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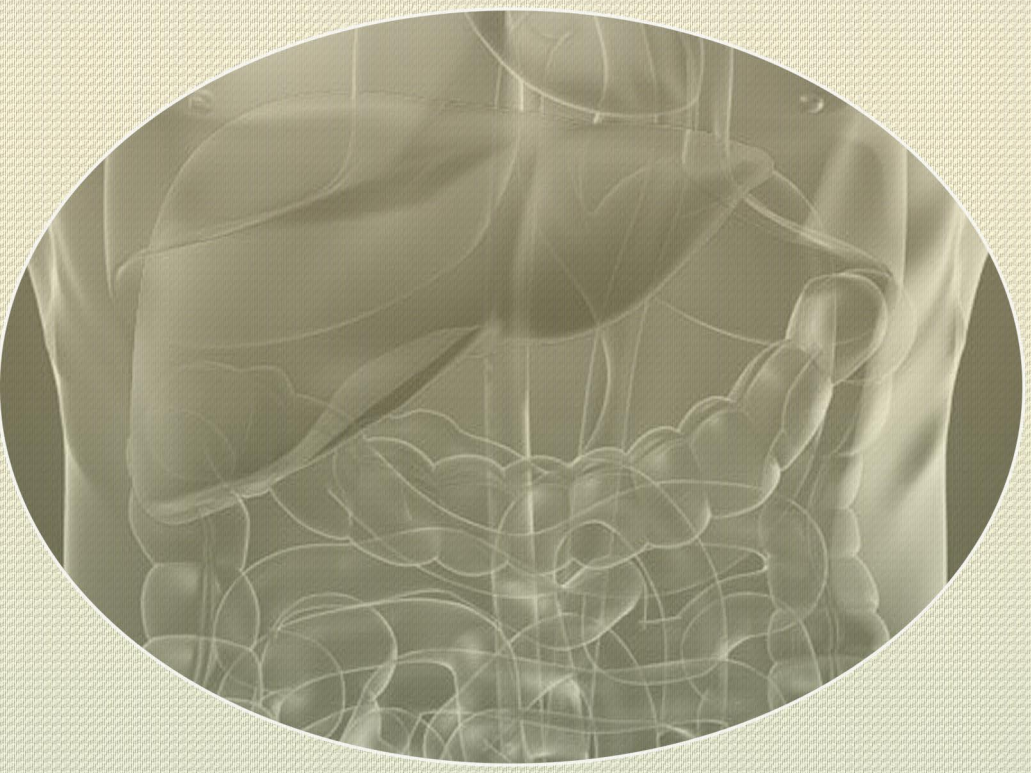

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Editorial

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Hepatitis C Update

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The pace of Hepatitis C Virus (HCV) drug development in recent years has accelerated dramatically. But, for patients to benefit from these impressive advances, practitioners (i.e. "us") need to know the most recent and accurate data on the diagnosis and treatment. In 2013, The American Association for Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA), put together web-based guidelines, which are frequently updated: www.hcvguidelines.org and www.aasld.org/practice-guidelines.[1] The size of the problem: In the USA, the prevalence is 1.8% (4.1 million), 80% of them are viremic. It is the principal cause of death from liver disease. It is the leading indication for liver transplantation in the USA. Although, HCV is a curable disease, it is under-diagnosed and under-treated.[2] Three quarters of individuals with HCV are unaware they are infected. 66-87% of patients diagnosed with HCV have not received antiviral treatment. Screening and diagnosis: 65-69% of anti-HCV positive patients were born between 1945 and 1964. Persons born between 1945 and 1964 had a 4.6 times higher prevalence of HCV than persons born prior to 1945 or after 1964 (3.7% *vs.* 0.73%).[3] Treatment: Before treatment, you need to know: genotype and viral load, previous treatment, and presence of absence of cirrhosis.[4] Generally speaking, 4 regimens are currently available. Ledipasvir/sofosbuvir × 12 weeks (8 weeks at discretion of practitioner), Paritaprevir/ritonavir/ombitasvir+dasabuvir + RBV × 12 weeks, Daclatasvir/sofosbuvir × 12 weeks and Sofusbuvir +Simeprevir±RBV × 12 weeks.[5]

HCV Genotype 1A

- Daily (400 mg) daclatasvir (60 mg) and sofosbuvirfor 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis).
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks.
- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis).
- Daily simeprevir (150 mg) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without the Q80K polymorphism) with or without weight-based RBV.

HCV Genotype 1B

- Daily (400 mg) daclatasvir (60 mg) and sofosbuvirfor 12 weeks (no cirrhosis) or 24 weeks with or without weight-based RBV (cirrhosis).
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks.
- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 12 weeks.
- Daily simeprevir (150 mg) and sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) with or without weight-based RBV.

HCV Genotype 2

- Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks.

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HCV Genotype 4

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks.
- Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks.
- Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks.

HCV Genotype 5&6

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks.

Whom to Initiate HCV Therapy? Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions. Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir stage F3), those with compensated cirrhosis (Metavir stage F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.

