Dextran Administration Associated with Large Volume Paracentesis Management of Patients with Cirrhosis and Ascites

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Özet: ASİTLİ SİROZ HASTALARINDA DEXTRAN-70 EŞLİĞİNDE BÜYÜK VOLÜM PARASENTEZİN TEDAVİDEKİ ETKİNLİĞİ

Günümüzde siroza bağlı asitin tedavisinde en çok kullanılan yöntem sodyumdan kısıtlı diyet ve diüretiklerdir. Fakat son yıllarda diyetle istenilen sonuçların alınamaması, diüretiklerle hepatik ensefalopati, böbrek yetmezliği ve elektrolit imbalansı gibi ağır komplikasyonların ortaya çıkması tedavide yeni arayışlara yönelinmesine neden olmuştur. Altermatiflerden biri; büyük volüm parasentezin yeniden gündeme gelmesidir. Çalışmamızda dextran–70 ile birlikte büyük volüm parasentezin etkinliği araştırılmıştır. 10 Child C gribinda olan siroz hastası çalışma grubuna alındı. Hastalara i.v 42,6 ± 4,3 gr (30–60) dextran – 70 (Macrodex Eczacıbaşı) eşliğinde 5,85 ± 0,56 lt. (4 – 9) parasentez uygulandı. Hastalarda işlem sonrasında kilo (p<0.001), serum sodyumu (p<0.008) ve serum albüminde düşme (p<0.001), protrombin zamanında uzama saptanırken (p<0.004), ejeksiyon fraksiyonu (p<0.03), kardiyak debi (p<0.019), kardiyak indekste artışlar saptandı (p<0.008). Hastaların daha sonraki izlemleri sırasında asitin tekrar hızla toplanmasının nedeni olarak bu makrolitin yarı ömrünün kısa olması gösterilebilir. Sonuç olarak i.v dextran–70 replasmanı ile uygulanan büyük volüm parasentezin erken dönemde sonuçlarının oldukça tatmin edici olmakla birlikte, geç dönemde asitin tekrar oluşması, asit tedavisinde erken döneme oranla geç dönemde daha az etkili olduğunu göstermektedir.

Anahtar kelimeler: Siroz, asit, dextran– 70, parasentez.

Summary: *Large-volume paracentesis (4-6 L/day) is an effective and safe therapy of ascites in patients with cirrhosis provided albumin is infused intravenously (i.v.). Given the high cost of albumin, 10 patients with cirrhosis and ascites were treated with large volume paracentesis using dextran-70, an inexpensive volume expander, instead of albumin. In this study hemodynamic evaluation was performed before and after large volume paracentesis (5.85 ± 0.56 lt) with administration of 42.6±4.3 gr of dextran-70. Twenty hours later after large volume paracentesis with administration of 42.6±4.3 gr of dextran-70, decreased significantly in the weight (from 63.45 ±3.82 to 58.35 ± 3.91 kg p< 0.001) albumin (from 2.71 ±0.15 to 2.18 ± 0.12 % gr, p<0.001), serum sodium (from 136.7 ± 1.23 to 132.2 ± 1.03 mEq/L, p< 0.008). Prothrombin time (from 19.8 ± 1.19 to 22.1 ± 1.53 sc, p<0.04) cardiac output and index increased from 4.78 ± 0.43 to 6.12 ± 0.64 lt/min, p<0.009 and from 2.94 ± 0.28 to 3.78 ± 0.40 co/m2, p<0.008) respectively. No significant changes in renal and hepatic functions were observed at the end of the study. In two patients developed hyponatremia that required no treatment. No developed renal failure. One patient died due to anaphlactic shock of dextran-70. This study shows that the administration of dextran-70 for large volume of ascites removed avoids the hypovolemic changes and the use of dextran-70 allows a 30 fold reduction in cost compared with albumin.*

Key words: Cirrhosis, ascites, dextran-70, paracentesis

Tense ascites is a common clinical problem in patients with chronic liver disease and portal hypertension. It can be uncomfortable, cause respiratory distress, promote the formation and

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rupture of umblical hernias and have negative effects on cardiovascular function1-4.

At present, the most widely used therapy for ascites in patients with cirrhosis is low sodium diet and diuretics. This treatment, however, is not entirely satisfactory. Because profound diuresis in these patients often associated with renal impairment, electrolyte disturbances, and hepatic encephalopathy, it is generally recommended that diuretic dosage should be adjusted to produce a loss of body weight of about 500 g/day5-9. This means that the mobilization of a tense ascites requires a prolonged hospital stay in most cases. In addition, despite long-term diuretic treatment, a high proportion of these patients have to be read mitted several times during the course of the disease because of reaccumulation of ascites. Finnally 20% cirrhotics with ascites admitted to a general hospital do not respond to diuretics10. It is not surprising, therefore, that alternative methods for the treatment of ascites are currently being investigated by several groups.

