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Comparative Analysis of the Effects of Vasoperssin and Norepinephrine on the Renal Function in Patients Undergoing CABG; A Randomized Clinical Trial

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Abstract

Background: Coronary artery bypass grafting (CABG) is one the most common heart operations, in which blood vessels from other parts of the body, like the saphenous vein, are grafted to the blocked arteries. Due to the widespread use of vasoactive drugs in the course of surgery, and renal complications of these drugs, we aimed to determine the effect of norepinephrine on the renal function of patients with CABG, visiting the cardiac surgery ward of a university affiliated hospital in Ardabil, Iran, with the purpose of maintaining renal perfusion and preventing renal dysfunction in patients undergoing CABG.
Objectives: This research aimed to determine and compare the effects of vasopressin and norepinephrine on the renal function of patients undergoing CABG.
Methods: This study was a randomized clinical trial. A total of 120 candidates for CABG in a governmental hospital, Iran, during years 2016 - 2017, were randomly assigned into two groups. The patients' conditions across the two groups were compared regarding hemodynamics during surgery and post-surgical complications, e.g., renal function (Bun, Cr, and CLCr), using a researcher made questionnaire.
Results: The results of our study showed that according to repeated measures test, there was no statistically significant difference during the intervention (P value $>$ 0.05). However, the Independent *t*-test revealed a statistically significant difference between groups following CABG, which related to the clearance creatinine level. It indicated higher clearance creatinine level in the norepinephrine group (72.83 $\pm$ 25.03 and 78.16 $\pm$ 27.31) than the vasopressin group (64.33 $\pm$ 17.47 and 86.33 $\pm$ 30.54) (P $<$ 0.05), however, the groups did not vary significantly from each other in other items.
Conclusions: According to the results of the study, it could be stated that probable renal complications during operation can be reduced to some extent in patients undergoing CABG using inotrope and vasopressor drugs such as norepinephrine.

Keywords: Coronary Artery Bypass, Function, Norepinephrine, Renal Failure, Vasopressin

1. Background

One of the most prevalent types of heart operations is the Coronary artery bypass grafting (CABG), in which blood vessels from other areas of the body, like the saphenous vein, are bypassed to the blocked artery, in order for the blocked path to be improved (1). This operation is considered as a basic method for treating cardiovascular diseases. In these patients, hypoperfusion may lead to kidney failure (2), a physiologic condition that reduces blood circulation, without damage to the renal tubules, and is considered as a pre-renal failure. Reduction of arterial perfusion leads to a reduction in the amount of blood filtration through glomeruli. When the perfusion pressure is less than 70 mm, self-regulating protection mechanism breaks down and causes further reduction in the kidney's glomerular filtration, if the reduction of perfusion persists, it can result in an irreversible damage to kidney tubules (1). In fact,

during surgery, in addition to liquid loss and myocardial depression, peripheral vasodilatation, as an effect of anesthetics, can lead to kidney perfusion; therefore, attending to fluid replacement and vasoconstrictors is of high value (3). Vasopressin is a vasoconstrictor drug. This hormone, other than an amino acid, is similar to oxytocin, however, its physiologic effect is completely different. In addition to anti-urogenital therapy, vasopressin is necessary for vascular hemostasis. Vasopressin has several receptors. Among the vascular receptors that are located on the smooth muscles and platelets and cause vascular contraction and prostaglandin secretion (4).

Stefan et al. showed that when vasopressin is administered to patients with low blood pressure resulting from trauma, less fluid is required.

In addition, Managho et al. estimated the mortality rate after revascularization of the coronary artery in patients with normal renal function at 0.9%, and in those with renal dysfunction 63% (4). It is also mentioned in a research that hemophilic patients as well as those with mild Von Willebrand factor (VWF) deficiency benefit from the administration of vasopressin during CABG (5). Acute kidney failure, regardless of its cause, has a mortality rate of 50% (6). Annually, in the United States, 50 billion dollars are spent on performing this surgery (7). Therefore, despite the advances in CABG and anesthesia, renal failure remains a major problem surrounding CABG. Moreover, considering the prevalence of inotropic drug use during CABG, the renal complications of long-term consumption of these drugs, and the necessity of choosing low-risk medicine, if vasopressin is of less renal complications, can be used as an inotropic drug. Therefore, we aimed at investigating the effect of vasopressin on reducing bleeding and maintaining renal perfusion and preventing renal dysfunction in patients undergoing CABG, compared to norepinephrine that is used to improve the overall survival rate among these patients.

