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# The dose-related effects of Dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study

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## Abstract

**OBJECTIVES**: Acute kidney failure after coronary artery bypass grafting (CABG) is a serious complication that increases morbidity and mortality rates. Early detection and prevention of this complication are very important. A novel biomarker named neutrophil gelatinase-associated lipocalin (NGAL) can play an important role in early diagnosis of acute kidney injury. Recent studies on the favourable effects of Dexmedetomidine on cardiac surgery have been published. The aim of this study is to investigate whether there is a dose-dependent positive effect of Dexmedetomidine on neutrophil gelatinase-associated lipocalin levels and renal functions when used after CABG.

**METHODS**: Our randomized, triple-blinded, placebo-controlled study was conducted among 295 patients scheduled for CABG surgery between August 2009 and March 2011 in a tertiary cardiac and vascular surgery clinic. A total of 90 consecutive patients who met inclusion criteria were randomized and divided into three groups. The first group received a placebo. The second and the third groups received 4 and 8 μg/cc concentration of the Dexmedetomidine infusion, respectively. Infusion rates were regulated to obtain sedation with a Ramsey sedation score of 2 or 3. Patients were regrouped according to the total Dexmedetomidine dose. Statistical analyses of variables including serum neutrophil gelatinase-associated lipocalin values and conventional renal function tests were made for all six possibilities before the blind was broken.

**RESULTS**: Results of conventional renal function tests were not significantly different. However, neutrophil gelatinase-associated lipocalin levels for the first postoperative day for placebo, low-dose and high-dose Dexmedetomidine groups were 176.8 ± 145.9, 97.7 ± 63.4 and 67.3 ± 10.9 ng/ml, respectively. These values were significantly different among the groups ($P$ <0.001).

**CONCLUSIONS**: In our study, we found that Dexmedetomidine infusion for sedation after CABG under cardiopulmonary bypass can be useful in the prevention of kidney injury. Conventional renal function tests, including blood urea nitrogen, serum creatinine, urine output and creatinine clearance rate measurements typically may not detect the development of acute kidney dysfunction in the first 48-h postoperative period. Differences were detected in renal function in the early postoperative period and the development of acute kidney injury, as determined by measurements of blood NGAL levels, was significant and dose-dependent.

**Keywords:** Coronary artery bypass grafting • Dexmedetomidine • Neutrophil gelatinase-associated lipocalin • Kidney injury

## INTRODUCTION

Acute renal failure after open-heart surgery is a rare (1–3%) but serious complication that increases the mortality rate up to 50–60% [1]. Transient kidney dysfunction not requiring dialysis after open-heart surgery occurs at a rate of 7–30% [2–5] and typically includes a decrease in urine output and an increase in blood urea and creatinine levels. Major factors leading to this situation during open-heart surgery include cardiopulmonary bypass. Comorbidity factors such as diabetes mellitus, hypertension, homocysteinuria, generalized atherosclerosis, kidney dysfunction and advanced age are common among candidates for coronary artery bypass grafting (CABG). These risk factors also lead to postoperative kidney dysfunction [6]. Early detection and prevention of acute kidney injury (AKI) are very important. A novel biomarker named neutrophil gelatinase-associated lipocalin (NGAL) can play an important role in early diagnosis of AKI.

The effects of Dexmedetomidine (Dex) (Precedex®, dexmedetomidine hydrochloride injection, 200 μg/2 ml (Hospira, Inc., Lake Forest, IL, USA))—as a selective alpha-2 agonist agent—on kidney functions of both animals and humans have recently been intensively investigated [7–10]. Outstanding studies on the favourable

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effects of Dex on cardiac surgery have been published [11]. The aim of this study is to investigate whether there is a dose-dependent positive effect of Dex on NGAL levels and renal functions when used after CABG.

