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Klinik Araştırma

Effect of Oral Isosorbide Mononitrate Therapy on Proteinuria in Patients with Nephrotic Syndrome †

Nefrotik Sendromlu Hastalarda Oral İzosorbid Mononitrat Tedavisinin Proteinüriye Etkisi

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ABSTRACT

Objective: *Proteinuria is the most important causitive factor in the progression of renal failure Angiotensin- converting enzyme inhibitors (ACEIs) and angiotensin- receptor blockers (ARBs) are shown to reduce proteinuria however in some patients, these drugs are not adequately effective. Oral nitrates may reduce proteinuria by way of glomerular vasodilation with resultant decrease in intraglomerular pressure. In this study the possible effects of oral isosorbide mononitrate (IMN) on proteinuria in patients with nephrotic syndrome was investigated.*

Material and Methods: *A total of 36 patients with nephrotic syndrome (proteinuria >1 g/day) requiring oral IMN for symptomatic ischemic heart disease were enrolled.*

Results: *Proteinuria was significantly decreased with the initiation of IMN (p=0.02) in all patients. In patients on combined ACEI and ARB treatment, IMN was effective in reducing proteinuria (p=0.01) however it was not effective in patients on single agent therapy as ACEI or ARB; (p=0.15). IMN was also effective in diabetic patients (p=0.02), but not effective in non-diabetic patients (p=0.33). IMN was ineffective in patients on calcium channel blocker treatment (CCB), (p=0.96). Decrease in proteinuria was associated with baseline proteinuria (p<0.001). Patients who responded to IMN therapy were significantly younger (p=0.01). In the logistic regression analysis for predicting the effectiveness of IMN, age, baseline proteinuria, ACEI, ARB, CCB use, presence of diabetes were included as independent variables. Only age and ACEI use were significant parametres.*

Conclusion: *Oral nitrates may be effective for reducing proteinuria in patients with nephrotic syndrome. This favorable effect seemed to be more prominent in younger, diabetic patients using both ACEI and ARB.*

Keywords: *nephrotic syndrome, proteinuria, isosorbide mononitrate*

ÖZ

Amaç: *Proteinüri, böbrek yetersizliğinin progresyonunda en önemli nedenlerinden biridir. Anjiyotensini dönüştürücü enzim inhibitörleri (ACEI) ve anjiyotensin reseptör blokerlerinin (ARB) proteinüriyi azalttığı birçok çalışmada gösterilmiştir fakat bazı hastalarda yeterli etkinlikleri yoktur. Oral nitratlar glomerüler vazodilatasyon ile intraglomeruler basıncı düşürerek proteinüriyi azaltabilirler. Bu çalışmada, oral izosorbid mononitratın (IMN) nefrotik sendromlu hastalardaki proteinüri üzerine olan etkisi araştırıldı.*

Gereç ve Yöntem: *Nefrotik sendromlu (proteinuri >1 g/gün), en az 6 aydır ACEI veya ARB kullanan, semptomatik iskemik kalp hastalığı nedeni ile daha önceden IMN tedavisi başlanmış olan 36 hasta çalışmaya alındı.*

Bulgular: *Tüm hastalar birlikte değerlendirildiğinde IMN tedavisi sonrasında proteinüride anlamlı düşüş gözlendi (p=0.02). Proteinüriyi azaltmada IMN tedavisi ACE ve ARByi kombine kullanan hastalarda etkiliyken (p=0,01), yalnız ACE veya yalnız ARB kullanan hastalarda etkili değildi (p=0,15). IMN aynı zamanda diyabetik hastalar da etkiliyken (p=0,02), tam tersine diyabetik olmayanlarda etkili değildi (p=0,33). Kalsiyum kanal blokeri kullanan hastalarda IMN etkisizdi (p=0,96). Proteinürideki azalma, bazal proteinüri seviyesi ile ilişkili saptandı (p<0,001). Çoğunlukla genç hastalar IMN tedavisine yanıt vardı (p=0,01). Lojistik regresyon analizine, yaş, bazal proteinüri, ACEI, ARB, CCB kullananlar, diyabet varlığı bağımsız değişkenler olarak dâhil edildi. Yalnızca yaş ve ACE kullanımı anlamlı parametrelerdi.*