2. Methods

2.1. Study Design/Sample

This randomized clinical trial study was performed with patients who were candidates for CABG and had been referred to the surgery department in the Imam Khomeini Hospital (governmental) of Ardabil over two years (2016 - 2017). A total of 120, i.e., 60 cases in each group, with 95% confidence and 80% test strength were included in the present study using Equation 1.

$$n = \frac{2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 P\left(1-P\right)}{\left(P_0 - P_1\right)^2} \quad (1)$$

2.2. Materials and Methods

The study patients were randomly selected from CABG candidates admitted to the Imam Khomeini Hospital Cardiac Surgery ward. They were homogenized in terms of age, sex, and renal function (Bun, Cr, and CLCr), as well as the mean arterial blood pressure. It means that, the selection of both groups was in the form of double-blind and was based on their similarity in their age range, sex, normal laboratory tests results, and the mean arterial pressure under the same CPB-pump. The participants were assigned into two groups of intervention and control by blocked randomization using cards in random blocks. Both groups during surgery underwent cardiopulmonary bypass (CPB). To control the mean arterial blood pressure, norepinephrine was administered to the first group during CPB to maintain their hemodynamics. A norepinephrine ampule (Noradrenaline, aguettant Ltd., Lyon, France) was diluted with 50 mL normal saline and was infused by a syringe-pump. The norepinephrine dose was 0.05 to 0.5 μg / kg / minute, which started when the mean arterial pressure was below 50 mmHg, and tapered and stopped when the pressure was above 50 - 60 mmHg. In addition, for the maintenance of hemodynamics in patients in the second group, 0.02 u/kg/minute vasopressin (Vasostrict®, Par Pharmaceutical Companies, Inc., N.Y, USA) was diluted and infused with normal saline, and was monitored. Then, based on a researcher-made questionnaire, the patients' hemodynamics, including renal function (Bun, Cr, CLCr), was compared across two groups during surgery and after surgery. To determine the validity, the questionnaire was evaluated by a group of professors and experts. A test-retest method was used to determine the reliability of the questionnaire. In addition, Cronbach's alpha coefficient was also used to determine the internal consistency of the questionnaire. Cronbach's alpha coefficient was 0.88.

The study was approved by the Ethics Committee of the Tehran University of Medical Sciences. Furthermore, researchers followed the Helsinki Declaration for medical research including human subjects. An informed written consent form was signed by each participant. The study was registered at the Iranian Registry of Clinical Trials (IRCT), available at http://irct.ir/, with registration number of "IRCT201412054256N4".

2.3. Inclusion Criteria

- Age over 30
- Not responding to medical drugs
- Urgency of undergoing CABG
- Confirmation of angiography result regarding coronary artery involvement

2.4. Exclusion Criteria

- Absence of chronic renal failure
- High levels of creatinine (over 1.5)
- Diabetes
- Hypertension

2.5. Statistical Analysis

Data analysis was done using IBM SPSS Statistics Software of Windows, version 21.0 (IBM Corp., Armonk, N.Y., USA) through descriptive and inferential statistics such as Chi-square, paired *t*-test, Independent *t*-test, and repeated measures. The level of significance was considered at $P < 0.05$. In addition, if participants leave the study, despite the necessary explanations, the Intention to treat approach and the per-protocol support method was applied for data analysis. However, no value was missed.

3. Results

The results of the study indicated that the participants in this study were homogenous considering age, height, weight, gender, place of residence, educational level, blood type (Table 1), systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate (Table 2), and the effect of dependent variables on independent variables were controlled.

In addition, the findings of this study showed that before and after the intervention the level of creatinine clearance in the norepinephrine group and vasopressin group was (72.83 ± 25.03 and 78.16 ± 27.31), and ($64.33 \pm 17.47$and 86.33 ± 30.54), respectively.

According to the results of the repeated measures test, there was no significant difference in the level of sodium, potassium, urea, creatinine, and creatinine clearance in the intervention (effect of norepinephrine before, during and after surgery). However, there was no significant difference between the two groups (norepinephrine and vasopressin) in terms of sodium, potassium, urea, and creatinine levels ($P > 0.05$); however, there was a significant difference in creatinine clearance level ($P = 0.03$) and the norepinephrine group had a higher creatinine clearance level than the vasopressin group (Table 3 and Figure 1).