## PATIENTS AND METHODS

Our randomized, triple-blinded, placebo-controlled, parallel design study was performed after approval of the local Human Investigations and Ethics Committee. The study was conducted among 295 patients presenting with coronary artery disease and scheduled for CABG surgery; the patients were evaluated between August 2009 and March 2011 in a tertiary cardiac and vascular surgery clinic. During this study period, we performed all the major operational procedures and delivered postoperative care with the help of uniform protocols. These perioperative practices were standardized from the beginning to the end of the study. During this process, regular investigational and surgical teams took their roles in our clinic. All patients were included in the study after informed consent was obtained. A total of 205 potential participants were excluded for various reasons such as a concomitant operation and refusal to participate. We also considered preoperative renal impairment and diuretic use as other exclusion criteria. There were no patients with peripheral vascular disease and chronic pulmonary disease. Patients had no history of previous cardiac surgery. Because of our exclusion criteria, there were no patients with emergency operations or different types of surgery except CABG. The study was conducted in accordance with the Helsinki Declaration, the Good Clinical Practice guide and the Consort 2010 Statement. A total of 90 consecutive patients were studied who were operated on under general anaesthesia and cardiopulmonary bypass. The circuit for all patients in this study was primed with 800 ml of Ringer's lactate solution, 100 ml of 18% mannitol and 5000 IU of porcine heparin. Patients were randomized according to a '4-variable block method' and were divided into three groups of 30 people. All of the infusions were prepared according to the randomization list by a single nurse outside the intensive care unit, and the list was kept secret until the end of the statistical analyses. The first group received a placebo, the second group received a 4 μg/cc concentration of the Dex infusion and the third group received a 8 μg/cc concentration of the Dex infusion. Patients received an infusion of Dex at a speed of 0.04 μg/kg/h in the intensive care unit follow-up period. Infusion rates of Dex or the placebo were regulated to obtain sedation with a Ramsey sedation score of 2 or 3. All patients received morphine for analgesia. The infusion dose of Dex (or placebo) increased up to 0.5 μg/kg/h according to the needs of sedation of the patient and was continued for a maximum of 24 h. Additional sedation therapies, including propofol, were not routinely used for all the patients but used for those who were in need of them. If heart rates fell below 60 beats/min or the mean arterial blood pressure fell below 60 mmHg during the Dex infusion, the infusion was interrupted for 30 min and fluid replacement was performed. After the recovery of these parameters at the end of the 30 min, the infusion of Dex was initiated with a dose of 0.05 μg/kg/h. These interruption periods were counted as part of the total infusion time period of 24 h. The preoperative, intraoperative and postoperative values were measured. Patients were regrouped according to the total Dex dose as placebo (Group 1), low-dose (total dose <8 μg/kg) (Group 2) and high-dose Dex (total dose ≥8 μg/kg) (Group 3) groups. Statistical analyses of variables were made for all six possibilities before the blind was broken.

Statistical power of the study according to the primary end-point (NGAL, mean ± standard deviation of NGAL values for placebo and high-dose Dex groups were 67 ± 10.9 and 176 ± 145.9, respectively, and the size of samples was 30 participants for each group) was calculated as 98.3% (for an alpha error level of 5%).

Serum NGAL levels (measured by using Triage® device; Biosite, Inc., San Diego, CA, USA), blood urea nitrogen, serum creatinine, 24-h urine output values, renal dysfunction risk according to the RIFLE classification and creatinine clearance rates were measured as primary end-points to investigate whether there was a significant difference among the groups that depended on the Dex dose. Serum NGAL values of higher than 149 ng/ml were accepted as abnormal.

Respiratory function parameters, intubated follow-up period, postoperative intensive care unit follow-up period, postoperative haemodynamic parameters, hypotension and bradycardia development, the development of postoperative agitation, postoperative furosemide needs and the development of atrial fibrillation were investigated as secondary end-points.

In this study, values are expressed as mean ± standard deviation or percentage values (*n*, %). The comparison of demographic data, preoperative, intraoperative and postoperative parametric variables with normally distributed data among the groups was made by using Student's *t*-test. Otherwise, the Mann–Whitney *U*-test was used. The $\chi^2$ test and Fisher's exact test were used for the analysis of non-parametric variables. One-way analysis of variance was used for normally distributed data, and for the comparison of renal function tests and NGAL values. Otherwise, the Kruskal–Wallis test was used. The *post hoc* comparisons were performed using the Mann–Whitney *U*-tests with Bonferroni correction for sub-groups showing a statistically significant difference.

