

# **Title: The effect of hemoglobin level on arteriovenous fistula survival in hemodialysis patients in Tehran**

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**Objective:** End Stage Renal Disease (ESRD) poses steadily growing challenges on the health care systems worldwide. Renal replacement therapy with hemodialysis (HD) or kidney transplantation is the only possibility for ESRD patients to survive. A full correction of anemia in HD patients may lead to an increased risk of vascular access (VA) failure, and some of the studies show that decreased levels of hemoglobin (Hb) had adverse effects on cardiac and brain function.

This study was designed to evaluate the impact of different risk factors, especially the Hb level on AVF survival.

**Methods:** Prospective observational data were analyzed from a non randomized sample (n=100) of HD patients. The patients who referred between April 2005 and December 2006 with < 1 month on HD were included .The relative risk (RR) of access failure was evaluated in four different groups of patients divided according to their Hb levels (<8 , 8 – 10, 10 – 12, and >12 g/dl). Other factors possibly influencing VA survival were also considered including gender, age, smoking, diabetes, hypertension, parathyroid hormone levels, ACE inhibitor intake and triglyceride levels. The analyses were performed using SPSS v.11.5; Kaplan Meier procedure; Cox regression and log rank test were used.

**Results:** In all 100 HD patients under survey, there was a statistically significant higher risk of VA failure in patients with Hb <8g/dl (RR=1.41; P=0.01).

Diabetes (RR=1.21; P=0.05), age>60 years (RR=1.41; P=0.06), were identified as predictive factors for AV failure. ACE inhibitor intake (RR=0.45; P=0.01) was found to be protective.

**Conclusion:** correction of serum level of hemoglobin can lead to a better result in VA survival and ACE inhibitor intake was found to be a protective factor.

**Key words:** Vascular Access -Hemoglobin- Diabetes -ACE inhibitor

## **Introduction**

A full correction of anemia in haemodialysis (HD) patients may lead to an increased risk of vascular access (VA) failure. Advanced kidney failure usually leads to anemia; primarily as a result of deficient renal erythropoietin production. Although rHuEPO has been used in dialysis patients since 1989, there is not yet a global consensus regarding the optimum haematocrit target in this patient population. Indeed, the appropriate target haematocrit for dialysis patients has been one of the most debated issues in nephrology throughout the last decade. In a random sample of 940 patients at 188 U.S. hemodialysis centers obtained before the initiation of this study, they found that 69 percent of the patients had hematocrits of 27 to 33 percent, 15 percent had values below 27 percent and 16 percent had values above 33 percent (unpublished data). Yet the normal ranges for hematocrit values are 37 to 48 percent for women and 42 to 52 percent for men, [1], prompting the question of whether increasing the doses of epoetin would benefit patients who are undergoing hemodialysis. Cerebral oxygen delivery among patients with ischemic cerebrovascular disease, for example, is maximal when the hematocrit is 40 to 45 percent [2]. Guidelines have suggested a target haemoglobin (Hb) >11 g/dl, with an average value of 12–12.5 g/dl (European Best Practice Guidelines) [3] and a haematocrit of 33–36% (Hb 11–12 g/dl; NKF-DOQI Guidelines) [4]. However, many studies have shown that by maintaining the Hb of dialysis patients at nearly normal levels, great advantages in terms of quality of life [5], cardiac function [6], brain function [7], hospitalization and cost [8] can be achieved without significant adverse effects. Nevertheless, there has been some concern that full correction of anemia may increase the risk of adverse effects, such as vascular access (VA) thrombosis, in dialysis patients [9]. The aim of this study was to determine if there is any relationship between Hb levels and VA survival. As secondary aims, other variables were examined to analyze their influence on VA survival: gender, age, smoking, diabetes, hypertension, parathyroid hormone levels, ACE inhibitor intake, triglyceride levels.

**Patients and methods:**

## **Subjects**

This database prospectively gathered demographic and clinical information on all end-stage renal disease (ESRD) patients admitted for haemodialysis (HD). It contained detailed information on VA with respect to VA surgery date, type of access, access site, date of failure and all access-related complications. All the HD patients who referred between April 2005 and December 2006 with < 1 month were enrolled in this survey on the bases of non randomized sample.

## **Study variables and outcome definitions**

The relative risks (RR) of access failure was evaluated in four different groups of patients divided according to their Hb levels (<8, 8 – 10, 10 – 12, and >12 g/dl). Other factors possibly influencing VA survival were also considered including gender, age, smoking, diabetes, hypertension, parathyroid hormone levels, ACE inhibitor intake and triglyceride levels. These conditions were defined based on the International Classification of Diseases.

## **Statistical analyses**

All statistical analyses were performed using SPSS software, version 11.5 s. Survival functions were described using the Kaplan–Meier technique. The log-rank test was used for univariate comparisons, Cox's proportional hazards regression was used to model time to event as a function of Hb level. All variables used in the equations were chosen a priori and retained in the models if there was biological plausibility or if univariate analyses suggested that they might be associated with the event or might confound the relationship between the covariate of interest and the event. The proportional hazards assumption was checked for each model by inspection of the complementary log-minus-log plots. A stepwise method was employed to obtain the best multivariate model. The  $-2 \log$  likelihood ratio ( $-2 \log L$ ) statistics were used for goodness of fit comparisons [10, 11]. Estimated RRs and the hazards ratios (HR) for time to event analyses and their 95% confidence intervals (95% CIs) were calculated using estimated regression coefficients and their standard error. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with  $P < 0.05$

considered significant. The *P*-value for variable removal within the multivariate analyses was set to 0.10.