Paracentesis, the oldest form of therapy for ascites, is a rapid and effective treatment of this complication. This procedure was after the introduction of the modern diuretics because it was generally considered at that time that it could induce serious complications, such as bacterial peritonitis, sever hypovolemia, renal failure, hyponatremia, protein depletion, and hepatic encephalopathy3,11-15. However, recently, it has shown that repeated large-volume parasentesis (4-6 L/day until disappearance of ascites) associated with intravenous (i. v.) albumin infusion (40 g after each tap) a) is more effective than conventional diuretic, b) is associated with a lower incidence of complications, and c) considerably shortens the duration of hospital stay16,17. They also performed a comparative study with and withouth albumin infusion, demonstrating that plasma volume expansion is necessary to avoid renal and electrolyte complications and activation of vasoactive hormones18.

Considering these conflicting findings and the high cost of albumin, we performed this study to evaluate:

1- The hemodynamic effects and renal and hepatic function after removing large volumes of ascites,

2- Whether dextran-70, an inexpensive volume expander, could be safaly used in cirrhotic patients with tense ascites to prevent the side effects of paracentesis.

MATERIALS and METHODS

The study was made in 10 patients admitted for the treatment of ascites in the Hospital of Ondokuz Mayıs University. The criteria used to admit patients into the study were the following: a) cirrhosis with tense ascites (diagnosis of cirrhosis was based on liver histology and on clinical and laboratory data, b) no clinical, laboratory, or echographic data suggesting hepatocellular carcinoma, c) absence of hepatic encephalopathy, gastrointestinal hemorrhage, or infection at entry, d) serum bilirubin <10 mg/dl, e) prothrombin time >40%, f) platelet count >40.000/mm3, g) serum creatinine <3 mg/dl, h) urinary sodium excretion <10 mEq/day. The etiology of cirrhosis was postnecrotic and hepatitis B surface antigen-associated in all patients.

After admission to the hospital patients were given a diet containing 50 mEq/day of sodium. In patients with hyponatremia (serum sodium <130 mEq/L) water ingestion was restricted to 500 ml/day. During the first 5 days patients did not receive diuretics. The urine volume was collected to measure electrolytes. The blood samples were taken to measure serum electrolytes, blood urea nitrogen (BUN), serum creatinine, and standard liver fonction tests. The cardiac index was measured by doppler ultrasound (Toshiba SAI-50-A). All these measurements were repeated within the first 48 h after the treatment. Methods used for these investigations have been previously described19-21. The patients who were treated with paracentesis (4-6 L/day) until disappearance of ascites were administered dextran-70 containing 6 g of dextran-70 per 100 ml saline isotonic solution (Macrodex-Eczacıbaşı Pharm. Co. Turkey) was given in an amount enough to obtain the same volume of paracentesis.

Tablo I: Clinical data of the patients.

Age(year)	51.8 ± 4.3
Sex (F/M)	
Cirrhosis (post-necrotic)	4/6
HBsAg+	10
Spider	10
Jaundice	9
Palmar erythem	10
Dupuytren contracture	3
Wight naile	3
Ginecomasty	22
Testicular atrophy	1
Hepatomegaly	0
Splenomegaly	10
Pretibial edema	8

Paracentesis was performed under local anesthesia in the left lower abdominal quadrant. Once the needle entered the peritoneal cavity, the inner part was removed. The duration of most paracentesis ranged from 20 to 30 min. After each tap, patients reclined for 2 h on the side opposite the paracentesis site to prevent leakage of ascitis fluid. Samples of ascitic fluid were routinely taken during each paracentesis for cell count, biochemical examination, and cultures. Body weight and urine volume were determined daily in all patients.

Once ascites had disappeared, patients were discharged from the hospital with diuretics to prevent recurrence of ascites and were followedclosely in the out patient clinic. Patients in whom tense ascites developed during follow-up were readmitted to hospital and treated according to their initial schedule.

In analyzing complications during the first hospitalization, a patient was considered to develop renal impairment when there was a 50% increase in serum creatinine up to a level > 1.5 mg/dl, hyponatremia when there was a decrease in serum sodium > 5 mEq/L to a level below 130 mEq/L, and hyperkalemia when serum potassium increased >1.5 mEq/L to a level above 5.5 mEq/L.

The analysis of the results were performed student's t-test. results were given as mean ± SEM.

