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The effects of dexmedetomidine infusion on renal functions after coronary artery bypass graft surgery: a randomized, double-blind, placebo-controlled study

Deksmedetomidin infüzyonunun koroner arter baypas greft cerrahisi sonrası renal fonksiyonlar üzerine etkileri: Randomize, çift kör, placebo kontrollü bir çalışma

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Background: This study aims to investigate possible effects of dexmedetomidine on renal functions following coronary artery bypass graft (CABG) surgery.

Methods: Between August 2008 and May 2009, consecutive 100 patients who underwent CABG surgery in our clinic were included in this double-blind and placebo-controlled study. Patients were randomized to either dexmedetomidine infusion or placebo. The sedation level of the patients was regulated using Ramsey Sedation Scale. Permuted blocks of four method was used to randomize patients.

Results: A total of 86 patients were included in the analysis including 49 in the dexmedetomidine group and 37 in the placebo group. There was no statistically significant difference in major intraoperative and postoperative variables between the groups. Postoperative day 1 creatinine clearances values above cut-off point of 110 μg/day were significantly different between the groups. These changes were not observed in postoperative fifth day creatinine clearances values.

Conclusion: Low dose dexmedetomidine has no major effect on urine output and renal indices such as urea, creatinine and creatinine clearances. However, it may have a positive effect on renal functions when total dose is uptitrated, particularly.

Key words: Coronary artery bypass graft surgery; dexmedetomidine; renal function.

Amaç: Bu çalışmada deksmedetomidinin koroner arter baypas greft (KABG) cerrahisini takiben renal fonksiyonlar üzerindeki muhtemel etkileri araştırıldı.

Çalışma planı: 2008 Ağustos - 2009 Mayıs tarihleri arasında kliniğimizde KABG cerrahisi uygulanan ardışık 100 hasta bu çift kör ve plasebo kontrollü çalışmaya dahil edildi. Hastalar deksmedetomidin infüzyonu veya plaseboya randomize edildi. Hastaların sedasyon düzeyi, Ramsey Sedasyon Skalası kullanılarak düzenlendi. Dörtlü permütasyon blokları yöntemi kullanılarak, hastalar randomize edildi.

Bulgular: Deksmedetomidin grubunda 49, plasebo grubunda 37 hasta olmak üzere, toplam 86 hasta analize tabi tutuldu. Gruplar arasında majör ameliyat sırası ve sonrası değişkenler açısından istatistiksel olarak anlamlı bir farklılık yoktu. Gruplar arasında ameliyat sonrası 1. gün kreatinin klirensi düzeyleri açısından, 110 μg/gün kesim değeri üzerinde anlamlı farklılık olduğu saptandı. Bu değişikliklerin ameliyat sonrası 5. gün kreatinin klirensi düzeylerinde olmadığı belirlendi.

Sonuç: Düşük doz deksmedetomidinin idrar çıkışı ve kan üre, kreatinin ve kreatinin klirensi gibi renal fonksiyon göstergeleri üzerinde belirgin etkisi yoktur. Ancak toplam dozdaki artışa bağlı olarak, renal fonksiyonlar üzerinde pozitif bir etkisi olabilir.

Anahtar sözcükler: Koroner arter baypas greft cerrahisi; deksmedetomidin; renal fonksiyon.

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Dexmedetomidine (DEX) is a sedative used in intensive care units (ICUs) to provide sedation without causing respiratory depression. Its mechanism of action is an agonist of alpha-2 receptors in certain parts of the brain.[1] Dexmedetomidine has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. It also reduces the volatile anesthetic, sedative, and analgesic requirements of the patient without causing significant respiratory depression.

The effect of DEX on renal functions has recently been intensively researched in both animal and human studies.[2-7] In addition, the positive effects of DEX infusion following cardiac operations have also been reported.[8] One mechanism that is responsible for the beneficial effects of alpha-2 agonist drugs on renal function is the stimulation of alpha-2b receptors at the central nervous system (locus coeruleus). This stimulation decreases norepinephrine levels according to the dosage, which leads to increased renal blood flow.[9] A second mechanism, alpha-2 selective agonist drugs, decreases surgical stress, resulting in increased renal blood flow.[10-12] Furthermore, DEX inhibits the presynaptic release of norepinephrine from the kidney cortex, which causes vasodilatation in the kidney vessels.[13]

In light of this information, the purpose of our study was to determine whether DEX, a selective alpha-2 agonist drug, has a positive effect on renal functions following cardiac surgery.