## RESULTS

The mean age of the patients was 60.5 ± 8.6 years. Twenty-three of the patients (26%) were female and 65 (74%) were male. The mean height of the patients was 167.5 ± 7.4 cm, the mean weight was 77 ± 11.8 kg and the surface area was 1.9 ± 0.2 $m^2$. A total of 74 patients (84%) had hypertension, 39 patients (44%) had diabetes mellitus and 42 patients (48%) had hyperlipidaemia. All the patients with hyperlipidaemia underwent lipid-lowering treatment. A total of 28 patients (31%) were using an angiotensin-converting enzyme inhibitor. The mean preoperative haemoglobin concentration was 13.5 ± 0.7 mg and these values did not differ among groups ($P = 0.79$). Preoperative comorbidity and demographic values were not distinctive among groups ($P > 0.05$). Intraoperative values and parameters of respiratory functions were not different among groups ($P > 0.05$) (Table 1). The total postoperative bleeding and blood transfusion rates did not differ among groups ($P > 0.05$) (Table 1). Postoperative agitation was found in 10 patients (11%): 7 (25%) in Group 1, 2 (7%) in Group 2 and 1 (3%) in Group 3. The difference was statistically significant ($P = 0.038$). The development of postoperative infection was not observed in any patient.

Hypotension developed in 44 patients (50%) and was observed more frequently in the Dex infusion groups than in the placebo group ($P = 0.023$) (Table 1). Hypotension recovered with a quick response after interruption of the Dex/placebo infusion and intravenous fluid replacement. Hypotension did not re-occur after

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**Table 1:** Respiratory functions (arterial blood gas analysis 2 h after the extubation) and perioperative patient data

| Variable | All groups ($n$ = 88) | Group 1[a] ($n$ = 28) | Group 2[b] ($n$ = 31) | Group 3[c] ($n$ = 29) | $P$-value |
|---|---|---|---|---|---|
| $pO_2$[d] (mmHg) | 121.8 ± 39.5 | 117.6 ± 36.8 | 133.8 ± 48.2 | 113.1 ± 28.1 | 0.099 |
| $SaO_2$[e] (%) | 98.1 ± 2.9 | 98.5 ± 2.1 | 98.4 ± 1 | 97.4 ± 4.5 | 0.30 |
| $pCO_2$[f] (mmHg) | 35.7 ± 8.3 | 36.8 ± 13.3 | 36.5 ± 4.7 | 33.9 ± 3.9 | 0.34 |
| $FiO_2$[g] (%) | 42 ± 4 | 42 ± 4 | 41 ± 4 | 42 ± 4 | 0.86 |
| Intubated follow-up (h) | 12 ± 4.8 | 10.6 ± 4.5 | 12.4 ± 4.9 | 12.9 ± 4.8 | 0.18 |
| ICU[h] follow-up (h) | 43.4 ± 6.3 | 44.1 ± 8.6 | 43.4 ± 6.1 | 42.6 ± 3.1 | 0.68 |
| Bleeding[i] (ml) | 1003.5 ± 407.1 | 1051.6 ± 357.1 | 915.5 ± 378.5 | 1051 ± 474.7 | 0.33 |
| Packed red blood cell transfusion[j] | 25 (28) | 8 (29) | 9 (29) | 8 (28) | 0.92 |
| Delirium | 1 (1) | 1 (4) | 0 (0) | 0 (0) | 0.32 |
| Atrial fibrillation | 8 (9) | 5 (18) | 1 (3) | 2 (7) | 0.14 |
| Reoperation | 4 (5) | 1 (4) | 1 (3) | 2 (7) | 0.84 |
| Furosemide (Postoperative1)[k] (mg) | 42.1 ± 27.9 | 42.5 ± 41.7 | 44.5 ± 17.9 | 39 ± 19.5 | 0.74 |
| Furosemide (Postoperative5)[l] (mg) | 10 ± 22.5 | 8.6 ± 19.2 | 11 ± 25.2 | 10.3 ± 23.1 | 0.92 |
| Furosemide inf (Postoperative1)[k] | 3 (3) | 2 (7) | 1 (3) | 0 (0) | 0.41 |
| Bradycardia | 4 (5) | 0 (0) | 2 (6.5) | 2 (6.9) | 0.54 |
| Hypotension | 44 (50) | 8 (29) | 19 (61) | 17 (59) | 0.023 |
| Volume[n] (ml) | 3032 ± 514 | 2984 ± 453 | 3114 ± 548 | 3038 ± 528 | 0.77 |
| Hospitalization (day) | 7.9 ± 1.7 | 7.9 ± 1.9 | 7.5 ± 1.7 | 8.4 ± 1.6 | 0.11 |
| Aortic cross-clamp time (min) | 67.7 ± 28.4 | 60.7 ± 27.7 | 68.3 ± 30.9 | 73.9 ± 25.5 | 0.21 |
| Total perfusion time (min) | 96.9 ± 32.1 | 91.1 ± 32.1 | 98.6 ± 34.7 | 100.7 ± 29.5 | 0.50 |
| Distal bypass | 2.4 ± 1 | 2.2 ± 0.9 | 2.3 ± 1 | 2.8 ± 1 | 0.071 |

