Hepatorenal Sendrom

Yrd.Doç.Dr.Mücahit Avcil

- Bir hastalığı tedavi etmenin tek yolu onu anlamaktır.

?

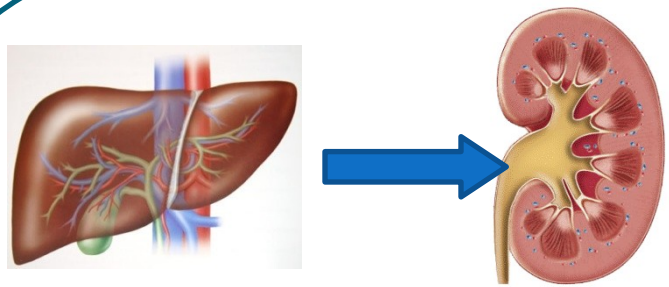
TİP1-TIP2
Ölümcül
Siroz komplik.

Genel bilgiler

KC

Splanknik alanda arteriyel vazodilatasyona

Renal vazokonsrik.
GFR de düşme



TEDAVİ

KC nakli
TIPS
Noradrenalin
Mitodrine/ocreotide
terliplessin

TANI

Creat ⬆
hipoNa
hipoTa
Başka neden yok

Tanım

- HRS sirozda veya ALF de şiddetli vazokonstriksiyon sonucu oluşan akut veya subakut böbrek yetmezliği demektir.

Sirozun Komplikasyonları

- Hepatik ensefelopati
- Varis kanamaları
- Portal ht gastropatisi
- Assit
- Hepatopulmoner sendrom

- Hepatorenal sendrom

- 1956 da tanımlandı

(Lancet 1956)

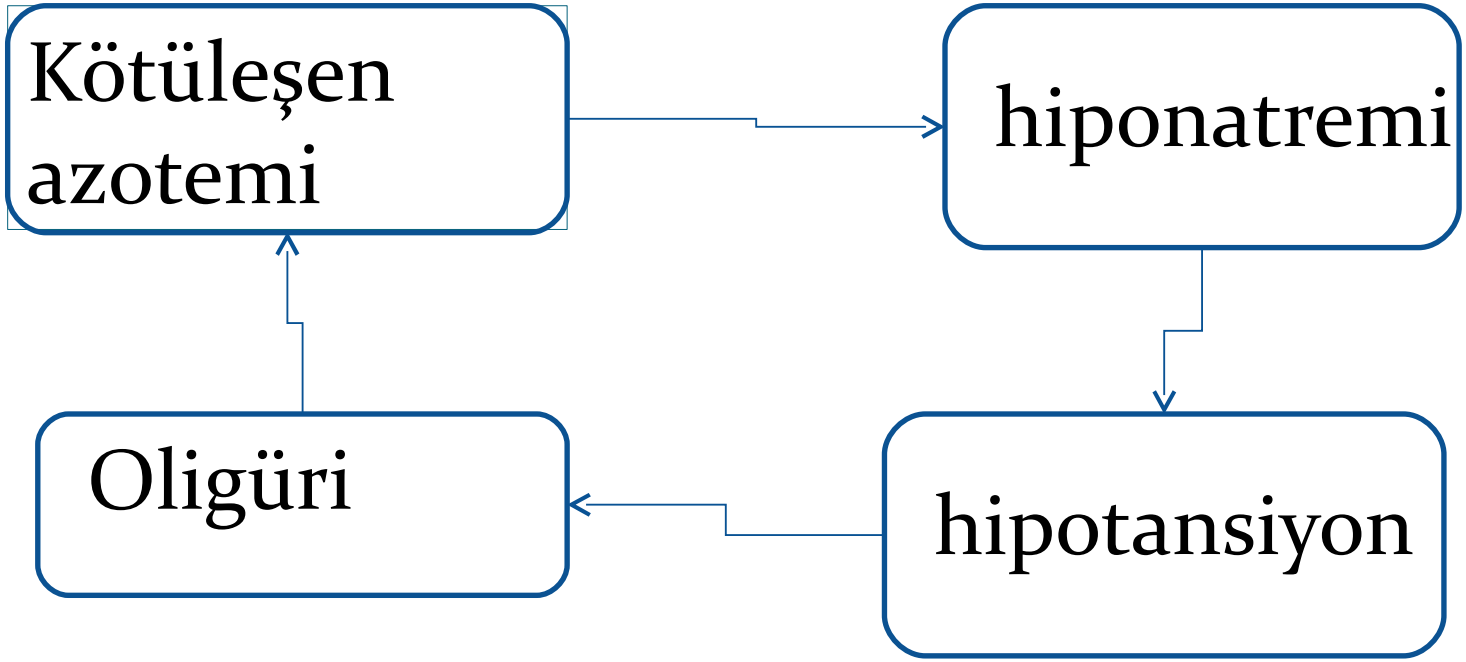
- Karaciğer nakli ile düzelebilir

(NEJM 1969)