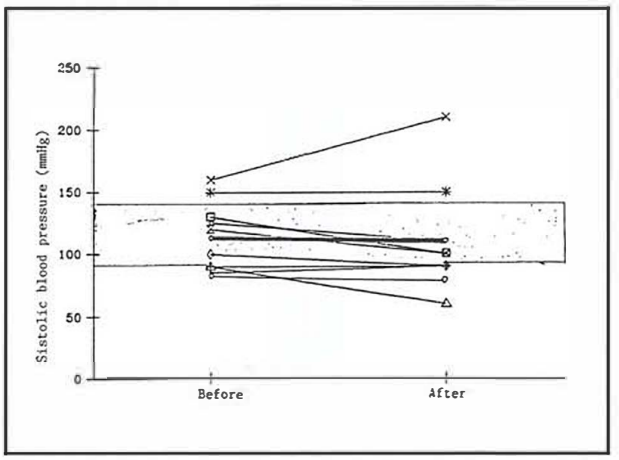

Figure 1. Sistolic blood pressure values before and after large-volume paracentesis plus i.v. dextran-70 administration.

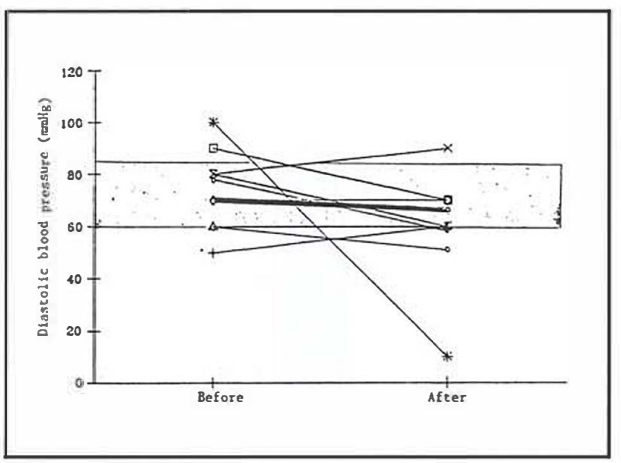

Figure 2. Diastolic blood pressure values before and after large-volume paracentesis plus i.v. dextran-70 administration.

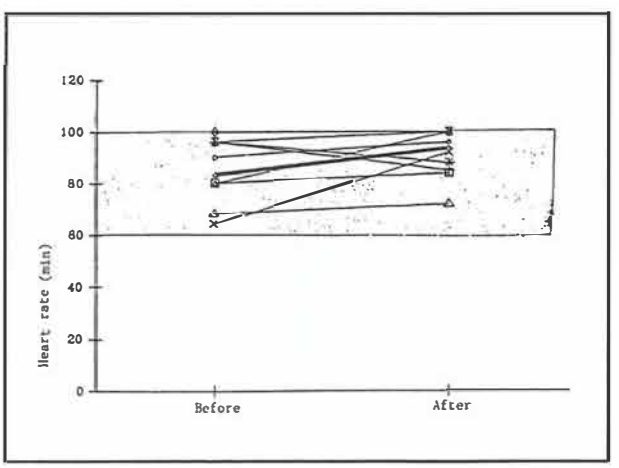

Figure 3. Heart rate values before and after large-volume paracentesis plus i.v. dextran-70 administration.

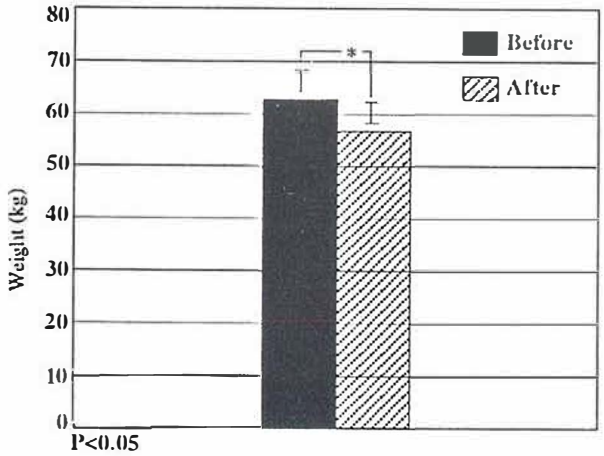

Figure 4. Weight values before and after large-volume paracentesis plus i.v. dextran-70 administration.

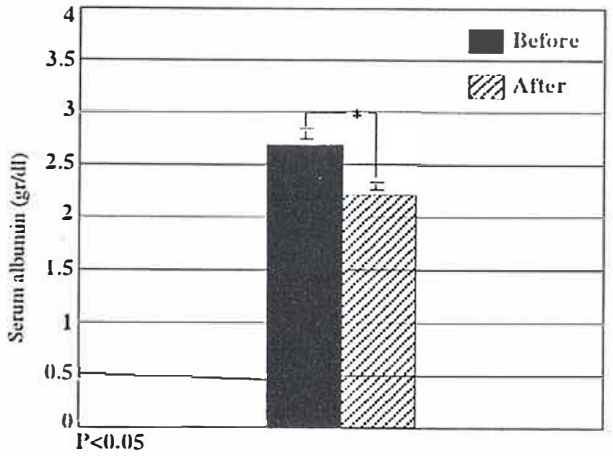

Figure 5. Serum albumin values before and after large-volume paracentesis plus i.v. dextran-70 administration.