[a]Placebo group.
[b]Total dose of Dex <8 μg/kg group.
[c]Total dose of Dex ≥8 μg/kg group.
[d]Partial oxygen pressure.
[e]Oxygen saturation.
[f]Partial carbon dioxide pressure.
[g]Fraction of inspired oxygen.
[h]Intensive care unit.
[i]Total bleeding during intensive care unit follow-up.
[j]The number of patients received at least 1 unit of packed red blood cell transfusion (PRBC).
[k]Postoperative 1st day.
[l]Postoperative 5th day.
[m]Total amount of volume received during the postoperative first 24 h.

restarting Dex/placebo infusion. There was no difference between groups in the mean values of the total amount of volume received ($P$ = 0.77) (Table 1).

The mean serum NGAL levels in the second postoperative hour were similar for all groups ($P$ = 0.98). NGAL levels for the 24th postoperative hour for Groups 1, 2 and 3 were 176.8 ± 145.9, 97.7 ± 63.4 and 67.3 ± 10.9, respectively ($P$ <0.001). Postoperative 5th day values of NGAL were not significantly different among the groups ($P$ = 0.066) (Table 2, Fig. 1). There were no significant differences among the groups in the mean values of conventional renal function tests such as blood urea nitrogen and blood creatinine, the total daily amount of urine output values and creatinine clearance rates ($P$ >0.05). Three patients (3%) were in the acute kidney dysfunction risk group according to Risk, Injury, Failure, Loss, End-stage renal disease classification (RIFLE) criteria. There was no significant difference among the groups according to RIFLE classification (Table 2). There was no renal replacement therapy requirement among the patient groups.

## DISCUSSION

The development of renal dysfunction is an important factor for morbidity and mortality after CABG [1]. According to a recent study, age, BMI, lipid-lowering treatment, hypertension, peripheral vascular disease, chronic pulmonary disease, haemoglobin concentration, serum creatinine concentration, previous cardiac surgery, emergency operation and operation type could affect the risk of AKI [12]. The risk of renal dysfunction according to a previously described risk model was found to be equal across all our study groups (Tables 1 and 2). The early diagnosis and treatment of acute tubular necrosis after CABG play an important role in the preservation of cardiac and kidney functions. NGAL blood values reached peak levels in the first 2 postoperative hours. This high serum level lasts for 48 h. These properties make NGAL more valuable than conventional renal function tests in the early detection of kidney dysfunction. Conventional tests used to determine kidney function typically cannot detect the development of acute kidney dysfunction in the first 48-h period; such a detection is valuable for the early treatment and prevention of AKI [13–17]. One of the major advantage in our study was the use of the NGAL biomarker to measure all forms of renal impairments, including the sub-clinical ones. A recent study in the literature showed an increase in the amount of urine output but no effect on renal function after CABG by the mean values of conventional renal function tests [18]. In this study, a 4-h infusion of Dex was used. Our study is in agreement with the results from the literature that, for the primary end-points of blood urea nitrogen, serum creatinine and creatinine clearance rates on the postoperative 1st and 5th days, there was no significant difference among groups.

