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Original Article

Large Volume Paracentesis in Patients with Liver Cirrhosis Temporarily Diminishes Blood Cell Count

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What's Known

- Large-volume paracentesis is one of the safest and most effective treatment options for severe and resistant ascites. It might be associated with several complications, including ascites fluid recurrence, intraperitoneal hemorrhage, circulatory dysfunction, and hepatorenal syndrome, and may shorten life expectancy. Some of these complications require particular intervention, while others resolve on their own.

What's New

- After large-volume paracentesis, we observed a significant decrease in blood cells. Without any intervention, this transient physiological condition began to restore 48 hours after the surgery.
- There is no need for unnecessary testing and patient annoyance, which minimizes related healthcare expenditures.

Abstract

Background: Large-volume paracentesis is the preferred treatment for patients with severe and refractory ascites. Several complications were reported during therapeutical paracentesis. However, there are very few published studies on the change in blood cell count after paracentesis. This study aimed to evaluate any changes in blood cell counts after ascites fluid drainage.

Methods: This study was conducted on patients with severe ascites and chronic liver disease who underwent large-volume paracentesis at Namazi Hospital, in Shiraz, Iran, between March 2021 and February 2022. A data gathering form containing the patient's medical history, cause of cirrhosis, ascites fluid volume, as well as routine tests including primarily sodium, potassium, and basal creatinine, was filled out. Before and after the surgery, the total blood cell count was measured. Before the procedure, adjustment was made in the case of coagulopathy and albumin deficiency. The effect of factors such as the volume of drained fluid, splenomegaly, antibiotics, and steroid use was assessed on the changes in the number of blood cells. Using the JAMOVI 2.3.9 software, a paired *t* test and multiple regression were applied for statistical analysis ($P<0.001$).

Results: The study included 37 patients. After the paracentesis procedure, the number of blood cells significantly decreased in all groups ($P<0.001$). The followings are the amounts of each type of blood cells before and after the procedure: Platelet=153837±91862 and 115648±69136, red blood cells=3.53±0.784 and 3.22±0.705, white blood cells=12.3±7.78 and 8.6±5.5. None of the study variables, including drained volume, splenomegaly, antibiotics, and steroid use, were significant predictors of the changes in the blood cell count after paracentesis ($P>0.001$).

Conclusion: The findings of the present study showed that children with tense ascites who had large-volume paracentesis might experience a sharp drop in blood cell count after the procedure, which was a transient physiological condition.

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Keywords ● Child ● Paracentesis ● Ascites ● Fibrosis ● Blood cells

Introduction

Cirrhosis-related ascites are a common complication in both children and adults. Management of ascites includes salt and

fluid restriction, diuretics, implantation of a portosystemic shunt, and ultimately, liver transplantation. Large-volume paracentesis (LVP) is one of the safest and most effective treatment options for tense and refractory ascites.[1] Ascites in patients who have respiratory distress, abdominal pain, or distension are considered tense ascites.[2] Wenger and colleagues performed the first pediatric paracentesis to diagnose peritonitis;[3] and it was later used to differentiate urinary, cardiac, traumatic, and chylous ascites.[4] There are several causes of ascites in fetuses, infants, and children, including non-cirrhotic hepatic causes, non-cirrhotic non-hepatic causes, and cirrhosis. Budd-Chiari syndrome and congenital liver fibrosis are among the causes of the first category. The second group comprises peritoneal infections, intestinal diseases such as Crohn's disease, pancreatic diseases namely acute pancreatitis, metabolic disorders, and malignancies.[5] The prevention and treatment of infection, sodium consumption restriction, diuresis, intravenous albumin administration, surgical shunts, paracentesis, and liver transplantation are just a few of the methods used to manage ascites. The treatment options, including the drugs and surgical procedures that are used for a patient with ascites, are determined by the etiology of the underlying disease.[6]