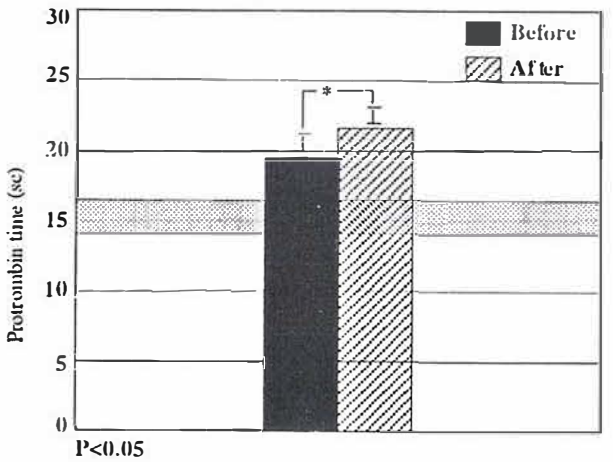

Figure 6. Protrombin time values before and after large-volume paracentesis plus i.v. dextran-70 administration.

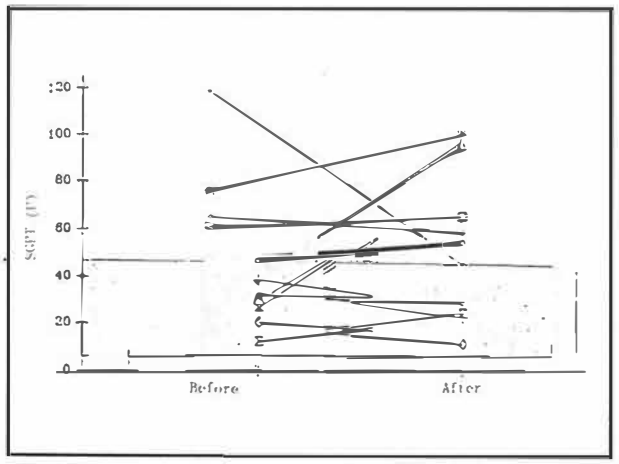

Figure 7. Change of serum SGPT values before and after large-volume paracentesis plus i.v. dextran-70 administration.

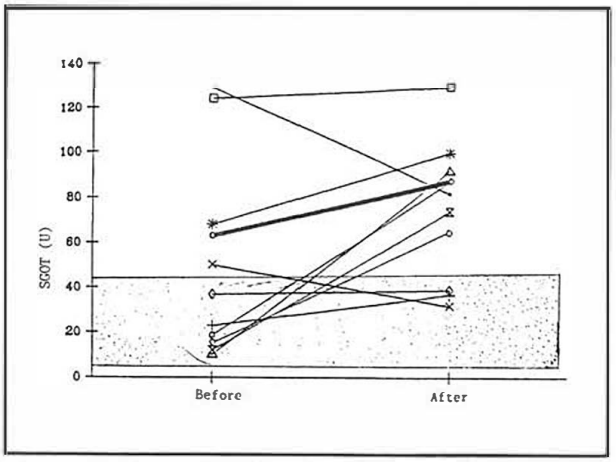

Figure 8. Serum SGOT values before and after large-volume paracentesis plus i.v. dextran-70 administration.

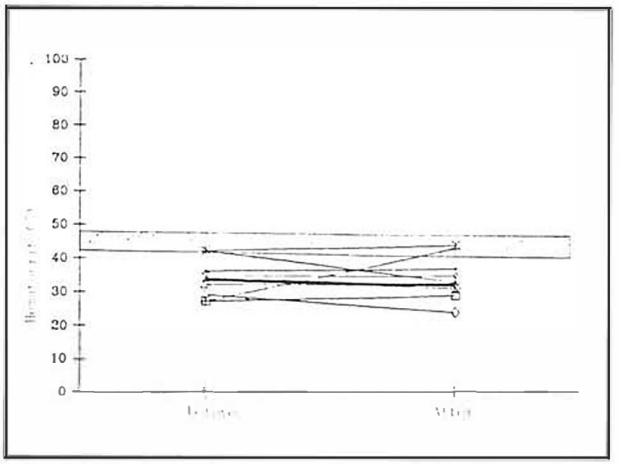

Figure 9. Hematocrite values before and after large-volume paracentesis plus i.v. dextran-70 administration.

Table II: Laboratory values before and after large-volume paracentesis plus i. v. dextran-70 administration.