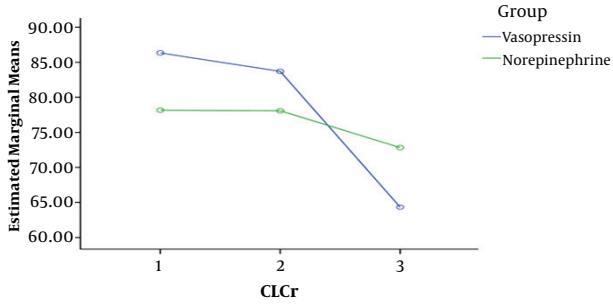

Figure 1. Estimated marginal means of repeated measures

4. Discussion

Although cardiac surgery is a reliable method for improving myocardial perfusion, it has multiple complications during and after surgery. One of the main problems in renal damage is vascular spasm, which is especially seen during CPB; conventional treatments and vasodilators are not successful in removing it. When the vasopressor drugs are used for various reasons, the process of renal injury intensifies (8). If the vasopressor medicine exerts less impact on vasospasm, it would be a more appropriate drug for being pumped. The comparison of two drugs of vasopressin and epinephrine in this study was made based on the assumption that the adverse effects of vasopressin on kidney vessels are lower than norepinephrine. As repeated measures in this study showed, there was no significant difference between the levels of sodium, potassium, urea, creatinine, and creatinine clearance during the intervention (the effect of norepinephrine before, during and after surgery). Mahoori et al. (9), suggested in their study that one of the most severe side-effects associated with heart surgery is kidney failure, and the best process for maintaining renal function is hydration during operation (10). Thus, due to the sufficient hydration in the intervention process, renal function had no significant depression.

Furthermore, there was no significant difference between the two groups (norepinephrine and vasopressin) in terms of sodium, potassium, urea, and creatinine levels ($P > 0.05$); however, there was a significant difference in creatinine clearance level ($P = 0.03$), and the norepinephrine group had higher levels of creatinine clearance than the vasopressin group. This means that patients with CABG who received norepinephrine had a better renal function than the vasopressin group. The concentration of serum creatinine is broadly subordinate to age, sex, muscle mass, muscle metabolism, and drug administration (11). Its increased concentration and sensitivity appear only when the disease progresses (12) and the decrease in glomerular filtration rate exacerbates creatinine tubule secretion. In addition, during acute glomerular filtration changes, serum creatinine does not correctly predict renal function until it reaches a balance basal usually two to three days after the onset of injury (13, 14). Lin and colleagues also mentioned serum creatinine level and urine volume, 24 hours prior to surgery, as valuable information for the prediction of acute renal failure in patients with CABG. However, the results

Table 1. The Demographic Characteristics of Patients in Two Groups (Mean ± SD)

Characteristics	Norepinephrine	Vasopressin	P Value[a]
Age (y)	62.80 ± 10.15	65.11 ± 9.80	0.20
Height (cm)	165.43 ± 9.81	164.43 ± 8.65	0.55
Weight (kg)	70.65 ± 10.14	70.88 ± 9.19	0.89
Ejection fraction (EF), (%)	47.41 ± 6.79	46.91 ± 7.97	0.71
Sex (n)			
Male	45	43	0.17
Female	15	17	0.68
Angiography (number of involved vessels)			0.25
1	2	1	
2	3	8	
3	55	51	

[a] P < 0.05 was considered significant.

Table 2. Hemodynamic Status of Patients in Two Groups (Mean ± SD)

	Norepinephrine	Vasopressin	Independent t[a]
Systolic blood pressure (mmHg)			
Before surgery	125.65 ± 19.17	128.43 ± 17.12	0.40
After surgery	113.17 ± 10.97	111.98 ± 12.18	0.57
Diastolic blood pressure (mmHg)			
Before surgery	78.16 ± 11/67	77.98 ± 9.5	0.92
After surgery	65.86 ± 10.96	67.06 ± 11.63	0.65
Mean arterial blood pressure (under pump) (mmHg)			
During surgery	66.68 ± 3.42	67.60 ± 3.86	0.17
Heart rate (per minute)			
Before surgery	75.88 ± 6.00	76.90 ± 5.14	0.32
During surgery	79.51 ± 6.97	79.86 ± 6.38	0.77
After surgery	85.00 ± 10.25	83.21 ± 12.24	0.38

[a] P < 0.05 was considered significant.

Table 3. Creatinine Clearance Level of Patients in Two Groups (Mean ± SD)

Clearance Creatinine Evaluation	Norepinephrin	Vasopressine	Independent *t*- Test	Intervention Effect Repeated Measures
Before surgery	78.16 ± 27.31	86.33 ± 30.54	t = 1.54; df = 118; P = 0.12	df = 1; P = 0.64; F = 1.60
During surgery	78.08 ± 25.38	83.70 ± 25.50	t = 1.20; df = 118; P = 0.22	
After surgery	72.83 ± 25.03	64.33 ± 17.47	t = -2.15; df = 118; P = 0.033	

of creatinine clearance were more accurate than other indicators of renal function and showed the renal function faster than creatinine. The obtained results in this study conforms to the finding of study of Lin et al. (15), as well.