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**Table 2:** Renal function tests and serum NGAL values

| Variable | All groups ($n$ = 88) | Group 1[a] ($n$ = 28) | Group 2[b] ($n$ = 31) | Group 3[c] ($n$ = 29) | $P$-value |
|---|---|---|---|---|---|
| Blood urea nitrogen (Pre)[d] (mg/dl) | 39.1 ± 10.9 | 38.9 ± 11.8 | 39.8 ± 9.1 | 38.4 ± 12.1 | 0.88 |
| Blood urea nitrogen (PO1)[e] (mg/dl) | 43.4 ± 15 | 40.9 ± 15.4 | 42.5 ± 12.9 | 46.8 ± 16.5 | 0.31 |
| Blood urea nitrogen (PO5)[f] (mg/dl) | 38.7 ± 14.3 | 40.8 ± 16.2 | 36.9 ± 11.9 | 38.6 ± 15 | 0.59 |
| Blood creatinine (Pre)[d] (mg/dl) | 1 ± 0.2 | 1 ± 0.3 | 1 ± 0.2 | 0.9 ± 0.2 | 0.095 |
| Blood creatinine (PO1)[e] (mg/dl) | 0.9 ± 0.3 | 0.9 ± 0.3 | 0.9 ± 0.2 | 0.9 ± 0.3 | 0.80 |
| Blood creatinine (PO5)[f] (mg/dl) | 0.9 ± 0.2 | 1 ± 0.3 | 0.9 ± 0.2 | 0.9 ± 0.1 | 0.13 |
| Total urine output (Pre)[d] (ml/24 h) | 1879.4 ± 1073.5 | 2054.6 ± 735.4 | 1931.6 ± 1284.3 | 1654.5 ± 1098.1 | 0.36 |
| Total urine output (PO1)[e] (ml/24 h) | 2867.3 ± 769.1 | 3016.4 ± 848.1 | 2760.7 ± 631.9 | 2837.2 ± 825.2 | 0.43 |
| Total urine output (PO5)[f] (ml/24 h) | 2590.5 ± 1287.3 | 2608.9 ± 1002.2 | 2962.9 ± 1546.2 | 2174.5 ± 1133.8 | 0.06 |
| CCR[g] (Pre)[d] (ml $min^{-1}$ 1.73 $m^{-2}$) | 84.5 ± 30.5 | 84.5 ± 24.5 | 86 ± 29.1 | 82.9 ± 37.4 | 0.92 |
| CCR[g] (PO1)[e] (ml $min^{-1}$ 1.73 $m^{-2}$) | 111.7 ± 45.3 | 111.7 ± 43.1 | 114.8 ± 45.3 | 108.3 ± 48.6 | 0.86 |
| CCR[g] (PO5)[f] (ml $min^{-1}$ 1.73 $m^{-2}$) | 87.2 ± 29.8 | 84.7 ± 24.3 | 94.1 ± 29.1 | 82.3 ± 34.6 | 0.27 |
| RIFLE risk[h] | 3 (%3) | 1 (%4) | 1 (%3) | 1 (%3) | 1 |
| NGAL[i] (PO2h)[j] (ng/ml) | 225.7 ± 150.4 | 230.9 ± 154.1 | 222.6 ± 148.7 | 224.1 ± 153.8 | 0.98 |
| NGAL[i] (PO24h)[k] (ng/ml) | 112.9 ± 100.6 | 176.8 ± 145.9 | 97.7 ± 63.4 | 67.3 ± 10.9 | <0.001* |
| NGAL[i] (PO5)[f] (ng/ml) | 91.4 ± 115.1 | 133 ± 196.1 | 73.6 ± 28.9 | 70.1 ± 25.4 | 0.066 |