	Before	After	P
SBP (mmHg)	110.5 ± 8.87	109 ± 12.77	NS
DBP (mmHg)	70 ± 5.37	68 ± 4.89	NS
Heart rate (min)	84.8 ± 4.57	89.3 ± 3.51	NS
Weight (kg)	63.45 ± 3.82	58.35 ± 3.91	0.001
Protrombin time (Sc)	19.8 ± 1.19	22.1 ± 1.53	0.04
Parsial tromboplastin time (sc)	38.4 ± 1.99	42.2 ± 3.15	NS
Albumin (gr/dl)	2.71 ± 0.19	2.18± 0.12	0.001
Globulin (gr/dl)	4.13 ± 0.36	4.22± 0.34	NS
BUN (mg/dl)	1.09 ± 0.17	1.04± 0.05	NS
Creatinin clerence (ml/dl)	17.8 ± 1.53	16.7± 1.78	NS
Serum sodium (mEq/L)	69 ± 4.49	65.2± 6.23	NS
Serum potassium (mEq/L)	136.7 ± 1.23	132.2± 1.43	0.008
Hematocrit (%)	4.34 ± 0.24	4.31± 0.22	NS
SGOT (U)	32 ± 1.81	33± 0.01	0.01
SGPT (U)	53.8 ± 1.81	66.7± 9.74	NS
Bilirubin (mg/dl)	47.6 ± 10.34	54.5± 10.6	NS
EF (%)	2.04 ± 0.44	2.9± 1.11	NS
CO (lt/min)	65 ± 1.76	66± 3.22	0.03
CI (Co/m^2)	4.78 ± 0.43	6.12± 0.64	0.019
	2.94 ± 0.28	3.78± 0.40	0.08

SBP: Sistolic blood pressure
DBP: Diastolic blood pressure
EF: Ejection fraction
CO: Cardiac output
CI: Cardiac index

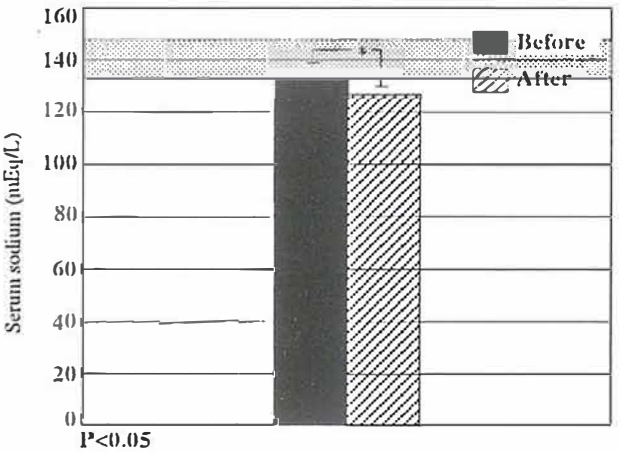

Figure 10. Serum bilirubin values before and after large-volume paracentesis plus i.v. dextran-70 administration.

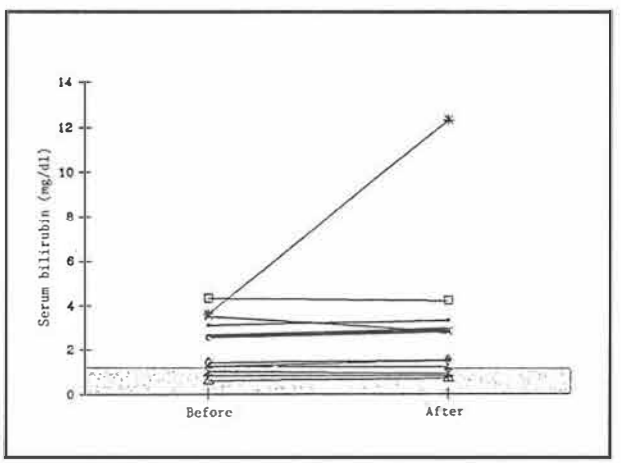

Figure 11. Serum sedium values before and after large-volume paracentesis plus i.v. dextran-70 administration.

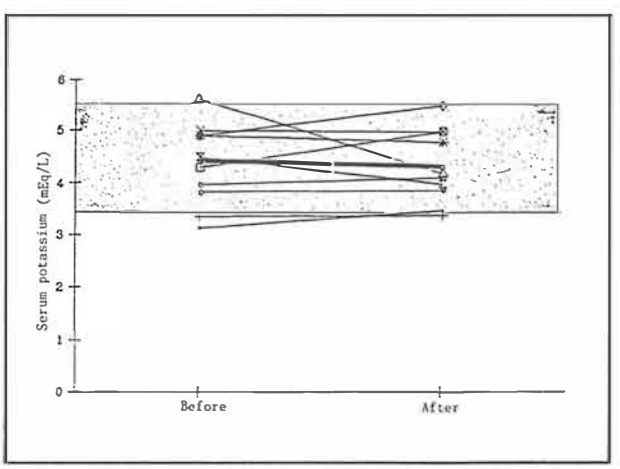

Figure 12. Serum potassium values before and after large-volume paracentesis plus i.v. dextran-70 administration.

