.78 (0.62-0.99)	
Yes	847	105 (12.4)	45/414 (10.9)	60/433 (13.9)	0.78 (0.55-1.13)	
Pulmonary disease						0.053
No	3951	301 (7.6)	126/1981 (6.4)	175/1970 (8.9)	0.72 (0.57-0.89)	
Yes	508	65 (12.8)	34/243 (14.0)	31/265 (11.7)	1.20 (0.76-1.88)	
Peripheral vascular disease						0.98
No	4079	312 (7.6)	136/2034 (6.7)	176/2045 (8.6)	0.78 (0.63-0.96)	
Yes	381	54 (14.2)	24/191 (12.6)	30/190 (15.8)	0.80 (0.48-1.31)	
Chronic Kidney Disease[3]						0.33
No	2255	33 (1.5)	12/1140 (1.1)	21/1115 (1.9)	0.56 (0.28-1.13)	
Yes	2208	334 (15.1)	149/1087 (13.7)	185/1121 (16.5)	0.83 (0.68-1.01)	
LVEF						0.90
>50%	3194	218 (6.8)	97/1612 (6.0)	121/1582 (7.6)	0.79 (0.61-1.02)	
30-50%	1034	110 (10.6)	46/502 (9.2)	64/532 (12.0)	0.76 (0.53-1.09)	
<30%	218	36 (16.5)	16/102 (15.7)	20/116 (17.2)	0.91 (0.50-1.66)	
Type of surgery						0.11
CABG	1767	97 (5.5)	38/879 (4.3)	59/888 (6.6)	0.65 (0.44-0.97)	
Valve	1310	90 (6.9)	49/658 (7.4)	41/652 (6.3)	1.18 (0.79-1.77)	
CABG + Valve	729	109 (15.0)	48/359 (13.4)	61/370 (16.5)	0.81 (0.57-1.15)	
Duration of CPB						0.97
<120 min	2626	137 (5.2)	60/1318 (4.6)	77/1308 (5.9)	0.77 (0.56-1.07)	
≥120 min	1808	230 (12.7)	101/897 (11.3)	129/911 (14.2)	0.80 (0.62-1.01)	
Use of cell-saving device						0.79
No	2197	128 (5.8)	55/1070 (5.1)	73/1127 (6.5)	0.79 (0.56-1.11)	
Yes	2244	237 (10.6)	105/1147 (9.2)	132/1097 (12.0)	0.76 (0.60-0.97)	

Figure 1. | AKI end points in the dexamethasone and placebo groups with stratified analyses for major adverse kidney events at 30 days, across patient and surgical subgroups. (A) We used a modified definition for KDIGO-AKI stage 1, excluding the increase in SCr ≥0.3 mg/dl in the first 48 hours (4). (B) *P* values refer to the significance of interaction terms testing for effect modification by subgroup. Higher EuroSCOREs indicate increased burden of comorbidities, and thus increased risk of perioperative mortality. CKD was defined as an eGFR <60 ml/min per 1.73 m^2 assessed using the CKD-EPI equation. BMI, body mass index; CABG, coronary artery bypass graft; 95% CI, 95% confidence interval; CPB, cardiopulmonary bypass time; DEX, dexamethasone; EuroSCORE, European System for Cardiac Operative Risk Evaluation; KDIGO, Kidney Disease Improving Global Outcomes; LVEF, left ventricular function; MAKE30, Major Adverse Kidney Events at 30 days; Pts, patients; RR, relative risk; SCr, serum creatinine.

patients and those with higher EuroSCOREs did not appear to benefit.

The age-related findings we report are consistent with observations in the original DECS trial, which found age-dependent beneficial effects of dexamethasone (particularly in patients aged <65 years old) on several major adverse events after cardiac surgery (2). These findings may be explained by the suggested higher risk of developing postoperative systemic inflammatory response syndrome in younger patients (6), resulting in greater benefit from glucocorticoids. These findings are also consistent with earlier hypotheses suggesting that chronic low-grade inflammation could result in an age-related decline in the capacity of immune cells to elicit a proper immune response (6). Our finding that a lower EuroSCORE, independent of age, also associated with greater efficacy of dexamethasone in preventing CSA-AKI suggests that an increased burden of comorbidities may diminish the efficacy of glucocorticoids.