PATIENTS AND METHODS

After approval by the local ethics committee (Istanbul University, Cerrahpasa Medical Faculty), we undertook a double-blind study featuring 100 consecutive patients who had previously undergone coronary artery bypass graft (CABG) surgery using a heart-lung machine. After 14 potential participants were excluded for various reasons such as additional procedures and missing perioperative values (Table 1), the subjects were ultimately randomized into a DEX infusion group (n=49) (Precedex®, dexmedetomidine hydrochloride injection, 200 μg/2 mL, Hospira, Inc., Lake Forest, IL, USA) and a placebo group (n=37) for a total of 86 patients (mean age 61.2±11.2; range, 34-78 years) Figure 1. There were 14 (28.6%) females in the DEX group and 9 (24.3%) in the placebo group (p=0.660) (Table 2). Informed consent was obtained from each patient, and the same surgeons who originally performed the CABG were selected for this study. Permuted blocks of four method was used to randomize patients.

The demographic characteristics, preoperative risk factors [hypertension, gender, hyperlipidemia, diabetes mellitus (DM), age, height, weight, body mass index (BMI)], preoperative use of angiotensin-converting enzyme (ACE) inhibitors, operative parameters (cross-clamp and perfusion times, number of distal anastomoses), and postoperative parameters [the total amount of postoperative bleeding, new onset atrial fibrillation (AF) in the postoperative period, the oxygen partial pressure (PO_2) value of the second blood gas analysis in the post-extubation period, the oxygen saturation (SO_2) value of the second blood gases analysis of the post-extubation period, the postoperative extubation time, intensive care unit (ICU) and hospital stays, and the total amount of diuretic (furosemide) used in the ICU were all recorded.

The DEX infusions were prepared according to the randomization list by a single nurse outside the ICU, and the list was kept secret until the end of the study. Infusion solutions were administered at a rate of 0.04 μg/kg/hour postoperatively in the ICU. The sedation of the patients was regulated by using Ramsey sedation scores (range, 1 to 6) with a goal of obtaining scores between two and three. According to the amount of sedation needed, the DEX or placebo infusion rate increased so that in a maximum 24-hour period, 0.5 μg/kg/hour infusion was administered. If bradycardia (heart rate <60/min) and/or hypotension (mean arterial blood pressure <60 mmHg) occurred, the DEX infusion was stopped for 30 minutes. After the parameters returned to normal, the infusion was restarted at the lowest infusion rate (0.05 μg/kg/hour). These

Table 1. The number of excluded patients and the reasons for exclusion

	Dexmedetomidine group	Placebo group	*Total*
Mitral valve replacement	–	2	2
Ascending aorta replacement	–	1	1
Missing value	1	5	6
Patient related	–	5	5
Total	1	13	14

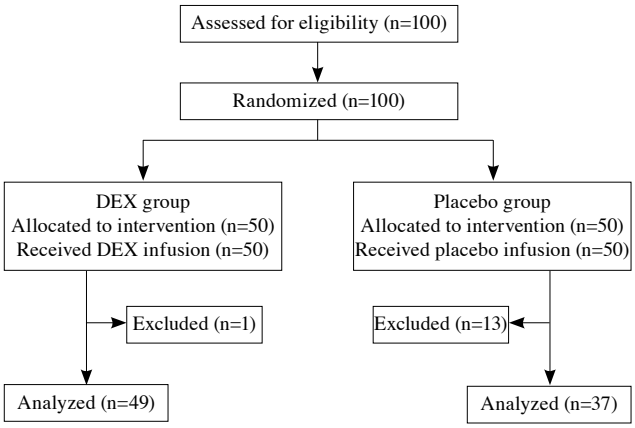

Figure 1. The design of the study.

30-minute intervals were included in the total infusion time (a total of 24 hours). In addition, all patients received intravenous morphine (2-4 mg) every 4-6 hours on an as needed basis.

