International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 7(A); July 2018; Page No. 13919-13923
DOI: http://dx.doi.org/10.24327/ijcar.2018.13923.2503

Research Article

ASSESS OF THE EFFECTS OF DEXMEDETOMIDINE ON RENAL FUNCTION IN RENAL TRANSPLANT RECIPIENTS

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A R T I C L E I N F O

Article History:

Received 10th April, 2018
Received in revised form 18th May, 2018 Accepted 26th June, 2018
Published online 28th July, 2018

Key words:

Acute kidney injury; dexmedetomidine; renal transplantation surgery.

A B S T R A C T

Introduction: Renal transplantation is the treatment of choice for renal replacement therapy in patients with end-stage renal disease. Acute kidney injury due to transplantation could cause adverse effects on the outcome of the transplantation, due to the injury to the transplanted kidney. New studies have demonstrated the effectiveness of dexmedetomidine in preventing acute kidney injury in patients undergoing surgery. This study was designed to assess the effects on dexmedetomidine on renal function in renal transplant recipients.

Materials and Methods: Thirty renal transplant candidates were randomly assigned to either of the control or intervention groups, receiving the standard maintenance or dexmedetomidine, respectively. Renal function was assessed at fixed intervals, using Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Results: Twenty patients were assigned to the control group and 10 were assigned to the intervention group. Overall average age was 41.5 years and male to female ratio was 0.88. There were no significant differences among the two groups regarding age, gender, duration of renal replacement therapy or prevalence of diabetes, hypertension or other comorbidities (p value= 0.32).

Discussion: According to our findings, dexmedetomidine did not have any statistically significant effects on renal function. This finding could be the result of small study sample size or insufficiently accurate measurement methods. Therefore, we suggest that further studies be carried out.

INTRODUCTION

Renal transplantation is the treatment of choice as renal replacement therapy, for patients with end-stage renal disease (ESRD). 1 Acute Kidney Injury (AKI) following renal transplantation could have deleterious effects on the outcome of the transplantation, due to the injury to the transplanted organ. 2 Protective measures during the surgical procedure, post-operation and after discharge play an important role in preserving renal function; one such measure is anesthesiologic care, particularly hydration, which prevents both acute rejection and AKI by maintaining adequate blood supply to transplanted kidney. 3

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Acute kidney injury (AKI) is a clinical syndrome that complicates the course and worsens the outcome in a significant number of hospitalized patients. Recent advances in clinical and basic research will help with a more accurate definition of this syndrome and in the elucidation of its pathogenesis. 4

AKI is a syndrome that rarely has a sole and distinct pathophysiology. 5

Recent evidence, in both basic science and clinical research, is beginning to change our view for AKI from a single organ failure syndrome to a syndrome where the kidney plays an active role in the progress of multi-organ dysfunction. 6

Acute Kidney Injury (AKI) is the term that has recently replaced the term ARF. 7

AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology. 6

Many patients with AKI have a mixed aetiology where the presence of sepsis, ischemia and nephrotoxicity often co-exist and complicate recognition and treatment. 8

Classification of AKI includes pre-renal AKI, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases. Of these, only 'intrinsic' AKI represents true kidney disease, while pre-renal and post-renal AKI are the consequence of extra-renal diseases leading to the decreased glomerular filtration rate (GFR). 9-11

If these pre- and/or post-renal conditions persist, they will eventually evolve to renal cellular damage and hence intrinsic renal disease.

Dexmedetomidine is an alpha-2-adrenergic agonist, which is used for induction of sedation in intensive care units, in patients undergoing mechanical ventilation 12; it has also been used as a "maintenance" medication in various surgical procedures. 13

There is evidence that use of dexmedetomidine during peri-operative period and for induction of anesthesia could increase renal blood flow, and decrease AKI, although this could not be achieved without proper hydration. 14-16

This feature of dexmedetomidine has lead to it being used during cardiac valvular surgeries 17, congenital heart diseases surgery 18 and coronary artery bypass graft surgery 19 to reduce AKI.

Dexmedetomidine has the added benefit that its metabolites don't have toxic effects of their own, so this medication does not need renal adjustment in patients with altered renal function. 20

Given the importance of preventing AKI during renal transplantation, and the effects of dexmedetomidine on preserving renal blood flow and decreasing AKI, this study was designed to assess the effects of continuous infusion of dexmedetomidine as a "maintenance" medication on renal function in patients receiving renal transplants from living donors.

MATERIALS AND METHODS

Of initial 50 participants who were recruited consecutively to the study, eventually 30 patients, who met the inclusion and exclusion criterion, completed the course of the study. Patients were randomly assigned to either of the control or intervention groups.

