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Original Article

Antihypertensive drugs on arteriovenous fistula maturation in patients with hemodialysis

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Abstract

Background: The maturation of the arteriovenous fistula (AVF) is necessary for successful hemodialysis treatment. However, the role of antihypertensive drugs in influencing AVF maturation remains uncertain. This study investigated the AVF maturation in patients with renal failure treated with antihypertensive medications.

Methods: A prospective cohort study was conducted on 73 patients who needed to be treated with hemodialysis through AVF. Demographic information, medication, underlying diseases, blood pressure changes, surgical information, and the time of AVF maturation were collected during the study. Descriptive statistics and survival analysis were employed to assess the outcomes.

Results: The mean age of patients was 53.96±13.65 years, with 38 (52.1%) males and 35 (47.9%) females. The mean AVF maturation time was 104.87±1.02 days, and the rate of AVF maturation was 87.7%. Among the comorbidities, the rate of AVF maturation in diabetic patients (78.4%) versus non-diabetic (97.2%) exhibited a notably diminished effect (P = 0.028). There was a significant association between mean intraoperative arterial blood pressure (123.45±2.89 mmHg) and AVF maturation time (P = 0.033). Furthermore, there were not any significant differences in the use of antihypertensive medications on AVF maturation time or rates.

Conclusion: Our study findings suggest that the administration of antihypertensive medications did not demonstrate a significant correlation with either the AVF maturation outcome or the time required for maturation.

Keywords: Arteriovenous fistula, Antihypertensive agents, Renal dialysis, Vascular patency, Blood pressure.

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Hypertension is highly prevalent among newly initiated dialysis patients, affecting more than 80 percent of this population, primarily due to the prevailing issue of volume overload (1). Furthermore, factors such as sympathetic overactivity, activation of the renin-angiotensin system, and the presence of arteriosclerosis collectively contribute to the hypertension observed in patients with hemodialysis (2-4). In a multicenter trial, it was reported that a substantial majority, 88 percent, of patients with hemodialysis were prescribed antihypertensive medications (5). The administration of antihypertensive agents has demonstrated noteworthy clinical advantages, including enhanced survival rates. However, it is essential to acknowledge that this therapeutic approach may also bear adverse consequences, particularly in relation to the maturation of the arteriovenous fistula (AVF) for efficient hemodialysis, as it can induce a reduction in blood pressure levels (6). The hemodynamic changes initiate vascular remodeling responses in both vessels (7-10).

Indeed, high blood flow and pressure are needed to provide a force on the AVF wall for remodeling and subsequent maturation. According to studies, up to 60% of AVFs may fail to mature, and only half of the matured AVFs maintain their efficiency in the first year (11-13). Some factors may affect AVF maturation, includeing demographic factors, clinical features like diabetes, and also medications (14). Several studies have investigated the effects of antihypertensive medications on AVF patency. Chen FA *et al.* in (2016) considered the effect of antihypertensive medications such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) on the long-term patency of AVFs. The results showed that using these medications is associated with a longer patency of AVF and prevents failure (15). However, few studies have evaluated the relationship between these medications and fistula maturation (13). The result of Wang K *et al.* study showed that the use of CCBs is associated with increased maturation rates and with a 25% lower risk of overall AVF maturation failure of newly created AVFs. Also, no significant relationship was found between using other antihypertensive medications and AVF maturation (13). However, it is important to note that these studies did not definitively establish a causal relationship between the use of these antihypertensive medications and improved AVF maturation (15). Considering the unspecified effect of these medications on AVF maturation and the importance of using AVF as the preferred method in hemodialysis, we aimed to study the effect of antihypertensive medication on maturation outcome.

Methods

Study design and participants

Study design: This study employed a prospective, observational cohort design to investigate the impact of antihypertensive drugs on AVF maturation in patients with hemodialysis. The study conducted at Ayatollah Rouhani Hospital of Babol University of Medical Sciences between 2020 and 2021.