NGAL: neutrophil gelatinase-associated lipocalin.
[a]Placebo group.
[b]Total dose of Dex <8 μg/kg group.
[c]Total dose of Dex ≥8 μg/kg group.
[d]Preoperative.
[e]Postoperative 1st day.
[f]Postoperative 5th day.
[g]Creatinine clearance rate.
[h]Risk group according to RIFLE classification of renal dysfunction.
[i]Neutrophil gelatinase-associated lipocalin.
[j]Postoperative second hour.
[k]Postoperative 24th hour.
*$P$ <0.001 for all groups. $P$ = 0.004 for Groups 1 and 2. $P$ <0.001 for Groups 1–3.

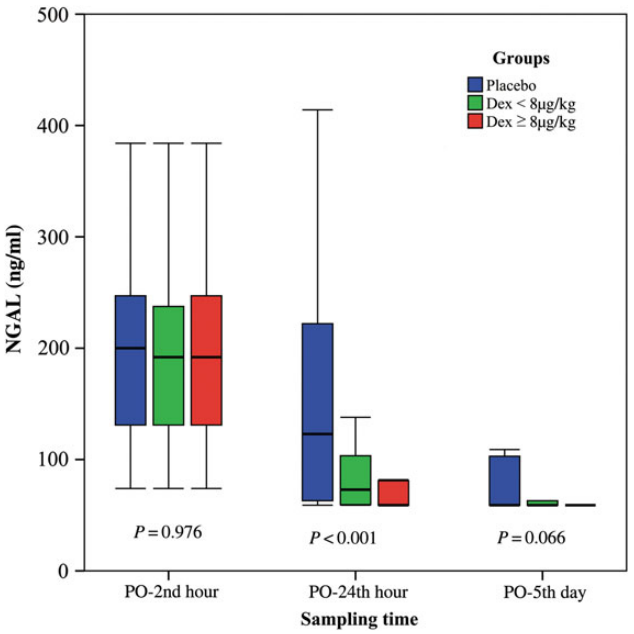



**Figure 1:** Serum neutrophil gelatinase-associated lipocalin (NGAL) values of the groups.

However, in contrast with the literature findings, our study showed no significant difference among the groups in the mean values of the amounts of urine output (postoperative 1st and 5th days; $P$ = 0.43 and $P$ = 0.058, respectively). Among the groups in our study, no significant differences through the use of furosemide that may affect the amount of urine output were found ($P$ >0.05). In contrast to the literature, we used a total 24-h Dex infusion protocol and NGAL measurements because Dex has a short-terminal elimination half-life of about 2 h. In addition, the use of conventional tests such as the blood urea nitrogen, serum creatinine levels, urine output quantity and creatinine clearance rate in the determination of AKI may create delays in the timely detection of kidney dysfunction compared with the diagnostic process of blood NGAL levels, which can lead to false-negative results. As a result, taking into account the difference in the total time of infusion of Dex and the use of a valuable biomarker such as NGAL for the early diagnosis of renal dysfunction are the most important advantages of our study.

Dex is a sedative and selective alpha-2 adrenoceptor agonist agent. The positive effects of alpha-2 agonists on renal function are proposed to be due to the stimulation of alpha-2b receptors on the locus coeruleus in the central nervous system. This effect causes a dose-related reduction in norepinephrine levels and is shown to increase renal blood flow [19]. Other mechanisms, both direct and indirect, set forth by the alpha agonists on kidney function can reduce the surgical stress response. Dex also enhances blood flow to the kidneys, depending on diminished norepinephrine releasing renal sympathetic activity in the presynaptic region, which leads to vasodilatation [20–23]. As a result of these effects in response to surgical stress, hypotension and/or bradycardia may occur. In the light of these studies, our protocol of Dex infusion excludes the initial loading dose that is typically applied in other studies in the literature and the total infusion time was