Paracentesis is one of the diagnostic and therapeutic procedures used in children and adults to diagnose the etiology of ascites.[4] The diagnostic paracentesis includes the counting of neutrophils or red blood cells (RBCs) to detect infection, and trauma, as well as measuring amylase to diagnose pancreatitis and small intestinal perforations conducted during diagnostic paracentesis.[7] Therapeutic paracentesis is frequently performed when a patient has diuretic-refractory ascites or a substantial volume of ascites has caused significant pain or respiratory distress. Reducing the volume of ascites increases the patient's appetite, which leads to better regulation of nutritional requirements.[8]

Therapeutic paracentesis may cause several complications, such as ascites fluid deaccumulations, circulatory dysfunction, and hepatorenal syndrome, all of which reduce life expectancy.[5] In addition, intraperitoneal hemorrhage caused by mesenteric varicose veins bleeding is a life-threatening complication, with about 70% mortality rate in adults.[9] To the best of our knowledge, there is very little evidence of changes in the blood cell count after therapeutic paracentesis in children (only one study was reported).[10] Therefore, additional research is required to evaluate various variables and compare the findings with the previous studies. This study aimed to investigate the changes in the blood cell counts after LVP to identify effective approaches for preventing unnecessary testing after paracentesis. The results of this study can be beneficial in developing more effective regulations and guidelines for paracentesis therapy in children in the future, preventing potentially detrimental attempts during the treatment and minimizing related healthcare expenditures.

Patients and Methods

Study Design, Setting, and Patients

This study was conducted on patients with tense ascites and different etiologies of cirrhosis between March 2021 and February 2022 at Namazi Hospital, Shiraz, Iran. All the patients who were admitted throughout the study period and met the study criteria were included in the study. Generally, a small percentage of the patients had these complications, and due to the COVID-19 pandemic, the number of patients was considerably fewer. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.sums.med.rec.1400.373). Written informed consent was obtained from all the patients or the patients' parents/guardians.

For this study, all children under the age of 18 with tense ascites who required paracentesis were included. Based on previous studies,[4, 11, 12] patients with unstable hemodynamics, extrahepatic portal venous obstruction, those taking beta-blockers, clinically apparent disseminated intravascular coagulation, surgical scars at the proposed paracentesis site, primary fibrinolysis, overt systemic infection, pre-existing renal failure at the initial evaluation (recorded by raised serum creatinine levels appropriate for age), massive ileus with bowel distention, and gastrointestinal bleeding in the last two weeks were excluded. According to the recommendations from another study,[4] LVP was terminated in case of hemorrhagic tap, developing hemodynamic instability necessitating resuscitation (systolic drop ≥20 mmHg with or without delayed capillary filling time >3 sec), or worsening of the previous grade of encephalopathy during the procedure.

After patients' admission, they underwent screening in accordance with the LVP inclusion criteria. If they met the inclusion criteria, they were considered for further evaluation. Before performing paracentesis, a data gathering form containing the patient's medical history, cause of cirrhosis, ascites fluid volume, and routine tests

such as sodium, potassium, and basal creatinine was filled out. A sample data-gathering form was provided in appendix 1.