Sonuç: *Oral nitrat kullanımı nefrotik sendromlu hastalarda proteinüriyi azaltmak için etkili olabilir. Bu etki ACE ve ARB'yi birlikte kullanan ve genç diyabetiklerde daha belirgindi.*

Anahtar kelimeler: *nefrotik sendrom, proteinüri, isosorbit mononitrat*

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INTRODUCTION

Presence of proteinuria/albuminuria indicates decline in renal functions and is independently associated with adverse cardiovascular outcomes [1]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are used commonly to reduce proteinuria/albuminuria [2,3].

In some cases ACE inhibitors and ARBs fail to reduce albuminuria and unfortunately there are no other drug classes recommended by the guidelines to ameliorate proteinuria/albuminuria.

Several studies suggest beneficial effects of nitric oxide on proteinuria. In a study conducted on rats isosorbide mononitrate (IMN) was used as nitrite oxide donor on rats with exercise- induced proteinuria and reduction in proteinuria was observed [4]. In another study by Roccatello et al. patients with Ig A nephropathy and proteinuria were administered isosorbide mononitrate and a decline in proteinuria was observed [5]. With this background in mind, in our study we aimed to investigate the effect of isosorbide mononitrate in patients with proteinuria using ACE inhibitors and/or ARBs in patients with proteinuria.

MATERIALS and METHODS

Patients with >1 gr/day proteinuria despite use of an ACE inhibitor and/or ARB for over 6 months were retrospectively selected from patient files of Istanbul Medeniyet University Goztepe Training and Research Hospital Nephrology Clinic. A total of 36 patients (mean age= 58±12, male/female= 12/24) with nephrotic syndrome (proteinuria > 1 g/day) requiring oral IMN for symptomatic ischemic heart disease were enrolled. Before and after the initiation of IMN, daily proteinuria was measured Among these patients, data of the cases using IMN for at least 3 months were used for analysis. Patients with similar demographic features, and proteinuria (>1 gr/day) despite use of an ACE inhibitor and/or ARB for over 6 months and those who has never been on IMN treatment were identified as the control group.

Exclusion criteria included active use of other proteinuria decreasing agents including cyclophosphamide, azathioprine, mycophenolate mofetil, prednisolone, rituximab. Patients' demographic features, drugs, baseline proteinuria were also analyzed accordingly. This retrospective study protocol was approved by Istanbul Medeniyet University School of Medicine Ethics Committee (2013-30/A).

Statistical Analysis

Statistical analyses were performed using SPSS software version 16. Inc., Chicago, Illinois, USA). The distribution of continuous variables for normality was tested with a one-sample Kolmogorov–Smirnov test and data were presented as mean standard deviation (SD) or median and interquartile ranges, as appropriate. Categorical variables were reported as frequencies and group percentages. Differences between groups in normally and non-normally distributed variables were evaluated by the unpaired t-test, the Mann-Whitney U-test, respectively, as appropriate. The Wilcoxon signed ranks test was used to compare the change in proteinuria between baseline and 3 months after. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of improvement in proteinuria. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. A 5% type-1 error level was used to infer statistical significance.

RESULTS

A total of 36 patients were in the nitrate, and 32 in control group. In the nitrate group, 24 patients were being treated with ACEI (n=24), ARB (n=26) or both ACEI and ARB (n=17). Table 1 shows the baseline characteristics of the patients. As expected, impairment in renal function was more common in the proteinuria group (lower glomerular filtration rate and higher creatinine level) than in normotensive controls. Comparison between the groups showed that age, creatinine, estimated glomerular filtrate rate (eGFR), glucose, and presence of diabetes mellitus differed significantly (Table 1).

When all the patients were included in the analysis, proteinuria was significantly decreased with the initiation of IMN (3.40±2.27 vs 2.72±1.82 g/day, p=0.02). In patients on combined ACEI and ARB treatment, IMN was effective in reducing proteinuria (2.92±1.57

Table 1. Baseline clinical characteristics and laboratory values of the study patients.