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Research

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Comparisons between Portosystemic Shunting Modalities in Patients with Liver Cirrhosis and Portal Hypertension

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ABSTRACT

During almost half of century period, in the Department of Surgery of Portal Hypertension and Pancreatoduodenal Zone of the JSC "Republican Specialized Center of Surgery (named after Academician V. Vakhidov"), portosystemic shunting (PSSh in the traditional variant) was performed on 925 patients suffering with portal hypertension (PH). Results and competitive prospects of PSSh in patients with PH are represented in this article. In accordance with literature data, as well as our own experience, competitive prospects of traditional PSSh, endoscopic methods and transjugular intrahepatic portosystemic shunting (TIPS), in patients with portal hypertension, were defined. For patients with functional class A and B (Child-Pugh), and in the absence of liver transplantation prospects, central partial or selective PSSh, can be considered as competitive alternative.

KEYWORDS: Liver cirrhosis; Portal hypertension; Bleeding from esophageal varices; Liver insufficiency; Transjugular Intrahepatic Portosystemic Shunting (TIPS); Sclerotherapy; Endoscopic ligation; Portosystemic shunting.

ABBREVIATIONS: PH: Portal Hypertension; TIPS: Transjugular Intrahepatic Portosystemic Shunting; PSSh: Portosystemic shunting; LC: Liver Cirrhosis; EGV: Esophageal and Gastric Varices; RSCS: Republican Specialized Center of Surgery; DSRSh: Distal splenorenal shunts; PSRSh: Proximal splenorenal shunt with splenectomy; LLSRSh: Latero-lateral splenorenal shunt; SSRSh: Splenosuprarenal shunt; H-SRSh: H-shaped splenorenal shunt; ALF: Acute Liver Failure; HE: Hepatic Encephalopathy; QoL: Quality of Life; CLDQ: Chronic Liver Disease Questionnaire; MELD: Model for End-Stage Liver Disease; IJV: Internal Jugular Vein.

INTRODUCTION

Currently, liver cirrhosis (LC) with portal hypertension (PH) is one of the leading causes of morbidity and mortality worldwide. Due to the high incidence of viral hepatitis, as well as the steady growth of factors such as alcohol, drugs or toxic liver injury, its social importance is steadily increasing in many countries.[1-3] Although the average age of patients with LC in Europe and the USA is 55±10 years, in Central Asian region tendency to "rejuvenation" of the disease, up to 25 years old and younger.[1]

Often determined by the fatal prognosis, the two main complications of LC are: bleed-

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ing of esophageal and gastric varices (EGV) and progression of liver failure with encephalopathy. A group at risk for potential EGV bleeding includes 20-50% of patients with PH. According to different authors, mortality associated with hemorrhagic syndrome ranges from 30% and above, and with the development of a hepatic coma, that rate rises to 80-90%.[4-6]

The only radical method of treatment for these patients is liver transplantation. However, liver transplantation is not only a potential possibility for radical treatment, but it is always interfaced with needs to resolve a number of difficult questions; among which are medical, social and organizational issues, both from the government point of view (juristic and legislative based), as well as from the practical health care point of view (hospital equipment, human resources, etc.).[7,8] Thus, even in countries with an advanced transplantation program, liver transplantation requirements are only, on average, 25-50% met.[9-11] Among the patients in the waiting list, 10-24% die before transplantation. More than a quarter of these deaths are due to esophageal and gastric varices bleeding. For this reason, prevention of complications from cirrhosis in patients with sufficient functional liver reserve is relevant.[10] Such high mortality rates necessitate the implementation of interventions aimed at preventing hemorrhagic syndrome. Among these, endovascular and surgical decompression of the portal system are considered the most optimal methods.[12,13]

It should be noted that, currently, interest in the traditional portosystemic shunt (PSSh) method has decreased slightly. On one hand, this decrease is caused by the widespread introduction of minimally invasive techniques, among which priority is given to endovascular interventions (TIPS) and endoscopic techniques (ligation and sclerotherapy), and on the other hand, by a influence on the demand of bypass surgery, which has exerted a vast introduction of radical treatment for LC.[14]

Numerous studies show that for patients of Child-Pugh functional class "A" and "B", PSSh must still be considered as an optional method for portal decompression, especially in patients with inefficient pharmacological and endoscopic treatment, and who lack the indication or possibility for liver transplantation. During indication observance, PSSh was proved to be an effective alternative to other methods, both in terms of preventing EGV bleeding as well as in the survival rate of patients with liver cirrhosis.[15,16] Therefore, different variations of traditional decompressive surgery still remain as a method of choice in the leading hepatology centers worldwide.[17]

Thus, the development of vascular surgery for PH, both as a stage of preparation for liver transplantation, as well as a part of a possible method for preventing EGV bleeding, remains as an urgent problem to solve in modern hepatology.