Study participants: One hundred forty patients with hemodialysis between the ages of 30 and 80 who had undergone AVF formation as a component of their renal replacement therapy were enlisted. The inclusion criteria included individuals with an End Stage Renal Disease (ESRD) diagnosis who began hemodialysis treatment with a freshly developed AVF and continued treatment with at least one prescription antihypertensive medication in accordance with the nephrologist's advice. It also noted that the identical upper extremity where the AVF was intended to create had never previously used hemodialysis catheters. The study excluded patients who had previously undergone an AVF, arteriovenous grafts in a specific upper extremity, or a kidney transplant. Patients who have undergone recent ipsilateral hemodialysis catheter placement or who started a new antihypertensive, antiplatelet, or anticoagulant regimen after surgery excluded from the trial. Patients who declined to take part in the trial were also excluded. Finally, 73 patients enrolled in this study. Patients who underwent AVF implantation, were monitored for changes in blood pressure and AVF maturation for six months. Clinical assessment and successful hemodialysis through the AVF used to establish its maturation.

Data collection

Baseline data: When the AVF created, demographic data, include age, gender, race, and comorbidities like hypertension, diabetes mellitus, and cardiovascular illnesses gathered. Additionally, baseline blood pressure and preoperative test values, such as serum creatinine and hemoglobin noted.

Antihypertensive medication assessment: Each participant's specific antihypertensive drug regimen was thoroughly documented. It comprised the brand name, dosage, frequency, and usage length of the medicine. Different kinds of antihypertensive medications, including ACEIs, ARBs, CCBs, beta-blockers, and diuretics, were established.

Outcome assessment

Primary outcome: The assessment of AVF maturity, which is defining as the achievement of sufficient flow for hemodialysis, was the main result of this study. The AVF maturity was assessed by the vascular surgeon in serial examinations after surgery. According to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline and North American Vascular Access Consortium, an AVF considered mature for hemodialysis when venous cannulation is associated with minimal complications related to puncture and is also able to provide the required blood flow during dialysis, which effective hemodialysis could perform through it for at least two sessions in one month (6, 16).

Secondary outcomes: The blood pressure changes valued as a secondary result. These results evaluated during routine follow-up appointments.

Statistical analysis: The baseline characteristics summarized by using descriptive statistics. The log-rank test used to evaluate the variations in survival outcomes during the Kaplan-Meier method-based survival study. We also ran a t-test to further analyze the results' significance.

These statistical analyses carried out to assess any significant differences between the groups, as well as the effect of the variables on AVF maturation rates. Statistical significance was established at a p-value ≤ 0.05.

Ethical considerations: The Institutional Review Board (IRB) of Babol University of Medical Sciences granted approval for this study with the code of IR.MUBABOL.REC.1399.459, and it carried out in compliance with the Declaration of Helsinki's principles. All participants gave their consent after being fully informed.

Data availability: The study's data will be safely maintained and provided to competent researchers upon reasonable request.

Results

Participant characteristics: The study included 73 end-stage renal disease patients with hemodialysis in total. Participants' ages ranged from 30 to 80 years old, with a mean age of 53.96+13.65 years. Table 1 provides a summary of the participant's demographics, including gender, comorbidities, and first laboratory results.

Antihypertensive medication: The study's participants received ongoing treatment with various antihypertensive medication classes. Table 2 provides more information on the distribution of antihypertensive drug classes.

Primary outcome: arteriovenous fistula (AVF) maturation: Six months following the creation of the AVF, 64 (87.7%) of the subjects had appropriate AVF maturation, enabling effective hemodialysis. Figure 1 displays the general AVF maturation rates for all subjects.

Impact of antihypertensive drug classes on AVF maturation: Participants were grouped according to the class of antihypertensive medicines they were taking in order to evaluate the impact of various antihypertensive drug classes on AVF maturation. The results show that the use of different antihypertensive medication classes has no appreciable impact on the maturation of arteriovenous fistulas (table 3).

Table 1. Participant demographics and baseline characteristics

Baseline Characteristics		Number (%)
Male		38 (52.1%)
Female		35 (47.9%)
Hypertension		67 (91.8%)
Diabetes		37 (50.7%)
Hyperlipidemia		33 (45.2%)
Coronary Artery Disease		0
Congestive Heart Failure		2 (2.7%)
Coronary Artery Bypass Graft		2 (2.7%)
Peripheral Artery Disease		0
Cerebrovascular Accident		2 (2.7%)
Hepatic Failure		0
Hypothyroidism		9 (12.3%)
Hyperthyroidism		2 (2.7%)
Smocking		4 (5.5%)
AVF site	Proximal	39 (53.4%)
	Distal	34 (46.6%)
Type of AVF Anastomosis	Side to Side	37 (50.7%)
	End to Side	36 (49.3%)
Baseline laboratory parameters		**Mean+Standard Deviation**
Hemoglobin (g/dl)		10.1±1.59
GFR (ml/min)		10.92±8.1