Large-volume paracentesis is the removal of ascitic fluid as much as possible to relieve the symptoms of a tense abdomen and dyspnea.[13] The volume of ascitic fluid, which can be safely removed, was not documented in any children's literature.[4] Thus, in the present study, paracentesis was performed as "tap to dry" provided that the patients' initial degree of encephalopathy did not worsen during the procedure, or there was no indication of hemodynamic instability necessitating resuscitation and hemorrhagic tap. Tap to dry means the ascites fluid is drained entirely. Based on the inclusion and exclusion criteria, 37 patients were included for paracentesis, and the number of paracentesis sessions was recorded for each patient. Before the procedure, albumin, international normalized ratio (INR), and prothrombin time (PT) were all regularly tested. Based on a previous report, all patients with platelets >19000 or INR<8.7 underwent LVP.[14] In the present study, the patients' pre-treatment minimum platelet count was 34000, and the maximum INR level was seven. Both before and after the paracentesis, the complete blood count (CBC) was assessed. Albumin (human Albumin 20% CSL, Behring Injection, Germany) at a dose of 0.5 to 1 g/Kg dry bodyweight was administered, and furosemide (20 mg/2 mL, Alborz Darou Co., Iran) was supplied at the initial dose of 1 mg/Kg with an increase up to 4 mg/Kg only for patients with hypoalbuminemia. Furosemide 1 mg/Kg was administered as the initial dose and was then increased (up to 4 mg/Kg) based on the blood Albumin level before paracentesis or having peripheral edema. According to previous studies, spironolactone (Aburaihan Pharmaceutical Co., Iran) was administered daily at 0.5 to 1 mg/Kg in infants and 1 to 3 mg/Kg in older children. Every 5-7 days, the dose may need to be increased to a dose of 2 mg/Kg and a maximum dose of 4 mg/Kg.[15-17] To prepare 1 mg/mL suspension, spironolactone tablets (25 mg) were crushed and dissolved in 25 mL of deionized water. For each patient, the appropriate dose was administered as previously mentioned. For individuals with peripheral edema, a combination of spironolactone and furosemide was administered (12 patients). For those with low albumin levels, albumin, spironolactone, and furosemide were administered (24 patients). One patient received only spironolactone. Antibiotics were administered to 27 patients. According to the prescribed dosage, the patients received metronidazole (solution parenteral 5mg/1mL, Samen Pharmaceutical Co., Iran), cefotaxime (sterile powder for injection, Exir Pharmaceutical Co., Iran), and vancomycin (sterile powder for injection, Exir Pharmaceutical Co., Iran).

A low sodium diet (44-88 mEq/day in adolescents and 1-2 mEq/Kg/day in younger children) was maintained for the patients. The procedure was explained to the patients and their caregivers. Then, paracentesis was performed in the supine position under local anesthesia with lidocaine cream 2.5% (Aburaihan Pharmaceutical Co., Iran) using a fenestrated stainless-steel gauge 15 (B BRAUN, Germany) by the "Z technique" in the infra-umbilical area. Vital signs were monitored before, during, and after the procedure.

The following items were recorded for each patient: Fluid characteristics (including appearance), cell count diff, albumin, culture, and antibiogram, diuretics doses, pedal edema, history of chronic liver disease, serum sodium (mEq/L), serum potassium (mEq/L), total serum bilirubin (mg/dL), serum albumin (g/dL), INR, Child-Pugh score (A/B/C), pediatric end-stage liver disease (PELD score), the model for end-stage liver disease (MELD score), the volume of ascites extracted (mL/Kg), and ascitic fluid infection after the procedure. The comparison of blood cell count before and after paracentesis was the primary outcome for statistical analysis and the final report.

CBC was performed for all patients before paracentesis, as well as six hours, 24 hours, and 48 hours after the procedure. Several essential parameters that might be involved in cell reduction such as steroids, which were administered in chronic liver disease especially due to autoimmune hepatitis, were evaluated.[18] Splenomegaly is a cirrhotic condition that causes splenic sequestration and thrombocytopenia.[19] In addition, antibiotics were frequently prescribed to cirrhotic patients for suspected infections such as spontaneous bacterial peritonitis.[20, 21] Therefore, the changes in the blood cell count were recorded and compared with variables such as the volume of fluid that was drained, splenomegaly, antibiotics administration, and steroid administration. According to the study variables, the patients were divided into four groups: corticosteroid use, splenomegaly, antibiotic administration, and none of the above variables (Group N).

Statistical Analysis

For statistical analysis, JAMOVI 2.3.9 software was used. Data were expressed as mean±SD. The results of the paracentesis

were compared using a paired *t* test. P<0.001 indicated a significant difference in the group. Multiple regression was employed to investigate, whether the study variables could be the predictors of the outcomes (all the variables were entered simultaneously); P>0.001 indicated a non-significant predictor.