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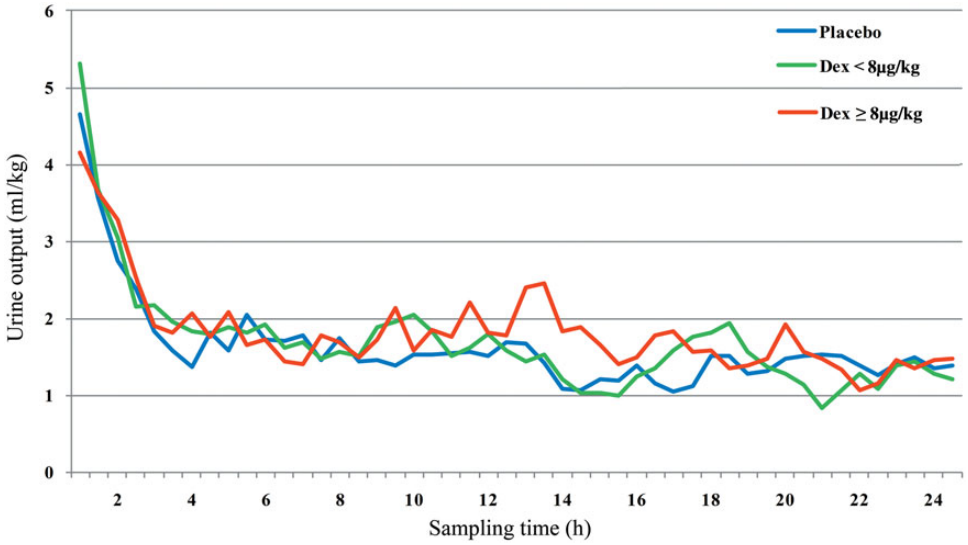



**Figure 2:** Urine output values of the first postoperative day.

extended to 24 h. Our results showed higher occurrence rates of hypotension among patients of Dex infusion groups (Groups 2 and 3) compared with the placebo group (Group 1). This effect can be explained by the mechanism of diminished sympathetic activity during Dex infusion. A temporary halt of infusion of Dex and fluid replacement caused a reprieve in hypotension and/or bradycardia occurrence. Effects of Dex on renal functions have recently been intensively investigated among both animals and humans [7–10]. Outstanding studies of the beneficial effects of Dex after cardiac surgery have recently been published [11, 24]. Existing literature showed that a positive effect of (Dex) on renal functions began at a dose of 110 μg/day and continued until 200 μg/day [11]. This previous study focused on this effect and not on its dose-dependent fashion. We focused on the dose-related effect by doubling the total amount of Dex between groups. We used NGAL measurements to cover all the patients who were affected sub-clinically, in contrast to the previously mentioned study. We adjusted the total amount of Dex to body weight. For these reasons, we accepted 8 μg/kg as the cut-off point to represent double dose (a total of at least 400 μg). By this we also hoped that our results could shed light on our clinical practice. Animal studies showed a positive alpha-2 selective effect at low or mild doses of Dex (10–300 μg/kg). This selective alpha-2 effect turned into a non-selective alpha-1 and alpha-2 agonistic effect at high doses of Dex (1000 μg/kg). In light of the literature, the total amount of infused Dex in our study can be thought of as a low or mild dose. In our study, the positive effects of Dex infusion can be assumed to be connected to selective alpha-2 agonistic effects. Although more complex mechanisms are involved, the effect of cardiopulmonary bypass can be explained by the mechanisms of ischaemia and reperfusion injury. One recent study examined the underlying mechanisms of positive effects of Dex on renoprotection against ischaemia and reperfusion injury [25]. They showed that Dex protects the kidney against ischaemia and reperfusion injury. The underlying mechanism was thought to be Dex's inhibitory effect on injury-induced activation of the JAK/STAT signalling pathway. Their suggestions for the use of Dex also reflect our approach to our study and support our results. Our findings bore the results of the previous study to our daily clinical practice.