Our previously demonstrated interaction according to baseline eGFR, in which greater efficacy of steroids was observed in patients with lower baseline eGFR (3), was not be seen in the current study. The reasons for these discrepant findings are unclear, but they raise interesting questions about the complex interactions between steroids and AKI according to both AKI severity and baseline renal function.

Moreover, our results differ from those observed in the substudy of the SIRS (Steroids in Cardiac Surgery) trial, in which there was no effect of perioperative methylprednisolone administration on the incidence of AKI (7). This could be due to important differences in the selection of trial participants. The SIRS trial only included patients with a EuroSCORE ≥6 in their cohort (8). In contrast, in our cohort, patients tended to have a lower EuroSCORE and thus fewer comorbidities. Consistent with the SIRS substudy findings, we found that the subgroup of patients in our cohort with EuroSCORE >6 had no benefit from glucocorticoid administration with respect to the incidence of MAKE30 (Figure 1B: relative risk, 0.92; 95% CI, 0.72 to 1.19) (7). These findings support the hypothesis that EuroSCORE might be an effect modifier of the association between glucocorticoid administration and MAKE30. Secondly, differences in the pharmacokinetic/pharmacodynamic profiles of dexamethasone and methylprednisolone could have contributed to the discrepant findings, with dexamethasone being more potent and having a longer $t_{1/2}$ than methylprednisolone.

This well powered study generated several novel findings with respect to potential protective effects of glucocorticoids on AKI across clinical subgroups. However, we also acknowledge several limitations. The results should be interpreted cautiously, because the analyses were not prespecified in the original DECS trial. Further, we did not adjust for multiple comparisons given the hypothesis-generating nature of the study and the limited number of subgroups analyzed. Nonetheless, this approach increases the chance of a type 1 error.

The role of perioperative corticosteroids in decreasing the incidence of adverse postoperative outcomes after cardiac surgery has now been assessed by two large randomized controlled trials: DECS and SIRS. These trials both failed to demonstrate significant protective effects of steroids on the primary composite end points that were assessed (2,8). However, overall negative findings in large heterogenous populations do not preclude a beneficial effect in subpopulations. Our current study underscores this by demonstrating several interactions between treatment assignment and various subgroups. Future trials of steroids in cardiac surgery should consider focusing on those most likely to benefit, namely younger patients and those with few comorbidities. Finally, the primary outcomes in both the DECS and SIRS trials were composites strongly determined by thrombotic events and not necessarily inflammation. Thus, beneficial effects of steroids on major adverse events that are mediated by inflammation could have been missed. The DECS-II trial (ClinicalTrials.gov NCT03002259), currently underway, will assess the effect of steroids on more clinically relevant patient-centered outcomes, such as hospital length of stay, and will provide additional data to help inform clinicians on whether to use steroids in this setting.

Author Contributions

J. Dieleman, K. Jacob, and D. Leaf conceptualized the study, reviewed and edited the manuscript, and were responsible for data curation, project administration, formal analysis, supervision, and validation; K. Jacob, D. Leaf, and H. Venugopal were responsible for methodology, resources, software, and writing the original draft; K. Jacob and D. Leaf were responsible for visualization; J. Dieleman was responsible for funding acquisition; and all authors were responsible for investigation.

Disclosures

D. Leaf reports industry-sponsored grant support from BioPorto Diagnostics (Copenhagen, Denmark) and consulting fees from AstraZeneca outside the submitted work. All remaining authors have nothing to disclose.

Funding

J. Dieleman is supported by the Netherlands Organization for Health Research and Development, the Dutch Heart Foundation, the Society of Cardiovascular Anesthesiologists, and the iPEGASUS heart failure genomics study. D. Leaf is supported by National Institute of Diabetes and Digestive and Kidney Diseases grant K23DK106448 and National Heart, Lung, and Blood Institute grant R01HL144566.

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