Induction was performed using the same medications and protocols, using 3-5 milligrams per kilograms (mg/Kg) body weight Sodium thiopental and 0.5-0.6 mg/Kg atracurium; lidocaine, fentanyl and midazolam were used as necessary.

The study was triple-blinded, and randomization was performed using open access randomized number generators; the order according to which patients received placebo or dexmedetomidine was kept confidential by a single individual. Patients received a combination of inhaled isoflurane and continuous infusion of either a placebo or 1 microgram per kilograms (μg/Kg) body weight of dexmedetomidine per hour. Hydration and use of diuretics were the same for both arms of the study. Both anesthesiology and surgical procedures were performed by a single team of specialists.

Confounders

Demographic information, underlying medical condition which required renal replacement therapy, duration of dialysis, initial laboratory values, duration of surgical procedure, duration between organ harvest and vascular anastomosis, use of inotropes during or following the surgery, hypotension during surgery (defined as a systolic blood pressure lower than 100 millimeters mercury), onset of diuresis, urinary output after the surgery, necessity of transfusion during surgery, and hypotension after the surgery were documented for all patients.

Endpoints

Glomerular Filtration Rate (GFR) was calculated daily using Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for a week following the surgery. AKI incidence was assessed in all patients following the surgery, and at daily intervals, for a week.

Statistical analysis

All variables were expressed as means and standard deviations, or percentages. Comparisons for parametric variables with normal distribution were performed by Student's t test; for variables without normal distribution, the Mann-Whitney U-test was used. Non-parametric variables were compared using chi-square or Fischer's exact test, as indicated. For all statistical analyses, p values less than 0.05 were considered statistically significant. All analyses were performed with the 24th version of the SPSS software (Ill., the United States).

Ethics

All participants filled out an informed consent form, which was evaluated by the ethics committee of Iran University of Medical Sciences, besides the overall design of the study. The study was registered at the Iranian Registry of Clinical Trials (IRCT).

RESULTS

Overall, 30 patients were recruited to the study, 20 of whom were in the control group with the rest in the intervention group. Mean age was 41.5 years (95% confidence interval (CI) = 30.1-48.7) and there was no significant difference between the two groups. About 46.7% of participants were male; even though only 40% of patients in the intervention group were male, overall, there were no significant differences among gender distribution between the two groups. There was no significant difference among the two groups regarding individuals' body mass index (BMI).

The progression towards end-stage renal disease (ESRD) was compared too, and the mean time to reach ESRD was 12.47 months (95% CI= 8.01-16.92); there were no significant differences between the two groups regarding the period leading to ESRD.

Majorities in both groups were undergoing hemodialysis prior to renal transplantation, and there was no significant difference between the two groups in this respect. The two groups did not

differ significantly, when compared for prevalence of hypertension (HTN) or diabetes mellitus (DM) (***Table 1***).

Table 1 Demographics

Variable		Group	Mean/ percentage	S.E.	p value	95% CI	
						Lower limit	Upper limit
Age		Control	39.4	4.1	0.367	30.11	48.69
		Intervention	45.8	5.06		31.74	59.86
Gender	Male	Control	50%	-	0.71	-	
		Intervention	40%				
	Female	Control	50%				
		Intervention	60%				
BMI		Control					
		Intervention					
Interval till ESRD		Control	10	1.8	0.367	5.93	14.07
		Intervention	17.4	4.64		4.51	30.29
RRT type	PD	Control	10%	-	0.65	-	
		Intervention	0				
	AVF	Control	40%				
		Intervention	60%				
	Catheter	Control	50%				
		Intervention	40%				
HTN		Control	60%		0.23		
		Intervention	100%				
DM		Control	20%		0.76		
		Intervention	20%				

Abbreviations are as the following: S.E. standard error; CI confidence interval; BMI body mass index; RRT renal replacement therapy; PD peritoneal dialysis; AVF arterio-venous fistula; HTN hypertension; DM diabetes mellitus.

When comparing the effect of dexmedetomidine and the standard maintenance regimens on renal function as measured by Cockroft-Gault method, CKDEPI or MDRD, following the operation, there were no significant differences between the two groups (*Table 2 and Figure 1*).

Table 2 GFR as calculated by Cockroft-Gault, CKD-EPI and MDRD methods

	df	F	p value	Effect size
Cockroft-Gault	1	0.026	0.875	
CKD-EPI	1	0.004	0.951	
MDRD	1	0.001	0.971	

Abbreviations are as the following: **GFR** glomerular filtration rate; **MDRD** modification of diet in renal disease; **CKD-EPI** chronic kidney disease epidemiology collaboration; **df** degree of freedom.