Blood urea and creatinine values, urine samples, and creatinine clearances (Ccr) were measured preoperatively and postoperatively on the first and fifth days. The blood urea and creatinine values were measured with a Roche/Hitachi Modular D analyzer (Roche Diagnostics GmbH, Mannheim, Germany) and the upper limits were established as 50 mg/dL for the blood urea and 1.2 mg/dL for the creatinine. The urine samples were collected to measure the total urine output, and the classical method was used to obtain the Ccr. After analyses of the main group, the Ccr of different subgroups were compared which contained cumulative dosage amounts ranging from more than 50 mcg/day to 200 mcg/day for each 10 mcg/day incremental dose. The preoperative renal function evaluations and exclusions were made according to the risk, injury, failure, loss, and end-stage renal disease (RIFLE) criteria.[14] The differences in postoperative first and fifth-day daily urine outputs, blood urea values, blood creatinine values, and Ccr rates for both the placebo and DEX infusion groups were then compared.

All perioperative variables were collected by the same resident, and the major postoperative morbidity and operative mortality rates were noted. The variables were expressed as mean ± standard deviation or as a percentage. Comparisons between the groups were performed with the chi-square and t-tests, where appropriate. Statistical significance was considered as a probability *p* value of less than 0.05. The study was also reported in accordance with a checklist published with the Consolidated Standards of Reporting Trials (CONSORT) statement.[15]

RESULTS

There were no statistically significant differences in the preoperative variables, for example age (DEX group: 58.0±12.5 vs. placebo group: 63.0±10.2 years, p=0.072) and body surface area (DEX group: 1.8±0.2 vs. placebo group: 1.8±0.2 m^2, p=0.303), between the groups (Table 3). In addition, the comorbidities [e.g., DM (p=0.245), hypertension (p=0.959), dyslipidemia (p=0.501), and preoperative ACE inhibitor usage] (p=0.268) revealed no significant differences (Table 2). Preoperatively, there was no prerenal azotemia or chronic renal failure, and inotropic agent transfusion and intra-aortic balloon pumps were not needed in either group. The mean cardiopulmonary bypass (CPB) and aortic cross-clamp times for the DEX and placebo groups were 102.3±35.8 (ranged, 64-134) and 74.5±32.1 (ranged, 45-119) minutes, respectively, and the two groups did not show any statistical differences related to the perioperative variables (Tables 2 and 3).

Moreover, no significant differences existed in the groups concerning postoperative infection (p=0.430), atrial fibrillation (AF) (p=0.444), bleeding that required reoperation (p=0.730), the need for bolus furosemide of more than 40 mg (p=0.639), or furosemide infusion (p=0.919) on postoperative first 48-hours. Neither were there significant differences related to mortality (0.382) (Table 2). Infusions were terminated due to hypotension or bradycardia in four patients (10.8%) in the placebo group and in 16 patients (32.7%) in the DEX group (p=0.018) as shown in Table 4.

Renal functions

A comparison of renal functions is provided in Table 4. There were no statistically significant differences between the postoperative first and fifth day urine outputs (p=0.983 and p=0.661, respectively), and there were similar results with the blood urea and creatinine values. As a consequence, the mean preoperative Ccr was 104.8±44.4 ml/min for the DEX group and 93.2±45.6 ml/min for placebo group (p=271). The postoperative first and fifth day mean values were similar as well (p=0.702 and p=0.994, respectively).

The Ccr comparisons for the different subgroups at different cut-off points are summarized in Table 5. The postoperative first day Ccr values, which became significantly different between the groups above the cut-off point of 110 mcg Dex (p<0.05), are shown in Figure 2. However, the same changes were not demonstrated in the Ccr values on the postoperative fifth day (Figure 3). The Ccr values were significantly

Table 2. Chi-square test analysis between the dexmedetomidine infusion and placebo groups