MATERIALS AND METHODS

During the period from 1976 to 2015, PSSh using the traditional technique was performed on 925 patients with PH in Republican Specialized Center of Surgery (RSCS) named after academician V.Vakhidov (Tashkent, Uzbekistan). The etiological factor of PH in 867(94.3%) patients was LC, whereas in the remaining 58(5.7%) patients it was an extrahepatic form of PH. The results of 689 PSSh performed in RSCS named after academician V.Vakhidov (Tashkent. Uzbekistan) from 2001 to 2015 in patients suffering LC were analyzed.

Statistic analysis was held using MS Excel with Systat Software (USA) program software. Quantitative data was submitted as mean (M)± standard deviation (m). The significance of differences was defined according to Student criteria. Difference were defined as statistically veracious in $p<0.05$. Mortality analysis was measured according to Kaplan-Meier.

The average age of all patients was 28.5±0.42 years EGV bleeding occurred in 483(70.1%) patients in other cases, PSSh was performed as a prophylactic measure due to the high risk of it being developed. Different types of PSSh were performed on all patients (Table 1). Among the types of bypasses performed, distal splenorenal shunts (DSRSh or Warren shunts) were performed on the majority of cases (350). In the other 339 cases, the following central type PSSh were performed: proximal splenorenal shunt with splenectomy (PSRSh), latero-lateral splenorenal shunt (LLSRSh), splenosuprarenal shunt (SSRSh), and H-shaped splenorenal shunt (H-SRSh).

Type of operation	LC	
	Number	%
Distal splenorenal shunt (Warren)	350	50,8%
Different types of central bypass	339	49,2%
Total	689	100%

Table 1: Type of portosystemic shunt performed in patients with PH.

RESULTS

The current status of surgery for PH in Uzbekistan is characterized by an individualized approach, which aims to choose the most optimized method of preventing complications, depending on factors such as: age of patient, risk level of developing hemorrhagic syndrome, portal pool angioarchitectonics features; By putting to use the technique of portocaval decompression limiting, when forming the central type of decompression. This technique was developed in 1998 (patent №IAP03265). The essence of the developed technique is the application of a calibrated restrictive cuff (vascular prosthesis), passed on top of the anastomotic vessel, when performing termino-lateral and latero-lateral shunting types, or on top of the insertion from the internal jugular vein (IJV), when forming H-SRSh. (Figures 1 and 2)

Postoperative Complications

Acute liver failure (ALF) development was one of the severe post-operative complications found in patients after central PSSh was performed. If considered in chronological order, over

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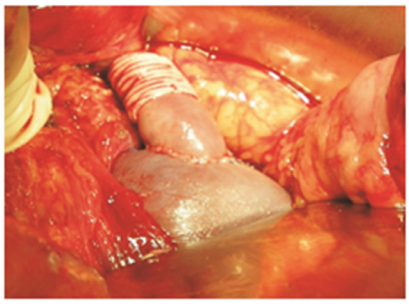

Figure 1: Scheme of PSSh with restrictive cuff.

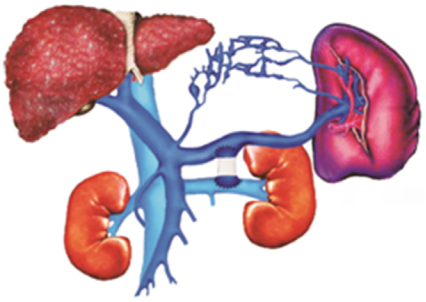

Figure 2: PSSh with restrictive cuff.

the last 5 years of monitoring, ALF frequency decreased to 8.8% in patients with central bypass and to 7.7% in patients with Warren procedure. Before the year 2000, however, frequency of ALF ranged between 25-30%. Similar data was obtained for other post-operative complications.

Hepatic encephalopathy (HE) frequency in the central anastomosis group decreased from 40% (before the year 2000) to 13.6% and in Warren procedure group (DSRSh group) from 33 down to 9.4% (Figure 3).

Of course, in the distant period of observation (3-5 years) mentioned complications were of fundamental importance. However, it is possible to ascertain a significant improvement in the quality of the surgical correction of PH by individual approach for bypass type and if necessary, formation of the partial discharge, which allows to preserve residual hepatofetal blood flow at an acceptable volume level. This explains the low incidence of ALF in 5 years follow-up. Also, thrombosis minemalization became possible because of the formation of a full size anastomosis chamber and limiting of vessel diameter.

Bleeding

Endoscopy was performed on 2nd-3rd month after operation in order to evaluate the effectiveness of decompression. Regression of varicose veins was found in the majority of cases. However, within the central bypass group there was no significant difference in the decompressive effect and regression was less pronounced in patients who had undergone the Warren procedure. A good decompressive effect (varices of 1st grade and less) was observed in 75.0% of patients in the total central bypass group, and in 72.5% of patients in the partial central bypass group. Such data reveals an adequate decompression for both options. However, after the Warren procedure the rate of decompression was observed in 46.8% of patients with up to 3 months monitoring. The aforementioned is possibly due to the selective decompression of the slow restructuring of portal circulation.