- Hastaların yaklaşık yarısı bu tanıyı aldıktan 2 hafta sonra kaybedilirler.

- Siroz, fulminan hepatik yetmezlik gibi hastalıklarda insidansı %8- 50 arasında değişir

- P maddesi ve endotoksnler
- Böb semp.uyarılması
- Efektif plazma h.azalması
- Lökotrienlerin yıkılmaması
- Kininojen azalır
- Prostaglandin azalması
- LCAT azalması


Kötüleşen azotemi
hiponatremi
hipotansiyon
Oligüri

Tanı kriterleri

- Assit oluşmuş siroz
- Serum creatinine > 1.5 mg/dL
- Diüretklerin kesilmesine ve albuminle plazma genişletilmesine rağmen düzelmeyen serum creatinine
- Şok bulgularının olmaması
- Nefrotoksik ilaç öyküsü olmaması
- Renal parankimal hastalık olmaması
  - Proteinüri >500 mg/gün
  - Mikrohematüri
  - Ultrasonda >500 mg gün proteini ve mikrohematüriyi açıklayacak bir parankimal patolojinin olmaması

- Bu hastalarda sık görülen böbrek yetmezliği nedenleri ekarte etmek gerekir.
  - Prerenal azotemi
  - Akut tübüler nekroz

Minör kriterler

- İdrar volum < 500 mL/24 h
- İdrar sodium <10 mEq/L
- İdrar osmolalitesi plasma osmolalitesinden büyüktür
- İdrar eritrosit < 50 per high power field
- Serum sodium <130 mEq/L

Curr Opin Organ Transplant. 2013 Jun;18(3):265-70. doi: 10.1097/MOT.0b013e3283614c7a.

Results of pretransplant treatment of hepatorenal syndrome with terlipressin.

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Abstract

PURPOSE OF REVIEW: Hepatorenal syndrome (HRS) is a dreaded complication of end-stage liver disease. The best treatment option for HRS is liver transplantation (LT) in suitable candidates. Pretransplant care of HRS is of utmost importance in order to secure a good posttransplant outcome. We review the advances during the last year in the diagnosis and management of HRS in candidates who are awaiting liver transplantation.

RECENT FINDINGS: New attempts at defining renal failure in cirrhosis using the Acute Kidney Injury (AKI) definition have been proposed, as this definition has the potential advantage of detecting earlier phases of kidney dysfunction. Patients who undergo liver transplantation with acute tubular necrosis recover renal function more slowly than those with HRS and have a higher incidence of chronic kidney disease at all time points after liver transplantation. Vasoconstrictor drugs, particularly terlipressin, are effective for the management of HRS; however, noradrenaline is a good choice if terlipressin is not available. Long-term treatment of HRS with vasoconstrictors until liver transplantation in those patients with HRS recurrence after the first treatment is beneficial as a bridge to liver transplantation. Data from the cohorts of patients treated with vasoconstrictors (terlipressin and midodrine) indicate that liver transplantation offers a clear survival benefit to patients with HRS regardless of prior therapy with these drugs.

SUMMARY: Ongoing advances in the management of patients with HRS before liver transplantation indicate that vasoconstrictors plus albumin should be offered to all suitable candidates. Liver transplantation remains the best treatment option for HRS.

- Uygun hastalarda en iyi tedavinin kc nakli olduğu, bu imkanın sağlanmasına kadar vazokonstiriktör (terlipressin)ve albumin ile tedavi edilebileceği ifade ediliyor.

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Ren Fail. 2013;35(5):633-9. doi: 10.3109/0886022X.2013.789969. Epub 2013 May 7.

Diagnostic significance of nitrates and nitrites and L-arginine, in development of hepatorenal syndrome in patients with end stage alcoholic liver cirrhosis.