	Dexmedetomidine group		Placebo group		
	n	%	n	%	*p*
Gender					
Female	14	28.6	9	24.3	0.660
Male	35	71.4	28	75.7	
Hypertension					
–	13	26.5	10	27.0	0.959
+	36	73.5	27	73.0	
Hyperlipidemia					
–	40	81.6	28	75.7	0.501
+	9	18.4	9	24.3	
Diabetes mellitus					
–	35	71.4	22	59.5	0.245
+	14	28.6	15	40.5	
Peripheral artery disease					
–	45	91.8	33	89.2	0.536
+	4	8.1	4	10.8	
Left ventricular dysfunction (ejection fraction <40%)					
–	46	93.9	35	94.6	0.432
+	3	6.1	2	5.4	
Preoperative angiotensin converting enzyme inhibitors					
–	31	63.3	19	51.4	0.268
+	18	36.7	18	48.6	
Infusion interruption					
–	33	67.3	33	89.2	0.018*
+	16	32.7	4	10.8	
Infection					
–	47	95.9	34	91.9	0.430
+	2	4.1	3	8.1	
Intraoperative inotropes					
–	46	93.9	34	91.9	0.520
+	3	6.1	3	8.1	
Postoperative inotropes					
–	45	91.8	33	89.2	0.536
+	4	8.1	4	10.8	
Intraoperative balloon pump					
–	48	98.0	37	100	0.382
+	1	2	0	0	
Atrial fibrillation					
–	38	77.6	26	70.3	0.444
+	11	22.4	11	29.7	
Revision					
–	47	95.9	36	97.3	0.730
+	2	4.1	1	2.7	
Furosemide >40 mg					
–	21	42.9	14	37.8	0.639
+	28	57.1	23	62.2	
Need for furosemide infusion					
–	42	85.7	32	86.5	0.919
+	7	14.3	5	13.5	
Mortality					
–	48	98.0	37	100	0.382
+	1	2	0	0	

*: p<0.05.

better in the patients who had total DEX dosage amounts of more than 110 mcg on postoperative day one when compared to those who had a placebo (p=0.04). In addition to the improvement seen with incremental doses, the statistical significance became more apparent at dosage amounts of 120 and 130 mcg/day (p=0.01 and p=0.005, respectively). At 140 mcg, the strength decreases, and at the 200 mcg cut-off point there was no longer any statistical significance.

Table 3. T-test analysis between the dexmedetomidine infusion and placebo groups

	Dexmedetomidine group (n=49)		Placebo group (n=37)		
	Mean±SD	Range	Mean±SD	Range	*p*
Age (years)	58.0±12.5	19-83	63.0±10.2	35-80	0.052
Body mass index (kg/m^2)	27.1±4.8	16.3-37.2	25.7±3.8	17.6-35.2	0.158
Body surface area (m^2)	1.8±0.2	1.5-2.2	1.8±0.2	1.4-2.1	0.303
Low density lipoprotein cholesterol (mg/dl)	128.5±37.3	57-183	128.4±86.7	57-334	0.997
High density lipoprotein cholesterol (mg/dl)	44.8±13.1	32-76	51.7±24.8	33-109	0.459
Triglycerides (mg/dl)	122.9±41.1	56-191	104.0±65.5	52-209	0.465
Total cholesterol (mg/dl)	202.70±42.7	1330-266	203.5±116.5	132-485	0.984
Cross-clamp time	71.5±27.1	16-126	78.2±34.2	15-155	0.313
Total perfusion time	99.4±35.3	33-204	104.0±36.6	35-190	0.565
Distal anastomosis	2.7±0.9	1-4	2.8±0.8	1-4	0.469
Postoperative bleeding	801.4±236.1	250-1200	814.3±206.2	450-1200	0.882
pO_2*	110.8±33.0	49.4-185	114.7±38.9	75.7-177	0.620
SaO_2**	97.8±1.8	64.2-99.7	94.1±15.5	95.7-99.6	0.156
Postoperative extubation time	13.4±13.5	2-89	13.7±13.8	3-124	0.918
Intensive care unit time (hours)	54.2±27.5	20-144	50.8±24.8	10-162	0.555
Hospital stay (days)	8.7±2.8	5-21	9.7±5.0	5-29	0.295
Total furosemide used (mg)	57.6±46.3	0-230	63.8±46.5	0-210	0.539
Preoperative blood urea (mg/dl)	40.5±12.1	18-64	45.5±21.3	13-132	0.201
Preoperative creatinine (mg/dl)	1.0±0.2	0.6-1.7	1.1±0.4	0.6-2.5	0.474
Total blood transfusion (units)	0.1±0.3	0-1	0.1±0.2	0-1	0.426
Erythrocyte transfusion (units)	1.4±0.6	0-2	1.5±0.8	0-3	0.560
Fresh frozen plasma transfusion (units)	0.5±0.5	0-2	0.4±0.5	0-2	0.351
Thrombocyte transfusion (units)*	0.2±0.8	0-4	0.2±0.9	0-4	0.776
Crystalloid transfusion (ml)	1793.2±380.2	1080-2500	1744.6±272.8	1220-2200	0.512
Colloid transfusion (ml)	454.1±341.1	0-1500	459.5±365.7	0-1500	0.944