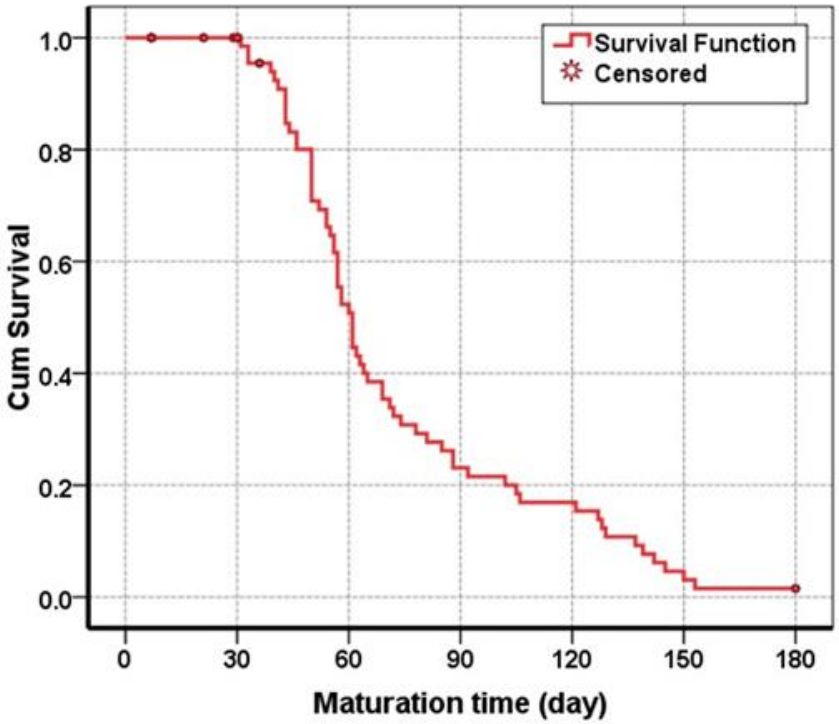

Figure 1. AVF maturation rates among all participants during six months follow up

Secondary Outcomes: Participants' variations in mean arterial blood pressure were also tracked by the study. The outcomes are shown in table 4. Furthermore, neither the type of anastomosis [side to side (91.9%) vs. end to side (83.3%)] nor the fistula's location [proximal (89.7%) vs. distal (79.2%)] showed statistically significant differences in the maturation rate of arteriovenous fistulas in these individuals (P=0.703). According to associated comorbidities, there was also not a significant variation in the maturation rate of arteriovenous fistulas.

Table 2. Distribution of antihypertensive medication classes

Antihypertensive Medication Classes	Number (%)
Diuretic	28 (38.4%)
Beta Blocker	16 (21.9%)
Vasodilator	9 (12.3%)
Calcium Channel Blocker (CCB)	37 (50.7%)
Angiotensin Converting Enzyme Inhibitor (ACE-I)	5 (6.8%)
Angiotensin Receptor Blocker (ARB)	39 (53.4%)
Renin Inhibitors	0
Aldosterone Receptor Antagonists	1 (1.4%)
Alpha-1 Adrenergic Receptor Antagonists	8 (11%)
Alpha-2 Adrenergic Receptor Antagonists	0

Table 3. Impact of antihypertensive drug classes on AVF maturation

Antihypertensive Medication Classes	Maturation Rate (%)	P- value
Diuretic	85.7%	0.819
Beta Blocker	93.8%	0.409
Vasodilator	88.9%	0.928
Calcium Channel Blocker (CCB)	89.2%	0.856
Angiotensin Converting Enzyme Inhibitor (ACE-I)	80.0%	0.533
Angiotensin Receptor Blocker (ARB)	89.7%	0.920
Aldosterone Receptor Antagonists	100.0%	0.312
Alpha-1 Adrenergic Receptor Antagonists	75.0%	0.411

Table 4. Changes in mean arterial blood pressure during the follow-up period

Time	Mean±SD mmHg	P-value *
Pre-Operative	99.15±1.86	A, D, E
During Operation	123.45±2.89	B
Post-Operative	106.41±1.77	C
After First Week	100.17±2.11	D
At Maturation Time	97.99±1.83	E

* The presence of similar letters means no significant difference between the two groups. ($p<0.001$).