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Abstract

Hepatorenal syndrome (HRS) represents a complication of the end-stage liver cirrhosis. The aim of the present study was to analyze concentrations of nitrates and nitrites (NO2 + NO3) and L-arginine in patients with liver cirrhosis and HRS as a possible predictive marker for the development of HRS. The research was performed in a group of 28 patients with cirrhosis and HRS, a group of 22 patients suffering from cirrhosis without HRS and a control group comprised of 42 healthy voluntary blood donors. In patients with end-stage alcoholic liver cirrhosis, with HRS, the concentrations of NO2 + NO3 increased and correlated with the degree of cirrhosis progression, compared to patients without HRS and significantly higher compared to the control group. The level of NO2 + NO3 was in a positive correlation with the degree of liver damage de Ritis coefficient (HRS = 0.72; cirrhosis: = 0.55; control = -0.10). Significant positive correlation was found between NO2 + NO3 concentration and inflammatory marker C-reactive protein (HRSC = 0.75; cirrhosis = 0.70, control = -0.25). The correlation between NO2 + NO3 concentration and creatinine concentration in patients with HRS was significantly higher compared to patients without HRS (HRS = 0.82; cirrhosis = 0.32; control = -0.25). By using binary regression analysis, on the basis of clinical criteria of HRS diagnosis, the strongest independent positive predictor for HRS development was NO2 + NO3, associated with 45.02 times higher incidence of HRS, compared to arginine (12.7 times higher incidence), creatinine (13.1 times higher incidence), and AST/ALT ratio (10.55 higher incidence of HRS). Since the determination of NO2 + NO3 represents a reliable and easily applicable method, it may be used as an early predictive marker for HRS development.

PMID: 23651488 [PubMed - in process]

- NO2-NO3 ve L –arginine sirozlu hastanın HRS ye ilerleyeceğini gösteren bir marker olabilir mi diye bakmışlar.
- 1.Grup : 28 kişi siroz+HRS
- 2.Grup: 22 kişi siroz

J Crit Care. 2013 Apr 22. pii: S0883-9441(13)00060-9. doi: 10.1016/j.jcrc.2013.02.016. [Epub ahead of print]

Effect of perioperative terlipressin infusion on systemic, hepatic, and renal hemodynamics during living donor liver transplantation.

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Abstract

BACKGROUND: End-stage liver disease is associated with marked hemodynamic disturbances that are further aggravated during liver transplantation. Terlipressin has been shown to be effective in the management of sepsis-induced hypotension and hepatorenal syndrome and recently has been tried as infusion during liver transplantation. This study assessed the effect of intraoperative and postoperative terlipressin infusion on systemic, hepatic, and renal hemodynamics during adult living donor liver transplantation.

METHODS: Eighty recipients were randomly allocated into control (C group; n = 40) and terlipressin (TP group; n = 40), in which, terlipressin infusion was started at the beginning of surgery at a dose of 3 μg kg^{-1} h^{-1} to be reduced to 1.5 μg kg^{-1} h^{-1} after reperfusion and continued for 3 postoperative days; vasoactive agents were used as appropriate in all patients. Systemic hemodynamics, hepatic and renal arterial resistive indices (HARI, RARI), and portal venous blood flow (PBF) were compared between both groups intraoperatively and for 5 postoperative days.

RESULTS: With terlipressin infusion, there were significant increases in both mean arterial pressure and systemic vascular resistance ($P < .001$), whereas heart rate and cardiac output decreased significantly ($P < .001$) throughout the study period compared with the C group. Vasoconstrictor drugs required during reperfusion were significantly lower in the TP group. There was a significant decrease in HARI, RARI, and portal venous blood flow in the TP group compared with the C group throughout the study period. There was no significant difference between both groups regarding liver function tests and serum lactate, whereas renal function tests were significantly better in the TP group.

- 80 kişi 40+40 iki gruba ayrılmış. Bir grup Kc transplantasyonuna başlarken terlipressin başlamışlar, sistemik hemodinamik, hepatik ve renal arteriel resistif parametreler, portal venöz kan akımı intraoperatif ve postop 5 gün boyunca ölçülmüş

Liver Int. 2013 Mar 28. doi: 10.1111/liv.12179. [Epub ahead of print]

Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study.

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Abstract

BACKGROUND: Various vasoconstrictors have shown promising results in the management of type 1 hepatorenal syndrome (HRS). However, there are very few studies on vasopressors in the management of type 2 HRS. Terlipressin has been used commonly; however, it is costly and not available in some countries. In this study, we evaluated the safety and efficacy of terlipressin and noradrenaline in the treatment of type 2 HRS.