SD: Standard deviation; PO_2: Partial oxygen pressure value of the second blood gas analysis of the post-extubation period; SO_2: Oxygen saturation value of the second blood gas analysis of the post-extubation period; * Each thrombocyte suspension pack included four units.

DISCUSSION

Acute renal failure, a rarely seen complication (1-3%) is associated with higher early mortality following cardiac surgery (50-60%).[16-20] Permanent renal dysfunction that does not require dialysis is characterized by an increase in blood urea and creatinine levels and a decrease in urine output. The incidence rate of this condition after open heart surgery varies between 7 and 30%.[17-20] Renal dysfunction in operations involving open heart surgery is associated with pre-, intra- and postoperative factors.[21] The use of a heart-lung machine for CPB is the primary factor that causes renal dysfunction, which is an important to know when considering morbidity and mortality. For patients undergoing open heart surgery, other comorbidities like DM, hypertension, homocystinuria, older age, and prevalent atherosclerosis may also cause renal dysfunction.[22] Efforts to enhance renal functions following open heart surgery would improve the overall success of the procedure.

Although it has been advocated that DEX infusion causes more hypotension[7] due to alpha-2 adrenergic stimulation and forces receiving more fluid than others, there was no difference in the fluid intake in our two patient groups. Again, there were significantly higher numbers of patients who required the interruption of the drug infusion in the DEX group. Although the need for increased fluid is an unfavorable effect of DEX, this may be outweighed by the diuretic effects of alpha-2 agonists through the inhibition of the antidiuretic hormone and rennin along with the release of natriuretic peptides.[23] In anesthetized dogs, low doses of DEX have been shown to inhibit vasopressin secretion, which causes aqueous diuresis.[24] This might protect the kidneys during ischemic events.

In contrast to previous studies, we found that DEX infusion had no overall effect on urine output and renal indices such as urea, creatinine and Ccr.[7] The patients were similarly managed during the postoperative period and had similar doses of furosemide. Furthermore, the postoperative renal

Table 4. Comparison of renal functions between the dexmedetomidine and placebo groups

	Dexmedetomidine group (n=49)		Placebo group (n=37)		
	Mean±SD	Range	Mean±SD	Range	*p*
Preoperative daily urine output (ml/24 hours)	1990.2±1140.3	500-5000	1809.5±1153.9	500-5000	0.471
Postoperative day one urine output (ml/24 hours)	2603.2±881.6	1340-4900	2599.1±743.2	1500-5000	0.983
Postoperative day five urine output (ml/24 hours)	2277.4±979.8	500-5000	2403.6±1305.2	750-6250	0.661
Preoperative blood urea (mg/dl)	40.5±12.1	18-64	45.5±21.3	13-132	0.201
Postoperative day one blood urea (mg/dl)	50.3±20.0	14-96	57.0±21.9	19-127	0.171
Postoperative day five blood urea (mg/dl)	44.8±23.1	15-115	54.6±33.3	17-156	0.141
Preoperative creatinine (mg/dl)	1.0±0.2	0.6-1.7	1.1±0.4	0.6-2.5	0.474
Postoperative day one creatinine (mg/dl)	1.1±0.3	0.5-2.0	1.2±0.6	0.5-3.4	0.130
Postoperative day five creatinine (mg/dl)	1.0±0.3	0.5-2.0	1.2±0.5	0.5-3.2	0.142
Preoperative Ccr (ml/minute)	30.5±9.9	12.0-52.1	24.5±11:8	9.1-51.7	0.271
Postoperative day one Ccr (ml/minute)	29.4±19.8	9.0-73.4	24.9±15.9	4.8-62.6	0.702
Postoperative day five Ccr (ml/minute)	28.5±11.7	7.7-47.9	22.6±12.2	8.3-57.8	0.994

SD: Standard deviation; Ccr: Creatine clearance rate.

function indices were similar in each group at postoperative days one and five.