Discussion

The goal of the current study was to determine how antihypertensive medication affected the maturation results of AVF, which showed an average maturation time of 104.87±1.02 days and a maturation rate of 87.7%. It is comparable to the Kyi Z Thant et al.'s study, which found that 375 AVFs matured at a rate of 16.1±10.7 weeks on average (17). No correlation between antihypertensive drug classes and maturation outcomes was discovered in the current investigation. This finding is significant from a therapeutic perspective since maturation of the fistulas does not require stopping or reducing the dosage of antihypertensive drugs. Of course, this conclusion differs from that of another research. When compared to other antihypertensive medication groups, investigations have shown that CCBs linked to superior maturation results and a 25% decrease in postoperative failure (11, 18). Bashar K et al. (2015) discovered a functional maturation rate of 53.7% for AVF and the patients who used calcium channel blockers showed better maturation rates (11). The strong correlation between CCBs and successful functional maturation outcomes and AVF patency can be explained by the drug's impact on the emergence of stable nitric oxide metabolites and venous dilatation (13). AVF maturation failure, on the other hand, has been linked to neointimal hyperplasia, so CCBs may improve fistula maturation outcomes by inhibiting calcium import via L-type calcium channels and preventing neointimal endothelial hyperplasia, which is a critical process for the growth and migration of vascular smooth muscle cells (13, 15).

Furthermore, a number of studies have discovered a correlation between the usage of ACE-I and ARBs and a rise in fistula patency. By stimulating the manufacture of growth factors, angiotensin II promotes the proliferation of vascular growth muscle cells. Thus, by blocking this mechanism and avoiding neointimal hyperplasia, the combination of ACE-I and ARBs enhances fistula maturation and patency (13, 15, 18). However, there was no correlation between the use of beta-blockers and diuretics on fistula maturation and patency (13). Therefore, it is advised that this class of antihypertensive drugs with cardiovascular protective effects be used during fistula

insertion and maturation because cardiovascular disease is ten times more common in dialysis patients than in the general population and is the leading cause of death in these patientS (19). Another intriguing finding from our study is how closely maturation time correlates with intraoperative Mean Blood Pressure (MBP). The maturation period was shortened as a result of the enhanced MBP during the treatment. The intra-operative MBP in our investigation was 121.79 mmHg, which is consistent with a 2013 study by J Wayne et al. that found intra-operative blood flow predicts primary and secondary fistula patency in 73 patients. Therefore, the relationship between a higher blood flow rate and a higher fistula patency rate is thus established. A slower rate of fistula development is associated with a lower MBP on the day of operation. Furthermore, there is a higher risk of fistula failure two weeks after surgery when intraoperative systolic blood pressure is less than 110 mmHg (20).

Cheng et al. (2016) discovered that decreased preoperative MBP was linked to early fistula failure seven days after surgery (21). On the other hand, high blood pressure, particularly uncontrolled hypertension, can change the arteries due to a complex interplay of many variables. Vasoconstriction is brought on by the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and inflammatory mediators. After inflammation, the arterial wall rebuilt, which caused atherosclerotic lesions, endothelial dysfunction, thrombosis, and stenosis (20, 22). A pathological rise in blood pressure causes turbulence and whirlwind flow in the vessels, which increases stress on the vessel wall and leads to cell proliferation and neointimal hyperplasia. The vascular wall's aberrant arterialization inhibits the fistula's capacity to develop. It may also have an impact on the fistula's durability after maturation (20, 22, 23).

Therefore, a suitable blood pressure range is needed for healthy maturation and afterwards to enhance the fistula's patency. Additionally, our data demonstrate that patients with diabetes had a decreased AVF maturation rate. It well established that diabetes mellitus and a number of vascular issues, including microangiopathy and macroangiopathy, which can adversely affect vascular health and function, are related. The proper maturation of AVFs may impaired by these pathological changes, which include diminished angiogenesis, increased atherosclerosis, and endothelial dysfunction (24, 25). There is no evidence of a significant relationship between antihypertensive medication use and either the outcome or the time necessary for AVF development, according to our findings. Diabetics, in particular, showed a decreased rate of AVF maturation. Furthermore, patients who had high blood pressure during surgery had a faster maturation of AVF. These findings contribute to a better understanding of how antihypertensive medications affect AVF maturation and highlight the importance of not changing these drug regimens during fistula implantation. More research is required to fully comprehend the complex interaction of these variables and their clinical implications.

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