METHODS: Forty-six patients with type 2 HRS were managed with terlipressin (group A, N = 23) or noradrenaline (Group B, N = 23) with albumin in a randomized controlled trial at a tertiary centre.

RESULTS: HRS reversal could be achieved in 17(73.9%) patients in group A as well as in group B (P = 1.0). Univariate analysis showed that the baseline model of end-stage liver disease score, urine output, urinary sodium, serum creatinine and mean arterial pressure were associated with response. However, in multivariate analysis only baseline serum creatinine, urine output and urinary sodium were associated with the response. Eight patients in group A and 9 in group B died within 90 days of follow-up (P > 0.05). Noradrenaline was less expensive than terlipressin (P < 0.05). No major adverse effects were seen.

CONCLUSIONS: The results of this randomized study suggest that terlipressin and noradrenaline are safe and effective in the treatment of type 2 HRS and baseline serum creatinine, urine output and urinary sodium are predictive of response. Noradrenaline is less expensive than terlipressin in the treatment of type 2 HRS (ClinicalTrials.gov, Number NCT01637454).

- Birçok vasokonstriktörler HRS 1 üzerine çalışılmış fakat HRS 2 üzerine çalışılmamış. Aynı zamanda terlipressin pahalı ve bulunmuyor. 23 hasta terlipressin, 23 hastaya da noradrenalin ve albumin verilmiş.

Indian J Pharmacol. 2013 Jan-Feb;45(1):54-60. doi: 10.4103/0253-7613.106436.

Survival benefits of terlipressin and non-responder state in hepatorenal syndrome: a meta-analysis.

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Abstract

OBJECTIVES: Terlipressin improves renal function in hepatorenal syndrome (HRS) is a known fact. However the reason for lack of its long-term survival benefits despite improvement in renal function remains unclear. The aim of this study was to analyze the survival benefits of terlipressin in HRS and to address the issue of non-responder state to terlipressin.

MATERIALS AND METHODS: Electronic databases and relevant articles were searched for all types of studies related to HRS and use of terlipressin in HRS. Reduction in all-cause mortality rate was the primary outcome measure. Reduction in mortality rate due to HRS and other causes of death were also analyzed.

RESULTS: With total 377 patients analyzed from eight eligible studies; terlipressin reduced all-cause mortality rate by 15% (Risk Difference: -0.15%, 95% CI:-0.26 to -0.03). Reduction in the mortality rate due to HRS at three months was 9% (Risk Difference:-0.09%, 95% CI:-0.18 to 0.00).

CONCLUSION: Terlipressin has long term survival benefits perhaps at least up to three months but only with HRS as a cause of death not for other causes of death. Benefits and role of antioxidants like N- Acetylcysteine (NAC) in non-responder patients' needs to be studied further. Long-term use of low dose terlipressin (<4 mg/d) plus albumin and addition of antioxidant NAC to this regimen may help in improving both HRS reversal rate and survival rate in non-responders to terlipressin.

- 8 ayrı çalışmada toplam 377 hasta analiz edilmiş. Terlipressin tü sebeplere bağlı ölümleri %15 düşürdü. 3 aylık mortalite düşüşü % 9 imiş.
- NAC henüz tam çalışılamamı. Terlipresin+albumin+NAC rejimi sonuçları ve hayatta kalımı artırabilir.

J Gastroenterol Hepatol. 2011 Jan;26 Suppl 1:109-14. doi: 10.1111/j.1440-1746.2010.06583.x.

Terlipressin in hepatorenal syndrome: Evidence for present indications.