Mortality

With regards to mortality, acute liver failure was a major fatal complication, presenting in more than 70% of cases. In the last period of follow-up on the background of preventive bypass with preservation of hepatofetal flow, mortality rate in the immediate post-operative period decreased to 2.7% for central bypass patients and to 3.9% for selective decompression (14.8% until year 2000).

Among the factors that most significantly influenced the decline of mortality rates in cirrhotic patients with PSSh were: 1) indications and contraindications for PSSh were fundamentally reviewed, 2) partial central[18] and selective[19] types of anastomoses were widely introduced, 3) the original procedures of portocaval discharge limitation were introduced, 4) the number of total central anastomoses was decreased to a minimum, 5) precision surgical technology with optical amplification during vascular anastomosis formation was used, and 6) range of liver drug therapy support during the post-operative period was substantially expanded.

The survival analysis held in each of the stratified groups revealed general and specific (unique to a certain type of PSSh) trends in mortality. Overall survival rate of patients

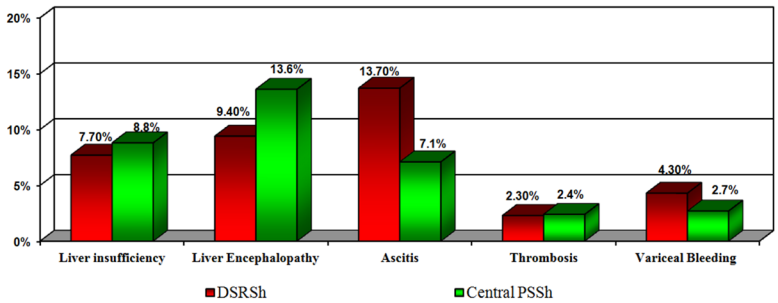

Figure 3: Frequency of specific complications after central and selective PSSh.

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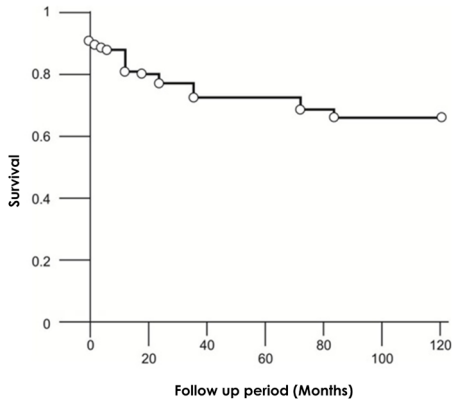

Figure 4: Survival rate after Warren procedure.

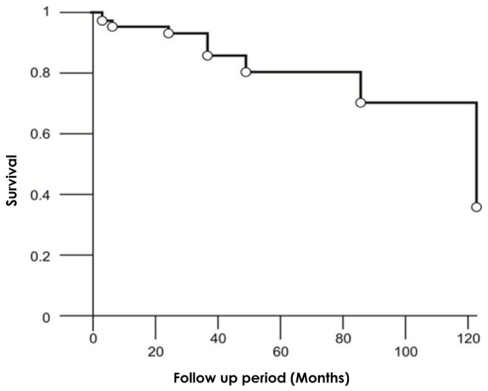

Figure 5: Survival rate in patients after central. PSSH.

after Warren procedure was as follows: 87.5% for up to 1 year, 74.4% for 3 to 5 years, and 71.3% for more than 5 years (Figure 4). Thus, the highest mortality rate was observed during the first three years of follow-up. Survival rates of patients after central PSSh were characterized by the absence of immediate post-operative mortality as well as the largest percentage (69%) of patients with a 10-year survival rate (Figure 5).

The main cause of general postoperative mortality in the 5-years follow-up, regardless of the PSSh procedure performed, was cirrhosis activation with expansion of hepatocellular insufficiency and further decomposition of the patient? And development of the expanded hepatocellular insufficiency.

Quality of Life

To assess "quality of life (QoL)" the chronic liver disease questionnaire (CLDQ), designed by Younossi et al[20] for patients with chronic liver disease, was used. The CLDQ is the first specific document for assessing quality of life. It includes 28 items distributed by the following six domains: 1) abdominal symptoms, 2) tiredness, 3) systemic symptoms, 4) activity, 5) emotional state, and 6) worries. Answers from respondents included seven possible options ranging from "all the time" to "never". Patients answer all questions and the middle amount of points are determined with a maximum of 196 points possible. In some domains points are defined by various questions (from 1 to 7 points). In summary, the higher the score obtained, the better the "quality of life" of the patient.

This "quality of life" analysis was performed in 248 patients with LC after PSSh. To compare the "quality of life" indicator, 50 people were included in the control group and were surveyed by the mentioned principle. It should be noted that for the purity? Of the study, the control group included healthy individuals matched for age (27.9±0.9 years), gender and location of living.

The "quality of life" analysis before and after PSSh is of particular interest. The group of 32 patients with liver cirrhosis was analyzed and their quality of life was analyzed before and after PSSh. Besides, all patients before PSSh, during the previous month, had a bleeding from EGV episode, which was stopped conservatively.