RESULTS

Of the 10 patients 6 were men and 4 women. The mean age was 51.8±4.3 years (range (18-65). The etiology of cirrhosis was postnecrotic and hepatitis B surface antigen associated in all patients. No patient associated with renal failure. Table 1 and 2 shows the clinic data liver and renal function tests. The mean volume of ascites removed was 5.85±0.56 liters (range 4-9) per patient. Dextran 70 administration was 42.6 ± 4.3 gr (range 30-60), the mean paracentesis time was 173 ± 29.8 minutes (range 120-210).

Twenty hours later after large volume paracentesis with administration of 42.6 ± 4.3 gr of dextran-70, decreased significantly in the weight (from 63.45 ± 3.82 to 58.35 ± 3.91 kg, p<0.001)

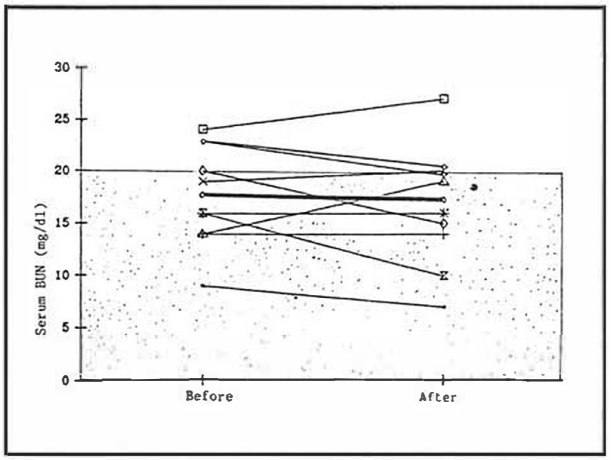

Figure 13. Serum BUN values before and after large-volume paracentesis plus i.v. dextran-70 administration.

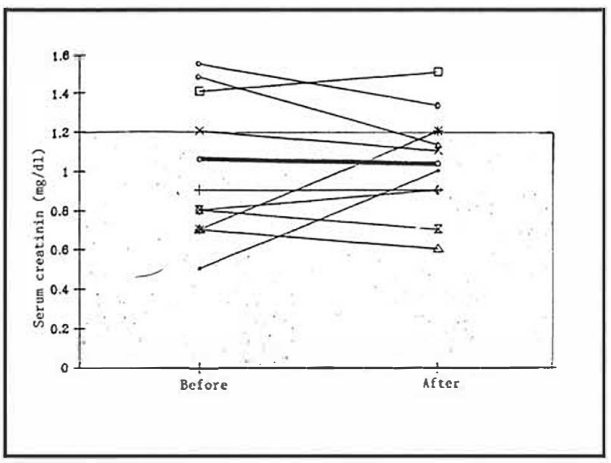

Figure 14. Serum creatinine values before and after large-volume paracentesis plus i.v. dextran-70 administration.

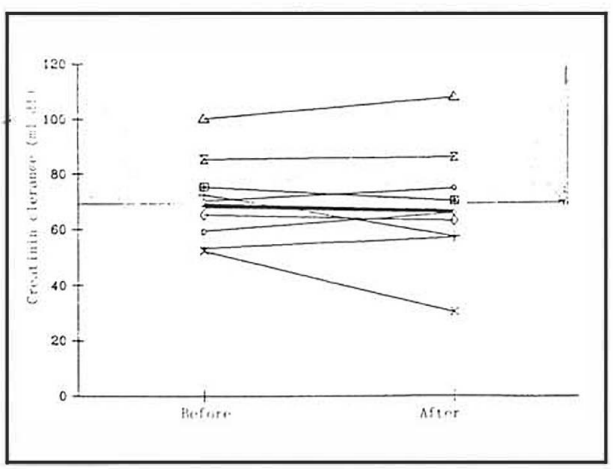

Figure 15. Creatinine clearance values before and after large-volume paracentesis plus i.v. dextran-70 administration.

albumin (from 2.71 ± 0.15 to 2.18 ± 0.12% gr, p<0.001), serum sodium (from 136.7 ± 1.23 to 132.2 ± 1.03 mEq/L, p<0.008), Prothrombin time (from 19.8 ± 1.19 to 22.1 ± 1.53 sc, p<0.04), cardiac output and index increased from 4.78 ± 0.43 to 6.12 ± 0.64 lt/min, p< 0.005 and from 2.94 ± 0.28 to 3.78 ± 0.40 Co/m2, p<0.008) respectively. No significant changes in renal and hepatic functions were observed at the end of the study. In two patients developed hyponatremia that required no treatment. No developed renal failure. One patient died due to anaphlactic shock of dextran-70.