	All (n=68)	Nitrate (n=36)	Control (n=32)	p
Age (year)				
Mean ±SD	56±12	59±12	52±11	0.03
Gender (n/n)				
Female/Male	40/28	23/13	17/15	0.37
Diabetes mellitus n (%)	20 (100)	15 (75)	5 (25)	0.02
Creatinine (mg/dL)				
Median	1.38	1.59	1.15	0.03
Interquartile range	0.93-2.01	1.10-2.12	0.83-1.66	
GFR (mL/min/1.73 m^2)				
Median	52	37	59	0.006
Interquartile range	33-80	26-63	44-96	
Fasting plasma glucose (mg/dL)				
Median	102	105	98	0.04
Interquartile range	91-123	95-136	87-107	
Total protein (g/dL)				
Median	6.9	6.9	7.1	0.15
Interquartile range	6.4-7.3	6.1-7.1	6.7-7.4	
Albumin (g/dL)				
Median	4.1	3.9	4.3	0.09
Interquartile range	3.7-4.4	3.8-4.2	3.7-4.4	
Baseline Proteinuria (g/day)				
Median	2.06	2.68	0.70	<0.001
Interquartile range	0.77-3.55	1.75-4.20	0.22-2.45	
ACE inhibitors n (%)	53 (100)	26 (49)	27 (51)	0.23
ARB n (%)	46 (100)	27 (59)	19 (41)	0.17
ACEI and ARB n (%)	31 (100)	17 (55)	14 (45)	0.69
CCB n (%)	22 (100)	18 (82)	4 (18)	0.001
Beta blockers n (%)	9 (100)	5 (55)	4 (45)	0.86

vs 2.23±1.95 g/day, p=0.01) however it was not effective in patients on single agent therapy as ACEI or ARB; (3.89±2.98 vs 2.93±1.57 g/day, p=0.15). IMN was also effective in diabetic patients (3.92±3.06 vs 2.52±1.54 g/day, p=0.02) and conversely not effective in non-diabetic patients (3.01±1.40 vs 2.87±2.03 g/day, p=0.33). IMN was ineffective in patients treated with calcium channel blockers (CCB), (2.74±1.43 vs 2.75±1.84 g/day, p=0.96). In addition, decrease in proteinuria was associated with baseline proteinuria (r= -0.650, p<0.001). Patients who responded to IMN therapy were significantly younger (56±10 vs 65±10 years, p=0.01). In logistic regression analysis for predicting the effectiveness of IMN (model -2 Log likelihood ratio= 27.96, p=0.01), age, baseline proteinuria, ACEI, ARB, CCB use, presence of diabetes were included as independent variables. Only age and ACEI use were significant factors.

Treatment with nitrate for three months was associated with a significant improvement in the proteinuria (Table 2). In nitrate group, proteinuria decreased significantly and in the control group, no significant change was observed. In nitrate group proteinuria decreased significantly more than control group (p=0.02). Multivariate logistic regression analysis to determine the predictor of improvement in proteinuria showed that age and nitrate therapy differ significantly (p=0.02 and p=0.003). The relationship between change in proteinuria is shown in Figure 1.

Table 2. The median proteinuria at baseline and 3 months later.

	Nitrate group (n=36)	Control group (n=32)	p
Baseline proteinuria Median (IQR)	2.68 (1.75-4.20)	0.70 (0.22-2.45)	<0.001
3 months after isosorbide mononitrate Median (IQR)	2.33 (1.18-3.97)	1.04 (0.29-2.97)	0.01
Δ proteinuria Median (IQR)	0.61 (-0.36 – 1.06)	-0.70 (-0.42 – 0.06)	0.003
p value	0.02	0.06	