Results of the "quality of life" questionnaires showed that, before PSSh, indicators were significantly worse than in the periods immediately following the operation. The mean total pre-operative score was 114.1±1.4 and in the term of three months after PSSh, it increased to 127.5±1.7. The latter score significantly differed from the baseline indicator (p<0.001). The increased score observed pre- and post-PSSh was caused not only by the decompressive effect resulting from the procedure, but also by the positive emotional and psychological state of post-operational patients. Patients also paid special importance to the objective indicators of their status improvement. Regression of PH and its complications causes not only the decrease of EGV bleeding risk, which, by itself, has a subjectively positive reflection in the neurological state of patients, but it also changes other objective criteria for assessing their own health.

In particular, the reduction or disappearance of the edematous-ascitic syndrome, which an etiologic factor was not only a protein synthetic failure of hepatocytes, but also an elevated PH. In addition, the reduction of portal pressure has a positive effect on the discomfort associated with splenomegaly syndrome, since PSSh facilitates the reduction of spleen size. Further, mean scores were examined by main domains. Within the period of up to 3 months following the procedure, the lowest scores were obtained by the following domains: "tiredness": 4.0±0.03, "activity": 4.4±0.03; "emotional state": 4.2±0.03, and "nervousness": 4.1±0.07. With all these indicators, values differed from those of the control with a high degree of accuracy (p<0.001). Subsequently, gradual, progressive deterioration of the quality of life indicators was observed in all the domains. The most pronounced deterioration was for the domains of "activity" and "emotional state", by which, during practically all periods, the mean score worsened reliably (p<0.05-0.001), unlike other domains, where there had been periods without considerable reduction.

Comparison with the control was more pronounced and within more than five year follow-up, accounted just for 41.0% in

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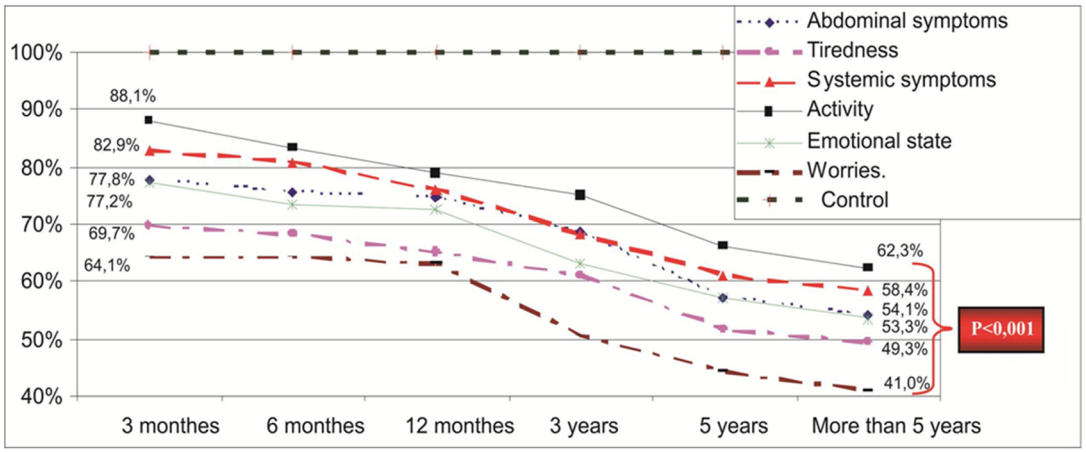

Figure 6: Quality of life dynamics relatively to the control group by the main domains of CLDQ.

comparison to the control by the domain «nervousness», and maximum 62.3% - to the control by domain «activity» (Figure 6).

In up to 5 years follow-up after PSSh, progression of the pathological process in the liver causes deterioration of the "quality of life" indicators. Using the physical state scale of the CLDQ questionnaire, it is from 78.6%, relative to the control value of 100%, to 55.3% (p<0,001) within the 3 months period after surgery. With the psychological state scale, these values go from 72.4% to 48.8% (p<0,001) within more than five years of surveillance.

Model for End-Stage Liver Disease (MELD)

Not less interesting is the study of the dynamics of the Model for End-Stage Liver Disease (MELD) score after PSSh. This scale is widely used in many countries to assess the optimal timing for liver transplantation. Unfavorable life prognosis is associated with a MELD>15-18.

The pre-surgery mean score was 10.19±0.24 points on the MELD scale and 7.13±0.17 points by the Child-Pugh classification. This score was reliably less than in the liver transplantation group. Thus, reevaluation to readdress the need for liver transplantation in the dynamics had to be carried out at least 1 time per year (MELD score less than 10) in 62.5% of patients, at least 1 time in 3 months (MELD 11-18 points) 37.5% of patients.

In the immediate period after traditional PSSh there was no significant deterioration in the MELD scale (10.19±0.24 *versus* 10.94±0.23 points). The progression of liver failure with a high degree of activity was found in 6.3% of patients within one year after surgery. In another 6.3% of patients, EGV bleeding accrued: in one case due to shunt thrombosis and in the other case from gastric erosions due to portal gastropathy. Six months after PSSh, 3.1% of patients died due to progressing liver failure.