There were no local complications related to the procedure in patients. In one patients ascitic fluid leaked from the puncture hole for several hours after the paracentesis. All of these results were demonsrated in Figures 1-18.

DISCUSSION

For many centuries paracentesis had been the only treatment that could be offered to patients with cirrhosis and ascites22. This procedure, however, was abandoned about 30yr ago concomitantly with the introduction of the modern diuretics. Reasons for this change were the effectiveness of these drugs in mobilizing ascites and the feeling that the abrupt decrease of intraabdominal pressure induced by large-volume paracentesis could be followed by a rapid reaccumulation of ascites, acute reduction of intravascular volume, renal failure, electrolyte disturbances, and hepatic encephalopathy23. Several studies reporting the occurence of these complications in patients treated with paracentesis contributed to the progressive abandonment of the procedure3,11-15,24,25. Currently, however, arguments against large-volume paracentesis do not appear as strong as in the past. The assumption that paracentesis adversely affects systemic hemodynamics and renal function in patients with cirrhosis has never been substantiated by carefully controlled prospective investigations. Therefore, it is not clear whether complications originally attributed to paracentesis were caused by this procedure or by coincidental events. In fact, some investigations per-

formed during the last three decades da not support the claim that large-volume paracentesis adversely affects systemic and renal hemodynamics in these patients2,26-30. One the other hand, from the current view of the pathogenesis of ascites, it is difficult to accept that intraabdominal pressure is of major importance in determining the rate of ascites formation31,32. Finally, diuretic therapy in cirrhotic patients is also associated with a substantial risk of adverse effects7. These considerations led us to compare paracentesis and diuretics in the treatment of cirrhotics with tense ascites.

Our results indicate that dextran-70 administration after removing of ascites, cirrhotic patients develop a significant increased cardiac output, and cardiac index.

Most of the hemodynamic studies performed in cirrhotic patients after paracentesis have shown conflicting results. However, since the amount of ascites removed varied from 1.5 to 15 liters and the hemodynamic observation were performed at different times after the paracentesis, it is not possible to compare the results obtained in those studies1,2,33,34. Several studies have shown an improvement on cardiac output within 3 hr of paracentesis, while the pulmonary capillary pressure dropped or remained unchanged34,35. It has been suggested that this improvement in cardiac output may be due to a decrease in cardiac transmural pressure brought on by the relief of intraabdominal pressure after paracentesis35.

Recently, Panos et al observed a compression of the right atrium before paracentesis in patients with large volume of ascites studied by two-dimensional echocardiography compared to patients with minimal ascites34. In this study the improvement of cardiac output was transient, because cardiac output and pulmonary capillary wedge pressure started to decrease progressively 3hr after paracentesis reaching the lowest level at 12 hr34. A similar decline of cardiac output and pulmonary capillary pressure after 1 hr of paracentesis was observed in the study of Simon et al35. In both studies these parameters kept declining at least until 24 hr after paracen-

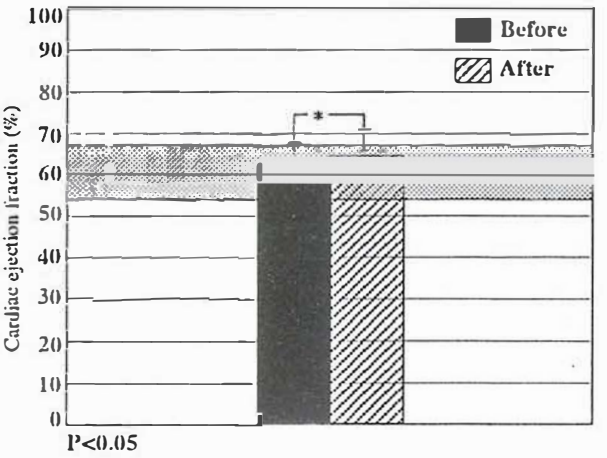

Figure 16. Cardiac ejection fraction values before and after large-volume paracentesis plus i.v. dextran-70 administration.

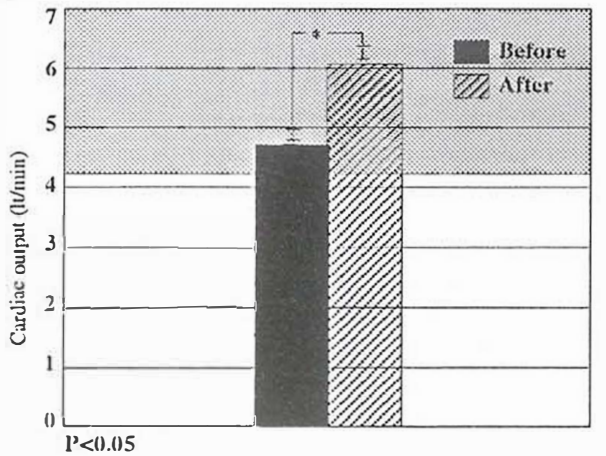

Figure 17. Cardiac output values before and after large-volume paracentesis plus i.v. dextran-70 administration.