The most clinically important finding in our study was the effect of cumulative doses of DEX on renal function. In total dosage amounts above 110 mcg/day, the Ccr values significantly increased, and these values were better than what was seen in the placebo group at the 110 mcg cut-off (p=0.041). As the cut-off point for the total DEX dosage increased, more significant differences existed up to the 130-140 mcg/day cut-off point. After this, the significance ceased. One of the possible reasons for this loss may be the decreasing number of patients who needed the higher dosage amounts as there were only 16 patients who received more than 160 mcg/day and only 13 who received more than 190 mcg. Therefore, this may have had a negative effect on the statistical analysis.

The beneficial effect of DEX on renal functions is still speculative, and the possible mechanisms of renoprotection may be dose-dependent. Hence, new studies need to be undertaken to verify our results. Myles et al.[25] demonstrated that the renal protective effects of clonidine occur by means of attenuating the sympathetic activation, and a small trial showed that the Ccr was higher in clonidine-treated

Table 5. Comparison of the effects of dexmedetomidine infusion versus a placebo on the creatinine clearance rate for different cut-off points

	CD	n	Postoperative day one Ccr	*p*	Postoperative day five Ccr	*p*
Placebo		37	93.2±45.6		79.1±47.3	
DEX	>50	46	106.7±45.4	0.212	79.9±28.0	0.936
DEX	>60	45	107.9±45.4	0.178	79.9±28.0	0.936
DEX	>70	43	107.3±45.9	0.203	77.9± 27.2	0.914
DEX	>80	37	112.0±46.2	0.101	81.5±27.0	0.826
DEX	>90	31	113.2±49.3	0.106	80.9±29.2	0.868
DEX	>100	25	116.9±48.9	0.068	81.3±30.6	0.847
DEX	>110	22	120.5±46.1	0.041	80.7±32.7	0.900
DEX	>120	21	124.7±43.2	0.018	82.9±32.3	0.776
DEX	>130	19	132.0±39.4	0.005	87.5±31.5	0.543
DEX	>140	18	131.0±40.5	0.007	87.5±31.5	0.543
DEX	>150	17	129.6±41.5	0.012	87.5±31.5	0.543
DEX	>160	16	129.6±41.5	0.012	86.5±32.4	0.606
DEX	>170	15	127.5±42.3	0.020	82.4±29.8	0.818
DEX	>180	14	125.4±43.2	0.034	80.0±29.7	0.953
DEX	>190	13	126.9±44.8	0.033	80.6±31.1	0.925
DEX	>200	9	116.5±48.6	0.207	76.3±34.8	0.879

CD: Total amount of dexmedetomidine infusion during 24 hours period in mcg; n: Number of cases; Ccr: Creatinine clearance rate.

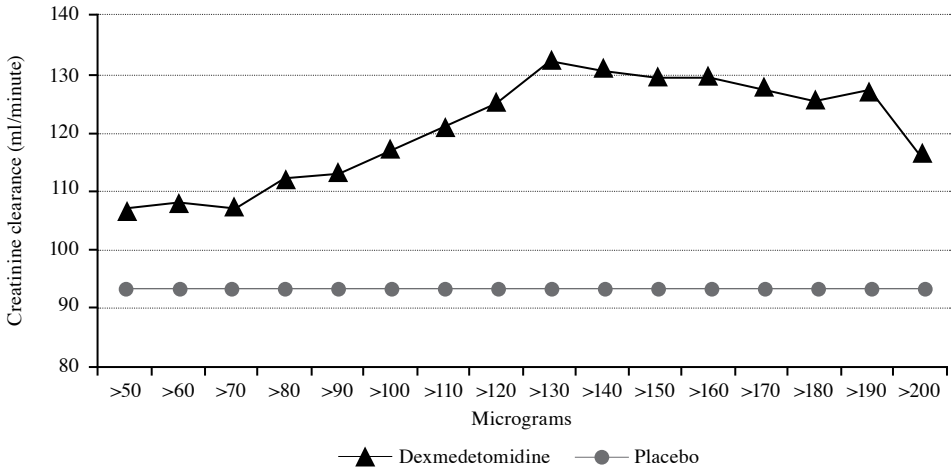

Figure 2. Postoperative first day creatinine clearance rates.