One year after operation, the MELD value changed from 10.86±0.22 points to 11.79±0.32 points (p<0.05). In addition, the MELD value higher than 15 points was found only in 10.3% of patients, they formed a group of patients that needed liver transplantation 15.6%.

DISCUSSION

At present, interest for traditional PSSh has markedly fallen. On one hand, this is due to the widespread use of minimally invasive techniques, including endovascular interventions, like TIPS, as well as endoscopic techniques such as ligation and sclerotherapy. On the other hand, introduction of radical treatment in many countries made a certain influence on the demand of PSSh producing.[16]

Furthermore, Rosemurgy et al[17] found that widespread use of TIPS continues although there is a certain lack of direct evidence of its effectiveness prior to surgical bypass.

Authors presented results of an 18-year follow-up of a prospective randomized study. Patient survival was significantly greater after traditional PSSh, as it was also for patients with a Child-Pugh class "A" (91 *vs.* 19 months) and Class "B" (63 *vs.* 21 months). Adequate shunt patency after PSSh was 45 months, whereas it was only 22 months after TIPS. The authors state that patients with Child-Pugh functional class "A" and "B" should have traditional bypass surgery rather than TIPS, leaving TIPS only for patients who present an initially severe (grade "C") condition.[17]

Interesting results were obtained in a randomized clinical trial that evaluated the efficacy of emergency TIPS *vs.* PSSh. The study compared efficiency of TIPS *vs.* PSSh as a way to stop acute bleeding in emergency situations and was conducted in 154 patients with liver cirrhosis of all Child-Pugh severity groups.[21]

PSSh showed the best results with 97.4% hemostasis and less frequent encephalopathy. Additionally, life expectancy was three times greater for patients with PSSh than with TIPS (uncovered). And, despite the recommendation of many surgeons who suggest that PSSh is a surgery that should be carried

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out in planned fashion in order to prevent bleeding, authors recommend the use of this intervention as a means of treatment for acute bleeding. It should be noted that in another study by Orloff et al[22] the advantages of PSSh compared to endoscopic procedures for bleeding control and recurrence prevention were also demonstrated. Puhl et al[23] believe that PSSh should be considered as an optional method in portal pressure decompression, especially in patients with insufficient endoscopic or drug therapy, as well as in patients with the absence of transplantation indications. This also applies to the secondary prevention of rebleeding in patients with good liver function.

According to the interstate archive data analysis made in the United States the following reasons for TIPS were identified: First of all, during 4 years of observation (2000-2003) in the second most populous state (Florida, USA), only 165 PSSh where performed (an average of about 41 shunts in a year). On the contrary, TIPS where performed in 1486 patients among 1321 patients that were nearly 10 times greater. Secondly, number of centers offering the TIPS procedure was almost 10 times higher (more than 100). In general, mortality after these procedures was almost identical (11.0% TIPS *versus* 12.7% PSSh). Thus, the cost of TIPS was significantly lower ($62,000 *vs.* $107,000). However, conducting analysis, authors claim that if the mortality after TIPS procedure was due to the severity of patients and did not depended on the level of the surgical hospital, the mortality rate after the traditional PSSh depended both on the level of the medical center and the surgeon's experience. Also, in spite of the advantages of the TIPS procedure, the authors summarized that, in long-term observation, traditional PSSh gave more superior survival rate prospects.[24]

Finally, a retrospective analysis by Elwood et al[16] broth that the Warren procedure should be considered as the first line approach for patients with high risk of bleeding in Child-Pugh classes "A" and "B", especially when endoscopic sclerotherapy is ineffective or in those cases where liver transplantation will not be needed within 5 years.

The effectiveness of the Warren procedure made under recommended readings is higher than that of TIPS. This option avoids the need of multiple stent patency monitoring and thus resenting.[16] According to several clinical trials, this TIPS technique can be complicated, in 75-82% of patients, with endovascular graft dysfunction or thrombosis in a period from 6 months to 1 year after surgery.[16,22]

It should be noted that the accumulated experience of different hepatology schools determines the selection of a particular method, thereby giving continuity to the centers' own results. For example, in some studies only the initial state of compensated liver function is considered as an indication for PSSh. In contrast, other authors only recommend alternative therapies. Thus, according to Semenova,[25] endoscopic bleeding prevention is of minimal risk, although it does not allow sustainable long-term results to be achieved. In turn, the Warren procedure has a clear advantage with respect to long-term effects, but has a higher risk of bleeding. In this connection, the Warren procedure is preferable for patients with compensated liver cirrhosis without a history of surgery for PH. When liver cirrhosis is in subcompensation and patient has a history of surgical treatment for PH, or suffers from severe comorbidity, endoscopic sclerotherapy should be carried out as first choice of treatment.[26]