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Abstract

Hepatorenal syndrome (HRS) is the most frequent life threatening complication of advanced liver failure and cirrhosis. HRS results from a functional renal dysfunction due to circulatory disturbances in patients with advanced liver disease and portal hypertension. Reduction in the effective circulating blood volume and hence hypoperfusion of the kidney is the basic underlying common pathogenetic mechanism for the development of hepatorenal syndrome. The prognosis for HRS remains very poor with types 1 and 2-both having an expected survival time of 2 weeks and 6 months, respectively. Although the available data are derived from studies including a limited number of patients mainly affected by type 1 HRS, vasoconstrictor drugs, in particular the vasopressin analog Terlipressin, seem to be the most effective approach for the management of HRS. Associated with albumin infusion, these drugs have been shown to lead to reduced mortality and improved renal function in HRS. Terlipressin administration significantly increases mean arterial pressure and systemic vascular resistance; while the heart rate, cardiac output, HVPG and portal venous blood flow decrease significantly. This decrease correlates well with the decrease in plasma renin activity. Thus the vasoconstrictor effect of Terlipressin reverses the basic pathology of HRS by reducing the plasma renin activity. The improvement in hemodynamics with Terlipressin is associated with an increase in glomerular filtration rate and deactivation of the vasoconstrictor and sodium-conserving hormones with reduced activity of the RAAS resulting in increased natriuresis. Terlipressin thus reverses HRS and is useful in bridging the patient to liver transplantation and may hence indirectly improve survival. Patients with HRS who show an improvement in renal function with Terlipressin and albumin seem to have an excellent post-transplantation outcome similar to that of patients without HRS. Thus, the use of Terlipressin has been shown to be safe, with minimal side effects that usually disappear after dose reduction, and results in an improved outcome in patients with HRS.

- Terlipresin albumin ile birlikte kullanıldığında güvenli ve etkilidir.

- **Özet :**Hepatorenal sendrom (HRS), akut veya kronik karaciğer hastalığı zemininde klinik, laboratuar veya histolojik olarak gösterilebilen bir neden olmaksızın gelişen, akutfonksiyonel renal yetmezlikle karakterize, sirozun mortalitesi yüksek bir komplikasyonudur.Splanknik vasküler yataktaki arteriyel vazodilatasyona ikincil renal dolaşımdavazokonstriksiyon ve vazokonstriktör sistemin hemeostatik aktivasyonu ile efektif kan akımının azalması patogenezde sorumlu tutulan mekanizmadır. Vazopressin analogları (terlipressin, ornipressin) sistemik ve splanknik vazokonstriksiyon

Tip 1 HRS

- Serum creatinine düzeyleri 2 hafta içinde 2.5 mg/dL üzerinde olacak şekilde ikiye katlanır
- Hızlı progresyon ve yüksek mortaliteye sahiptir
- Spontaneous bakterial peritonit ve varis kanaması ile presipite olabilir

Tip 2 HRS

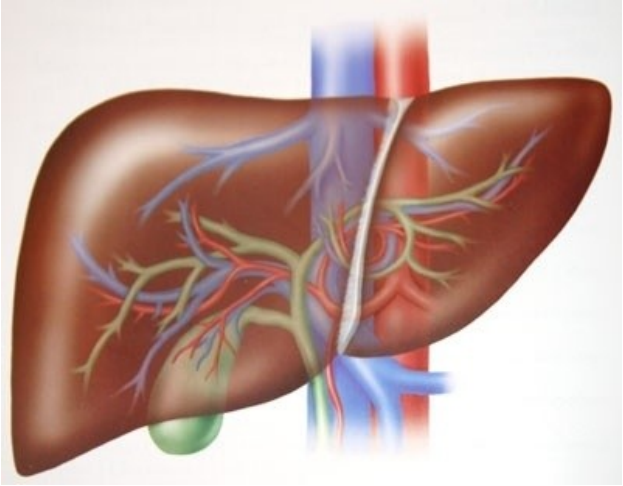
- Serum creatinine yavaş artar
- Birçok tip 2 HRS altta yatan presipitan faktör yüzünden dönebilir.
- Survival 6 aydır

TEDAVİ

- Hepatorenal sendromun tedavisi karaciğer naklidir.

- TIPS

- TIPSS



- ✓ Endojen vazokonstriktör sistemi suprese eder.
- ✓ Creatinine seviyelerini düşürür
- ✓ Assitin daha iyi konrol altına alınmasını sağlar

Midodrine /octreotide

- Midodrine (a selektif alfa-1 adrenergic agonist)
- Octreotide (somatostatin analog)ile kombine tedavi etkili ve güvenlidir

- Midodrine sistematik vasoconstriktördür
- Octreotide endojen vasodilator salınımını inhibe eder kombine tedavi renal ve sistemik hemodinamiyi düzeltir

Terlipressin

- Terlipressin, V1 vasopressin analoğu
- “Glypressin 1 mg “
- Sistemik ve splanknik vazokonstriksiyon yaparak efektif arteriyel kan akımını artırır ve endojen vazokonstriktör sistemin (RAS ve sempatik sinir sistemi) aktivitesini azaltır, böylece renal kan akımı