Results

Of 77 patients admitted to our hospital with ascites, 42 patients had tense ascites. Five patients were excluded from the study based on the exclusion criteria. Finally, 37 patients aged between 2.5 months to 18 years old underwent the LVP procedure. In this study, the five categories of liver disease etiologies were as follows (figure 1). History of chronic liver disease was evaluated in all the patients. Six patients had MELD (23.8±10.6), and 31 patients had PELD (36.4±11.9). These results indicated that all patients were classified as child-pugh class C with no evidence of specific contra-indications for LVP after paracentesis. Antibiotics were given to 27 patients. One patient had a positive blood culture, and 26 patients (70.3%) had spontaneous bacterial peritonitis (SBP).

All patients with a value of INR up to 8.7 underwent LVP. Before the tap, the patients' total bilirubin level was 0.5-43 mg/dL (18.2±10.5). The K^+ concentration was 3.4-5.4 mEq/mL (4.18±0.54), and the Na^+ was 115-146 mEq/mL (134.2±6.8). The drained fluid volume was 11.2-212 cc/Kg (77.03±50.8). Since the drained fluid accounted for more than 10% of each patient's body weight, all of the patients in our study received therapeutical paracentesis. The total volume ranged from 100-4200 cc (1136±1.35).

After the surgery, blood cells significantly decreased in all groups. However, their count began to restore 48 hours post paracentesis (table1 and figures 2, 3, and 4). Based on the multiple regression P values, none of the study variables, including the volume of drained fluid, splenomegaly, antibiotics, and steroid use, was a significant predictor of the procedure outcomes, i.e. change in the number of blood cells after paracentesis (table 2). Although these variables could temporarily affect the blood cell count, the correlation was not statistically significant.

Discussion

The primary aim of this study was to assess the effects of therapeutic paracentesis with different variables on the number of blood cells in children

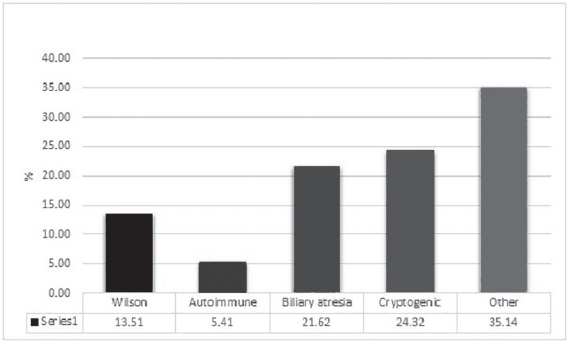

Figure 1: The figure shows the liver disease etiologies in this study.

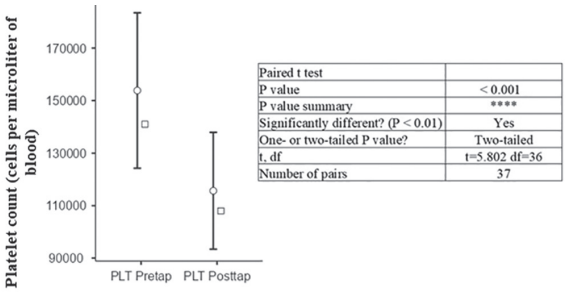

Figure 2: The graph illustrates the difference in platelet count pre- and post-paracentesis.

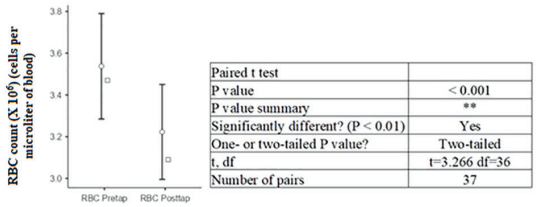

Figure 3: The graph depicts the difference in red blood cell (RBC) count pre- and post-paracentesis.