In another study, complications after PSSh were observed in 27.3% of cases, with a postoperative mortality of 4.5%. The author recommends H-type splenorenal bypass with a vascular graft insertion for patients with Child-Pugh Class A and a blood flow of 1000 ml/min through the portal vein. In patients with Child-Pugh class "B", an inactive or low activity phase, and portal vein blood flow less than 1000 ml/min, the Paciora procedure is recommended. In decompensated (Child-Pugh class "C") patients, the recommendation is to refrain from active surgery.[26,27]

In a study by held I.I. Dzidzava,[28] the survival rate of patients after endoscopic ligation in the one year follow-up was 57.3%; in three years, 38%; in five years, 33.1%. In turn, long-term results in PSSh patients are characterized by the absence of rebleeding, thrombosis, and satisfying survival rates: one year, 84.8%; 3 years, 68.6%; 5 years, 51.3%; 10 years, 25.8%. The authors conclude that the performance of selective and partial PSSh is indicated in patients with liver volume more than 1200 sm^3 and positive values of the liver dysfunction index.

Given the above, it can be concluded that, over the past decade, the development of minimally invasive methods, in order to prevent bleeding, has led to a decrease in the number of traditional PSSh performed. However, the conducted literary analysis shows that, even in centers which perform all kinds of operative treatments, including radical ones, traditional decompression of the portal system remains the method of choice. Furthermore, using adequate approach to indications, the results obtained with the mentioned procedure of choice are greatly superior in comparison with those of alternative endoscopic methods.

CONCLUSION

At the present time, leading Hepatology Schools have different views regarding which is the best choice for bleeding prevention. In most cases, surgeons prefer minimally invasive techniques, among which endoscopic procedures and TIPS are the most popular.

Now-a-days liver transplantation is the only radical treatment for liver cirrhosis, though for countries without transplantation service portosystemic shunts remain as an actual method of rebleeding prevention. In terms of highly developed transplantological service, minimally invasive techniques are optimal because bleeding itself can be viewed as an indication for liver transplantation. Additionally, performing TIPS or an

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endoscopic procedure provides the necessary time interval to find an organ donor and prepare the patient for radical surgery. Also in favor of minimally invasive technologies is the fact that these procedures are available to patients who are in serious, critical condition and abdominal surgery is associated with an unnecessary risk. On the other hand, when TIPS *vs.* PSSh results are compared, it can be seen that endovascular techniques have their negative side as well.

Obtained own findings objectively prove the effectiveness of PSSh in terms of hemorrhagic syndrome prevention with a high survival rate, as well as its important role in decreasing the need for liver transplantation. In the absence of bleeding risk, the possibility for dynamic patient monitoring, drug therapy and thus lengthening of the time period becomes opened before the transplantation what should be carried out in decompensated functional state of hepatocytes.

In portal hypertension surgery, PSSh remains one of the optimal ways to prevent bleedings from EGV. The conceptual importance of this type of intervention is determined not only by limited ability to perform liver transplantation, but also by a competitive perspective to reduce the demand for radical interventions in patients with functionally compensated LC. Thus, for patients with Child-Pugh functional class A and B, and in the absence of prospects of liver transplantation, traditional surgical methods, such as central partial or selective PSSh, should be considered as an actual competitive alternative.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Mini Review

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Iron and Copper Toxicity in Rat Liver: A Kinetic and Holistic Overview

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ABSTRACT

Iron (Fe) and copper (Cu) overloads in rats showed a dose and time dependent metal accumulation in liver with its associated toxicity. The increased contents of the transition metals markedly enhanced the endogenous free-radical mediated processes of phospholipid peroxidation. *In vivo* liver chemiluminescence showed an increased production of $^1O_2$, and a consumption of reduced glutathione (GSH), the main intracellular antioxidant. Results fit with a Haber-Weiss type molecular mechanism in which Fe or Cu and endogenously produced $O_2^{\cdot-}$ and H_2O_2, yield $HO^{\cdot}$ that initiates free-radical mediated phospholipid peroxidation and protein oxidation.

KEY WORDS: GSH: Reduced glutathione; SOD1: Cu, Zn-superoxide dismutase; GPx: Glutathione peroxidase; Nrf2: Nuclear factor erythroid 2-related factor 2.

INTRODUCTION

Iron (Fe) and copper (Cu) are bioelements and vital transition metals whose deficiency or excess in the organism are associated with pathologic situations. Both metals are clearly hormetic, they are required at low levels for human health (Recommended Daily Intake: 10-15 mg Fe/day and 1-3 mg Cu/day) but at higher levels (more than 30 mg Fe/day or 8 mg Cu/day) they produce toxic effects in liver and brain.[1-4] The metal toxicity seems due to their participation in the Haber-Weiss redox reaction that produces the highly reactive $HO^{\cdot}$.[5,6] The intracellular steady-state concentrations of reactive oxygen species indicate that H_2O_2 and ROOH are the quantitatively predominant species by a factor of 10^4-10^{11}.[7]