Pilarczyk and his colleagues suggested sensitive and specific biomarkers, such as TIMP and IGFBP, as appropriate means for early diagnosis of acute renal damage after CABG compared to serum creatinine (16). Canty and Kim also stated that during heart surgery, low dose routine norepinephrine infusion is due to the reduction of hemodilogue and blood transfusion without serum creatinine increase (17). Morimatsu et al. (18), also reported in their study that norepinephrine does not increase the serum creatinine concentration after cardiac surgery in patients

with hypotension. Moreover, the study of Hagen Ewa and colleagues, in 2016, indicated that the administration of norepinephrine is helpful for maintaining the mean blood pressure about 80 mmHg during CABG. However, maintaining the mean arterial blood pressure was done without reducing O_2 saturation (19). The results of their study were consistent with ours in that the mean arterial blood pressure was maintained about 70 to 80 mm Hg during CABG.

The study conducted by Yimin Ho and colleagues, in China in 2013, showed that vasopressin is better than norepinephrine in maintaining a stable hemodynamic status. Their study was performed on 10 patients treated with vasopressin and 10 patients treated with epinephrine (20). The present study was conducted with 60 patients in each group (vasopressin and norepinephrine) to reduce the error arising from low sample size. In addition, it was shown that there was no significant difference in hemodynamic parameters between the two groups.

Similarly, Krejci et al. (21), concluded that vasopressin causes a significant reduction in blood flow to the kidneys. They have also noted that the increase in urinary output is not due to the proper function of the kidneys. The results of this study are consistent with the present study that indicates that vasopressin did not have a beneficial effect on the maintenance of renal function. In the study conducted by Jayanta Kay et al., titled as "Vasopressin: Its role in anesthesia", which was done over 10 years of ongoing research, vasopressin has been recommended as the best vasopressor. They suggest that clinical and experimental studies support the effect of low dose vasopressin infusion in vasodilator shock. They have also claimed that although this medication increases arterial blood pressure and possibly increases urinary output, there is not enough support for using vasopressin and its usefulness in septic shock and other cases (22). In this study, they also attributed the mean arterial blood pressure rise to the effect of vasopressin, however, no difference was reported between the efficacy of vasopressor and norepinephrine. In the same vein, the the present study didn't find sufficient evidence to support the efficacy of vasopressin. Miller's study, in 2015, also showed that use of vasopressin with or without epinephrine had no benefit for the survival of those under treatment (23), which is in line with the results of the present study, suggesting that the use of vasopressin didn't have any superiority over norepinephrine regarding maintaining renal function. Besides, due to the high cost of vasopressin, it is not recommended to be used.

It should be noted that there were some factors that confined our study such as time limit, number of people, number of CABG surgeries, and considering the fact that Imam Khomeini Hospital (RA) was the only heart surgery center in the province. Therefore, it is suggested that this study be replicated in other cities as well as in more equipped centers.

4.1. Conclusion

In the present study, only the level of creatinine clearancehad a significant difference (P = 0.03) after surgery, and norepinephrine group had higher levels of creatinine clearance than the vasopressin group. This means that the candidates for CABG, who were receiving norepinephrine, had a better renal function than the patients receiving vasopressin. However, in regards to sodium, potassium, urea, and creatinine levels no statistically significant difference was detected between the groups (P > 0.5). In addition, there is not noticeable superiority of vasocontriction effect of one drug over the other one (vasopressin and norepinephrine) in patients who were candidates for CABG.

Furthermore, since the cost of vasopressin is higher than norepinephrine, it is better nor-epinephrine to be used in this group of patients.

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Footnotes

Authors' Contribution: Study concept and design: Jafar Vakili and Nasrin Samadi; acquisition of data: Jafar Vakili and Mohammad Hasanpor Dargah; analysis and interpretation of data: Khatereh Isazadefar, Mohammad Hasanpor Dargah, Susan Mohammadi Kabar and Ali Reza Mohammad Zade; drafting of the manuscript: Nasrin Samadi and Jafar Vakili; critical revision of the manuscript for important intellectual content: Jafar Vakili and Mohammad Hasanpor Dargah; statistical analysis: Khatereh Isazadefar and Nasrin Samadi and Jafar Vakili; administrative, technical, and material support: Susan Mohammadi Kabar and Mohammad Hasanpor Dargah; study supervision: Mohammad Hasanpor Dargah, Mohammad Rahim Vakili and Ali Reza Mohammad Zade.

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