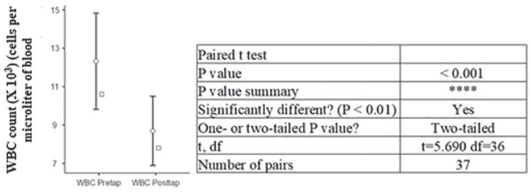

Figure 4: The graph depicts the difference in white blood cell (WBC) count pre- and post-paracentesis.

Table 1: The complete blood count (CBC) analysis before and after large-volume paracentesis

Variable	Before paracentesis (n=37) mean±SD	After paracentesis (n=37) mean±SD	P value
Platelet count (cells per microliter of blood)	153837±91862	115648±69136	<0.001
RBC count (×10^6, cells per microliter of blood)	3.53±0.784	3.22±0.705	<0.001
WBC count (×10^3, cells per microliter of blood)	12.3±7.78	8.6±5.5	<0.001

Paired *t* test analysis was performed. P<0.001 was statistically significant.

Table 2: The results of multiple regression analysis with all study predictors entered simultaneously

Predictor	Estimate			SE			t			P		
	Platelets count (cells per microliter of blood)	RBCs count (cells per micro-liter of blood)	WBCs count (cells per micro-liter of blood)	Plate-let	RBC	WBC	Platelet	RBC	WBC	Plate-let	RBC	WBC
Volume of drained ascites fluid (mL)	-1.13	2.56e-4	2	146	0.00222	1.5061	-0.0078	0.115	1.3248	0.994	0.909	0.195
Antibiotics	23052.49	-0.0439	2.23e-4	15641	0.23816	0.014	1.4739	-0.185	0.0159	0.15	0.855	0.987
Splenomegaly	-5935.16	0.0752	-2	16943	0.25798	1.6315	-0.3503	0.291	-1.2234	0.728	0.773	0.23
Steroids	-39958.26	-0.2309	-4.75	33540	0.51069	3.2297	-1.1914	-0.452	-1.4703	0.242	0.654	0.151

The outcomes are A) Platelets count, B) red blood cells (RBC) count ($\times 10^5$), and C) white blood cells (WBC) count ($\times 10^3$). P>0.001 indicates a non-significant predictor. SE indicates the Standard Error.

with different etiologies of ascites. The findings of this study confirmed that all blood cells decreased significantly during the first hours following paracentesis, and their counts began to restore 48 hours post-procedure.

LVP is considered a safe and effective treatment for ascites in cirrhotic patients with cirrhosis receiving albumin therapy.[1, 22] Kramer and others found that the amount of fluid removed during LVP in pediatric patients aged six months to two years was approximately 118±56 mL/Kg over three hours, with no significant adverse clinical complications reported.[4] The side effects of paracentesis therapy were investigated in adults. These complications were classified into two categories including early and late. An earlier study reported that 12% of the complications were early, and 5% were late. The presence of ultrasound, coagulopathy status, and drainage fluid had no impact on the complications.[23] Several studies reported that therapeutical paracentesis in children can cause a variety of complications.[24] Hematocrit, platelet count, and coagulation evaluation (INR, PT) are frequently performed as part of preoperative evaluations. However, no proven evidence exists to support the routine administration of fresh frozen plasma (FFP) or platelets before paracentesis in individuals with coagulation disorders. It is not necessary to start treatment before LVP for INRs as high as 8.7 or platelet counts as low as 19000/mL.[13] Although CBC is routinely tested before LVP, knowing the number of blood cells after LVP is critical for managing complications, especially in patients who require surgeries, invasive procedures, or repeating LVP.