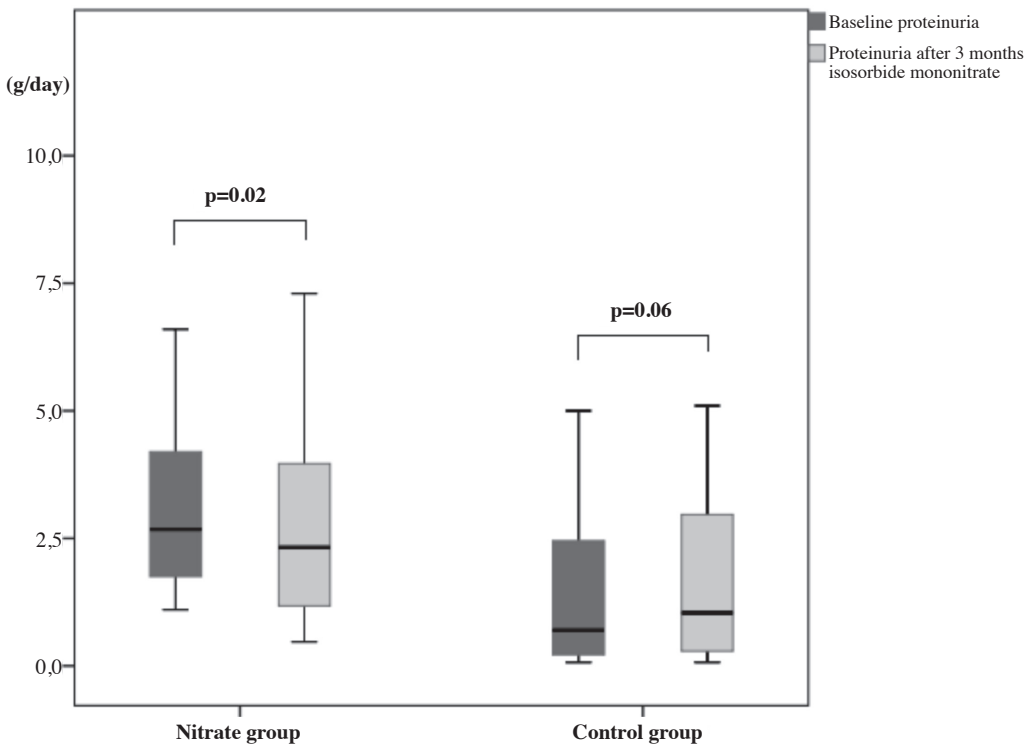

Figure 1. Univariate analysis.

DISCUSSION

RResults of this retrospective study have shown a statistically significant decrease in proteinuria with the initiation of isosorbide mononitrate treatment. Although nature of the study is observational, there are animal research data that may support and enlighten the pathogenesis of this effect.

Nitrates are nitric oxide donors and nitric oxide is known to improve endothelial dysfunction [6]. In some hypertension models nitric oxide plays an important role. Especially its anti-oxidant features have renoprotective effect. In a study by Rajapakse, an nitric oxide donor amino acid L- arginin was given to rats with angiotensin II - induced hypertension [7]. As a result, L-arginin prevented renal damage compared to the rats that were given saline. In another study by Schram, rats with acute renal failure had improved glomerular filtration rates after L-arginin and superoxide dismutase administration [8]. These results may support our study findings, but further studies are warranted to confirm our findings.

In an animal study by Tamura et al. [9] a novel nitric oxide donor, nicorandil, has shown decrease in albu-

minuria. In the same line, Lee et al. (10) also observed a reduction in proteinuria with nicorandil therapy. Although considered as effective in amelioration of endothelial dysfunction, there are numerous dermatologic side effects of this drug and therefore safety is still an issue. In one clinical study, Lee et al., has compared the effects of placebo, isosorbide dinitrate and nicorandil on proteinuria in well-controlled hypertensive patients [11]. They observed a significant decrease in proteinuria in nicorandil group whereas they showed that isosorbide dinitrate did not reduce proteinuria significantly. The diminished effect of isosorbide dinitrate in this patient group may be due to its blood pressure controlling effect . In our study baseline proteinuria was associated with decrease in proteinuria. Also, although they are both nitric oxide donors, mononitrate and dinitrate are not the same drugs.

There are several limitations to this study. First, this is a retrospective, single-center study with a small sample size. Second, the primary cause of proteinuria is important because we may observe different reduction in proteinuria with treatment. Third, the duration of treatment is short.

As a conclusion, addition of nitrate therapy to ACEi or ARB might be a novel agent for lowering proteinuria. It is time to conduct randomized-controlled prospective multi-center studies with large sample-size to elucidate the effect of nitrate therapy on proteinuria.

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