groups.[26] Additionally, an experimental animal model for contrast-induced nephropathy revealed that DEX and clonidine have the ability to attenuate the decrease in renal blood flow and subsequent development of nephropathy in mice.[3] Leino et al.[27] showed that the use of DEX was associated with an increase in postoperative urinary output; however, it did not alter the Ccr rates with a total DEX dosage of more than 250 mcg. This effect also may be dose-dependent. The total infusion time of DEX was limited to four hours postoperatively in the study by Leino et al.,[27] whereas we limited the total infusion time to 24 hours. This might also have affected the changes in renal function.

The primary limitation of our study was the low sample size. However, considering the double blind, randomized, placebo-controlled design of the study, the sample size may not be relevant. It is probable that the low number of patients and involvement of early outcomes in our study led to no observed differences in the mortality rates of the two groups (Table 2). However, even minimal changes in the postoperative CCr have been associated with substantial decreases in survival.[21] Another argument may involve the days chosen for the analysis. Reversible renal failure has been demonstrated to occur within nine days of open heart surgery,[28] and the mean duration of hospital stay was approximately nine days in both of our groups (Table 2). In order to see the early postoperative values and values before discharge, we chose to perform the renal function tests on the postoperative first and fifth days.

In conclusion, our study showed that low-dose DEX has no cumulative effect on urine output and renal indices such as urea, creatinine and Ccr; however,

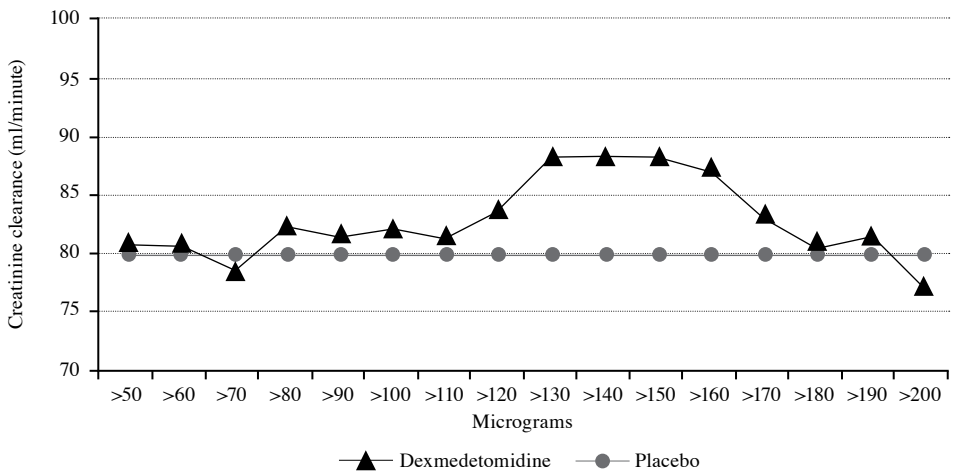

Figure 3. Postoperative fifth day creatinine clearance rates.

it may positively effect renal functions following cardiac surgery with certain dosage amounts. These positive effects only became significant after a total daily dosage of 110 mcg of DEX infusions without a loading dose. Furthermore, the Ccr levels were significantly higher in the DEX group on postoperative day one, and these values were similar to the those in the placebo group on postoperative day five.

For patients undergoing CABG surgery with CPB, renal dysfunction is an important factor that affects morbidity and mortality.[29] Our findings show that DEX infusion may have beneficial effects on renal function in the early stages after open heart surgery, and these occur after a total daily DEX infusion dosage of 110 mcg. The benefits of a cumulative dosage of DEX above 200 mcg are not so clear; therefore, further studies are needed.

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