The majority of the information in the literature focuses on other complications such as post-paracentesis circulatory dysfunction (PPCD), which is related to albumin administration. Fluid draining of more than 197.5 mL/Kg is associated with PPCD. If albumin is not prescribed, the fluid extraction rate should be limited to a maximum rate of 680 mL/h and no more than 200 mL/Kg of dry body weight. Otherwise, the patient's risk of PPCD and hyponatremia increases. PPCD were observed in 80% of cases of ascites in adults and increased the mortality rate.[25] Other reported side effects included intestinal perforation, hemorrhage, early paracentesis-induced thrombocytopenia (EPIT),[9, 10, 13] lower epigastric artery pseudoaneurysm,[26] and pulmonary edema,[27] acute cardiovascular events (acute coronary syndrome),[28] and midline varicose veins.[29] Abdominal wall hematoma and peritoneal hematoma are the most common types of bleeding complications after therapeutic paracentesis.[13] PICD is another frequent but hidden unnoticed complication following paracentesis. In patients with cirrhosis and ascites, left ventricular diastolic function is a critical factor, which may lead to premature hepatic cardiomyopathy.[30] Fortunately, none of these complications were observed in patients of the present study.

Research on this subject and its application are still in its infancy. Only one study reported the occurrence of temporary post-paracentesis thrombocytopenia. The researchers claimed that this phenomenon was a transient physiological condition brought on by an alteration in splenic hemodynamics caused by a reduction in post-paracentesis intra-abdominal pressure (IAP) after paracentesis. This condition leads to increased cardiac output, which causes splenic congestion.[10] The findings of the present study indicated that the amount of fluid removed during LVP was not a significant predictor of therapeutical paracentesis. These findings seem to contradict the findings reported by Shah and others.[10] In line

with a previous study,[10] the multiple regression analysis revealed that splenomegaly, antibiotic use, and steroid therapy did not reduce blood cells in our research. It is worth mentioning that among the drugs administered in the current research, metronidazole, and spironolactone might cause pancytopenia in some patients. However, in our study, none of the patients had any of these drugs' adverse effects. In general, a very small percentage of patients experienced pancytopenia caused by the injection of drugs such as metronidazole and spironolactone. In this study, every single patient had a paracentesis-related adverse event. However, we did not rule out the probability of developing pancytopenia in a small number of our patients due to drug administration. Furthermore, the majority of the patients were taking medications before beginning the paracentesis, Therefore, it was included in their baseline CBC. Additionally, the reported pancytopenia was a transient symptom that went away two days after the procedure. Thus, according to all of the aforementioned justifications, the paracentesis procedure caused pancytopenia. Therefore, this phenomenon is not considered the consequence of a pathologic condition or a pharmacological adverse effect. Practitioners who treat patients with chronic liver disease with tense ascites should be aware of this "pathophysiological" condition to avoid unnecessary diagnostic evaluations and patient aggravation following the procedure. These approaches might avoid harmful treatment attempts and minimize the related healthcare expenses. One of the major limitations of this study was the small number of patients due to the COVID-19 pandemic. Furthermore, some patients were unable to endure the procedure properly, which led to an early termination of the treatment process. Therefore, the entire procedure had to be repeated by the care staff.

Conclusion

Our research demonstrated that a sudden decrease in blood cell count after LVP was a transient physiological condition, brought on by a reduction in intra-abdominal pressure, caused by a rise in splenic arterial flow. We hypothesized that this condition led to splenic congestion and consequently increased splenic sequestration of blood cells.

Acknowledgment

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Authors' Contribution

M.H: initial plan, interpretation of data, drafting, and critical revision; M.A: initial plan, interpretation of data, and drafting; N.H: data acquisition and organizing the clinical data before statistical analysis, care for the patients, and drafting; SM.D: study design, interpretation of data, data analysis, and revising the article; M.S: initial plan, interpretation of data, data acquisition, organizing the clinical data before statistical analysis, data analysis, and final revision; SM.MM: initial plan, care for the patients, interpretation of data, data acquisition, organizing the clinical data before statistical analysis, data analysis, and final revision; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Dr. Mohammad Hadi Imanieh, as the Editorial Board Member, was not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the is article without his knowledge.

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