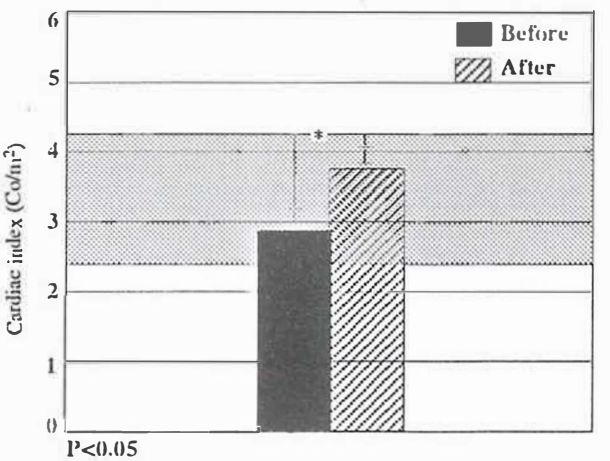

Figure 18. Cardiac index values before and after large-volume paracentesis plus i.v. dextran-70 administration.

tesis. Dextran 70 was then administered to avoid renal impairment. In this regard, the study of Simon et al showed an increase in plasma renin and a decrease in creatinine clearance 24hr after paracentesis without expansion35. Moreover, Gines et al reported hyponatremia and renal failure in patients after paracentesis without albumin administration36. However, despite this clear observation showing the need of albumin in large volume paracentesis, its high cost limits its use.

Dextran 70 is a polysaccharide consisting of glucose molecules with different molecular weights fractions and this mixture ranges between 15.000 and 160.000 daltons37. About 45-60% of dextran 70 administered is recovered in the urine within 48 hr and the rest is metabolized by dextranase in liver, spleen, kidney, and lung or eliminated through the gastrointestinal tube38,39. Recently, in a randomized, controlled trial performed by Planas et al, 88 cirrhotic patients with tense ascites were treated with total paracentesis and dextran 70 versus total paracentesis and albumin intravenously40. The incidence of renal impairment, hyponatremia, or hepatic encephalopathy after paracentesis were similar in both groups of patients. However, the effects of paracentesis on effective intravascular volume as measured by plasma renin activity and aldosterone concentration showed a significant increase on the sixth day in 51% of patients treated with dextran 70 and in 15% of those treated with albumin. The authors suggest that this difference may be due to human serum albumin's larger half-life elimination compared to dextran 70. In normovolemic healthy subjects and in patients with normal glomerular filtration rate, the elimination half-life of dextran 70 ranges between 23 and 25.5hr37 and 1.8 days41. However, these values may represent only the initial decline and refer to drug distribution and the elimination of fractions with lower molecular weight. Since dextran 70 has been detected in the circulation after six weeks, the true elimination half- life may be much longer37. The elimination half-life of human serum albumin in patients with cirrhosis and ascites is about 21 days42,43, but is unknown in the case of dextran 70 administered to patients with chronic liver disease and ascites. Nevertheless, as the incidence of complications found in our study and in the Planas study was low, the true clinical significance of the rise in plasma renin activity and aldosterone concentration in these patients needs further investigation. No side effects of dextran 70 in patients with liver disease have been reported. A decrease in factor VIII and platelet alteration has been found in patients receiving dextran 70 in doses above 1-1.5 g/kg/day and has been shown both experimentally and clinically to reduce the frequency of postoperative thromboembolic complications41,44,45.

In the present study one patient died during the study due to anaphlactic reaction of dextran-70 administration. Albumin and dextran appeared to be equally safe. There was no difference with respect to anaphylactic reactions. Of the three commonly used colloids hydroxyethyl storch has the highest incidence of total anaphylactoid reactions (0.085%), followed by albumin (0.011%), anddextran with haptid (0.03%)46.

In summary, the results of the present study indicate that in cirrhotic patients repeated large-volume paracentesis associated with intravenous dextran 70 infusion does not adversely affect systemic hemodynamics, renal and hepatic function and clinical outcome in terms of readmission to hospital and servivala. This therapeutic procedure is more effective than conventional diuretic treatment, is associated with a lower incidence of complications, and considerably shortens the duration of hospital stay.

The administration of approximately 100 ml of dextran 70 for each 100 ml of ascites removed improved these parameters and is complications related to paracentesis.

Finally, the estimated 30 fold reduction in the cost of treatment using dextran 70 instead of albumin appears to be a very important reason for using dextran 70 during therapeutic paracentesis. Although these results strongly suggest that paracentesis and dextran-70 administration should be considered as treatment of choice in cirrhotic patients with tense ascites, further controlled studies should be performed before advocating its wide-pread use.

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