One of the leading studies on this subject was made by Ji *et al.* Although this study was conducted among larger patient groups, they consisted of heterogeneous clusters, including CABG, valve replacement etc. Because of this, they needed to make a propensity match for groups. Another handicap of this study was its retrospective nature. In our study, we investigate this in a more homogeneous group. We conducted the study prospectively, in a randomized, placebo-controlled and triple-blinded way. We focused on dose-dependent effects of Dex on AKI as a primary endpoint in contrast to previous studies. Our primary question was 'Is there a positive and dose-dependent effect of Dex on the acute kidney injury process in the early postoperative period after cardiopulmonary bypass?'. We found no relevant difference among the groups in the mean values of the postoperative second hour NGAL measurements. There was a significant difference between the placebo group and the Dex infusion groups ($P$ <0.001) after Dex/placebo infusions were administered. This difference in blood NGAL levels was found to no longer be statistically significant in 5th postoperative day measurements ($P$ = 0.066). The reason for this result can be explained by the short-terminal elimination half-life of Dex ($t_{1/2}$ = 2 h). As a result, the most significant positive impact of Dex on renal functions can be interpreted while the infusion of Dex is administered.

In conclusion, the findings of this study reveal that Dex infusion for sedation after CABG under cardiopulmonary bypass can be useful in preventing the aggravation of AKI. Conventional renal function tests, including blood urea nitrogen, serum creatinine, urine output and creatinine clearance rate measurements typically may not detect the development of acute kidney dysfunction in the first 48-h postoperative period. Differences in renal function were detected in the early postoperative period and the development of AKI, as determined by measurements of blood NGAL levels, was significant and dose-dependent.

## Our institutional experiences and comments

Among all the routinely used sedative agents, Dex has a special place in our clinical experience. In the early follow-up period after CABG, we are faced with the negative effects of extracorporeal

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circulation and the inflammatory surge because of this. As the primary endpoint of our study, AKI has an important role in postoperative morbidity and mortality. Routine clinical use of Dex after CABG could be helpful at this period. We use more doses of Dex. Also, during the early postoperative period before extubation, unwanted high sympathetic activity can be easily diminished by the help of Dex. Furthermore, as a sedative agent, it does not affect the extubation time by providing conscious sedation. It also decreases the incidence of delirium in the intensive care unit follow-up. As a result, Dex has a significant role in our postoperative CABG patient management owing to these valuable properties.

NGAL's role as an early biomarker of AKI has been well validated. The conventional criteria of AKI can underestimate the real acute injury to the kidneys after cardiopulmonary bypass. Because of this, NGAL plays an important clinical role in patients' follow-up.

In our opinion, similar urine output levels for all groups can be used to hypothesize that Dex caused these positive effects without any change in urine output (Fig. 2). This finding displays parallels to recent studies that showed that there was an underlying mechanism such as inhibition of JAK/STAT signalling activation [25].

## Limitations of our study and suggestions for further studies

Dex has a major indication of postoperative sedation. Our clinical practice also reflects this kind of use of Dex. We planned and conducted our study as a phase 4 study. In our study, we hypothesized that AKI occurs not only at a limited time point but during a time period. This period extends beyond cardiopulmonary bypass, including the follow-up period at the intensive care unit. The major aim of our study was to evaluate the positive effects of Dex during early follow-up. However, further studies focusing on the use of Dex pre-emptively, before CPB, can be useful to evaluate the prevention of AKI rather than the aggravation of AKI by the postoperative inflammatory surge.

Although NGAL plays an important clinical role as an early biomarker of AKI, further studies are still needed to only use NGAL levels in determining indications.

Additional randomized, placebo-controlled, parallel design, double/triple-blinded and multicenter studies with larger patient populations are recommended to clarify and further evaluate the current findings from our study.

**Conflict of interest:** none declared.

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