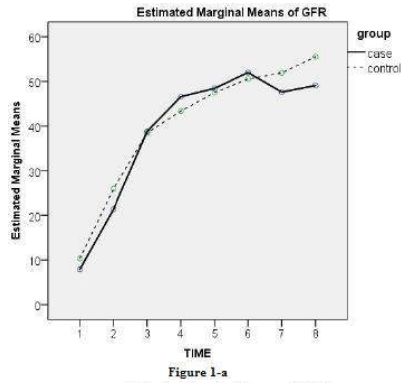

Figure 1-a

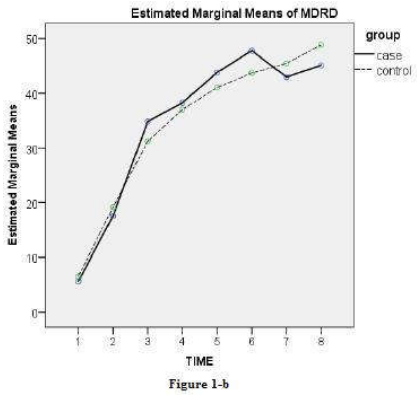

Figure 1-b

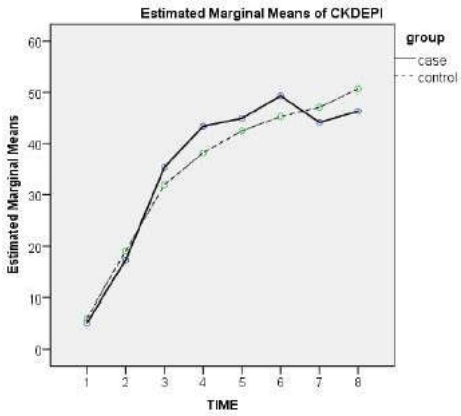

Figure 1-c

Figure 1 GFR among control and intervention groups, plotted against time, a. as calculated by Cockroft-Gault, b. MDRD and c. CKD-EPI equations

DISCUSSION

Comparing the demographics, there were no significant confounding differences between the two groups. We didn't find any differences between dexmedetomidine and the routine maintenance protocol which was used in our center, with respect to their effects on transplanted kidney function, during the operation and immediately afterwards.

There are several studies on the protective renal effects of dexmedetomidine, during and after major organ transplantation surgeries, but since some of these studies don't focus on renal transplant, comparisons should be made carefully.

When comparing our findings to those of another study on coronary artery by-pass graft (CABG) surgery 21, we found that the authors reported only significant effect of dexmedetomidine on urinary output on the fifth day after CABG; the overall effect of dexmedetomidine on renal function after CABG was not significant. A study on protective effects of dexmedetomidine on renal function in

children undergoing congenital heart diseases surgery in 2017 22, there were significant differences among serum creatinine levels prior to operation, after induction, and at 5-minute, 2-hours, 1-day and 2-days intervals after surgery; therefore, the authors concluded that dexmedetomidine could contribute to prevention of acute kidney injury (AKI) after congenital heart diseases surgery in pediatric patients.

According to another study on the effects of dexmedetomidine in open-heart surgery, the authors reported significant decreases in mortality, AKI, sepsis, delirium, hospital stay, re-admission during a 30-days period and the necessity to undergo mechanical ventilation. 23 In a study on patients with lung cancer who underwent surgical resection, dexmedetomidine did not exhibit renal protective effects, as by preventing AKI. 24

When dexmedetomidine was prescribed post-operatively, in pediatric patients who had undergone surgery for congenital heart diseases, the medication exerted significant effect on preventing AKI, but was not associated with the duration of requiring intubation. 4

In another study on renal attributes of dexmedetomidine, it was reported that continuous infusion of the medication at a rate of 0.4 micrograms (μg) per kilograms (Kg) body weight per hour (hr) for up to 48 hours-post surgery, was associated with both much lower rates of AKI, and shorter ICU stay. 25

CONCLUSION

Our findings suggest that dexmedetomidine does not exert renal protective effects, following its administration in patients undergoing kidney transplantation surgery.

Limitations and suggestions

Limited sample size could be a significant limiting factor, and larger randomized trials are strongly recommended. Studies focused on renal transplantation are warranted, as well. Designing studies to study the timing of dexmedetomidine administration could clarify the medication's role in preventing AKI, following any surgery. Also, longer follow-up periods could enhance our understanding of this medication.

***Disclosure**:* The authors declare no conflicts of interest.

Acknowledgment

The authors of this paper are very grateful to all personals and colleges of departments of anesthesiology and pain medicine, Hasheminejad Hospital, Iran university of medical science Tehran IRAN .

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How to cite this article:

M Mesbah MD *et al* (2018) 'Assess of the Effects of Dexmedetomidine on Renal Function in Renal Transplant Recipients', *International Journal of Current Advanced Research,* 07(7), pp. 13919-13923.
DOI: http://dx.doi.org/10.24327/ijcar.2018.13923.2503

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