## Results

In this survey, there was a statistically significant higher risk of VA failure in patients with Hb <8g/dl (RR=1.41; *P*=0.01). There was no statistically significant difference in the RR of VA failure between patients with Hb 8–10g/dl and those with Hb 10–12g/dl or >12 g/dl. Patients with Hb between 10 and 12 g/dl had an RR of AVF failure of 1.32 (0.84–2.08; *P* = 0.249), but patients with Hb >12 g/dl showed a lower RR of fistula failure, 0.77 (0.31–1.91; *P* = 0.59).

Other findings including Diabetes (RR=1.21; *P*=0.05) and age>60 years (RR=1.41; *P*=0.06) were identified as predictive factors for AV failure and ACE inhibitor intake (RR=0.45; *P*=0.01) was found to be protective.

The Kaplan–Meier analysis revealed a cumulative survival for fistulae of 87% and 80% after 12 and 24 months, respectively. The shortest VA cumulative survival was found in patients with Hb <8 g/dl (AVF 20.65 months).

## Discussion

Any of the previously described advantages of complete correction of anemia for dialysis patients has to be balanced with the potential adverse effects of this practice. In the context of our study, we focused particularly on the possibility of an increased incidence of VA thrombosis. It is well known that complications of VA are the primary causes of morbidity (hospitalizations) in HD patients. The matter is of utmost importance in clinical practice; and any practice that increases the incidence of these complications must be avoided. Regarding the potential association between VA thromboses and higher levels of Hb we found no significant differences in fistula survival in patients with Hb levels between 8 and 10 g/dl and those with Hb between 10 and 12 g/dl or Hb >12 g/dl; therefore, we assume that normalization of Hb levels was not an RR factor for fistula survival in our population. Moreover, it was shown that the severely anemic patients (Hb <8g/dl) were the group with a statistically significant shorter fistula survival; therefore, anemia was a significant RR factor (*P* = 0.01) for fistula failure in our population. VA survival in non-anemic patients was longer than anemics in

our population. This result is in conflict with a previous large sample, randomized clinical trial published by Besarab *et al.* in 1998 [9]. They have discussed different aspect of normalization of Hb in HD patients in their 'Normal Hematocrit Cardiac Trial' (NHCT) and concluded and recommended against the normalization of Hb levels in these patients. In this well-controlled clinical study, a stratified cohort of 1265 HD patients with clinically evident cardiac disease were randomized to achieve a maintenance haematocrit of either  $42\pm 3$  or  $30\pm 3\%$ . Increased access thrombosis was found in the cohort of patients randomized to achieve the higher haematocrit of 42% (39 vs. 29%;  $P = 0.001$ ). However, VA thrombosis was not associated with either the achieved haematocrit level or the dose of rHuEPO, making interpretation of these results difficult. Our study, however, is an epidemiological evaluation, where the target Hb is established by the European Best Practice Guidelines [3, 15], but the physicians are not forced to normalize Hb in patients resistant to correction. Our finding of association of higher risk of VA failure with severe anemia can be explained by the association of the anemic state with inflammatory states and presence of co-morbidities in many HD patients. This hypothesis is in accordance with the findings of a study by Miller *et al* [12, 15]. Apart from anemia correction, we found other factors influencing VA survival including gender, age, smoking, diabetes, hypertension, parathyroid hormone levels, ACE inhibitor intake and triglyceride levels. Diabetes and the age over 60 years were associated with a higher risk of VA failure while treatment with an ACE inhibitor was associated with longer VA survival. The protective effect of ACE inhibitors has already been described in the literature [Saran *et al*13]. Moreover, an ACE inhibitor or ARB may improve blood flow by increasing cardiac output associated with after load reduction. In addition to the classic atherogenic risk factors (diabetes and age), iPTH has recently been suggested as a potential cause of vascular disease [Grandaliano *et al*14].

## Conclusions

In our population, anemia (Hb <8 g/dl) was associated with VA failure. No significant differences were found in VA fistula and survival between patients with nearly normal Hb and those with Hb in the range of 8 and 10 g/dl. Our study showed that HD patients should benefit from correction of anemia without incurring any increased risk of VA failure. A significantly protective effect of ACE inhibitors on VA survival was detected. In contrast, older age (>60

years), diabetes were predictive risk factors for access failure in our study. ACE inhibitors, already recommended for their protective effects on the heart, should also be considered for their potential beneficial impact on VA survival.

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| factor predictive<br>(AV Fistula) | Relative Risk (CI95%) | P-Value |
|-----------------------------------|-----------------------|---------|
| >60 years                         | 1.41                  | 0.06    |
| Diabetes                          | 1.25                  | 0.05    |
| Hb <8g/dl                         | 1.41                  | 0.01    |

The relative risk of access failure associated with different parameters