Currently, there are two hypotheses for the molecular mechanism of transition metal toxicity in mammalian organs. The two hypotheses are not incompatible and it is likely that the two processes occur simultaneously. The first one considers that the reduced forms Fe^{2+} and Cu^+ catalyze the homolytic scission of the O-O bond in H_2O_2 and ROOH in a Fenton-like reaction to produce $HO^{\cdot}$ and $RO^{\cdot}$ radicals. The second one considers the reaction of Fe^{3+} and Cu^{2+} with intracellular reduced glutathione (GSH), due to the high affinity of the two metals ions for the thiol (-SH) group. This depletes cells of GSH that is equilibrated with essential thiol groups in enzymes and regulatory factors. Concerning the first hypothesis, there are two points of view of the O-O bond homolysis: a classical one where Fe^{2+} or Cu^+ directly catalyzes the reaction and a second one, in which Fe^{2+} and Cu^+ bind to a specific peptide or protein that reacts with H_2O_2 generating $HO^{\cdot}$, that is able to oxidize neighboring amino acids and to produce protein cross-linking, fragmentation and denaturation.[1,2,8] The last mechanism seems to apply to β-amyloid in Alzheimer's disease.[9]

The toxicological effects of Fe and Cu overloads were studied in rat liver by a kinetic and holistic approach, considering the time ($t_{1/2}$) and the metal liver content (C_{50}) for

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half maximal effects. The kinetic approach refers to the central role of the $t_{1/2}$ to define the sequence of events in the liver, and the holistic concept considers the whole organ, as in liver chemiluminescence and homogenate determinations.

TOXICITY PROCESSES IN Fe AND Cu OVERLOADS

Sprague Dawley male rats (200-230 g) received i.p. (a) for Fe $t_{1/2}$ determination, 30 mg/kg rat of ferrous chloride ($FeCl_2.4H_2O$), that corresponds to 8.42 mg Fe element/kg; (b) for Fe C_{50} determination, 5-60 mg/kg of ferrous chloride, corresponding to 4.1-49.2 mg/kg of Fe element/kg; (c) for Cu $t_{1/2}$ determination, 10 mg/kg rat of cupric sulfate ($CuSO_4.5H_2O$), that corresponds to 2.54 mg/kg of Cu element/kg; and (d) for Cu C_{50} determination, 3-30 mg/kg of cupric sulfate, corresponding to 0.763-7.63 mg/kg of Cu element. Control rats received a similar volume of saline solution.

The effects of Fe and Cu intoxications in rat liver are summarized in Table 1. Both metals produced a situation of oxidative stress, that was originally described as an unbalance between oxidant production and antioxidant defense.[10] The concept has been updated and now considers that oxidative reactions lead to a disruption of redox signaling and control, and to molecular and cellular damage.[11] A high content of cellular –SH groups is considered essential for cell regulation and survival.

The description of the metal effects in rat liver given in Table 1, is based on the time ($t_{1/2}$) and on the metal liver content (C_{50}) for half maximal effects. The $t_{1/2}$ describes the kinetics of the effect at the used doses. At variance, C_{50} establishes the effect concentration dependence.

In Fe overload, 90% of the rats survived the observation time of 48 h, whereas in Cu overload, 85% of the animals survived 24 h and 60% survived 48 h.[3] Metal accumulation in the liver was dose- and time-dependent.[1] The liver content of Fe increased 1.6 times and the one of Cu 11-fold after 48 h of metal overloads. The Fe and Cu contents observed in rat liver are similar to those in patients with haemochromatosis[12] or with Wilson's disease, respectively.[13]

LIVER OXIDATIVE STRESS AND DAMAGE

The increased intracellular levels of Fe^{2+} and Cu[1] (Figure 1) lead to an enhanced homolytic cleavage of H_2O_2 yielding $HO^{\bullet}$ and initiating phospholipid peroxidation and protein oxidation. The spontaneous light emission from *in situ* mammalian organs is a physiological phenomenon and also an assay for the determination of the rate of lipid peroxidation, from singlet oxygen ($^1O_2$) steady states.[14] The molecular mechanism of light emission includes the Russell's reaction in which two secondary or tertiary peroxyl radicals ($ROO^{\bullet}$) yield $^1O_2$ or excited carbonyl groups (>C=O*) as products and the $^1O_2$ dimol emission. Two $^1O_2$ molecules upon collision produce a photon at 634 or 703 nm, whereas >C=O* yields photons at 460-470 nm.[14]

Increased liver chemiluminescence indicates an enhanced rate of free-radical mediated lipid peroxidation. This process was also monitored by the determination of the lipid peroxidation product TBARS. Similarly, carbonyl groups, >C=O were determined as products of protein oxidation. The indicators of oxidative reactions and damage (chemiluminescence, TBARS, and >C=O) exhibited about similar $t_{1/2}$, considering the experimental error.

Antioxidants are enzymes or small molecules that decrease the level of oxidative chemical species. The small molecules able to trap free-radicals and to reduce the extent of phospholipid peroxidation and of protein oxidation, are GSH (mM range), α-tocopherol and β-carotene (μM range). Other kind of antioxidants, more important from a physiological consideration, are the enzymes Cu, Zn-superoxide dismutase

Table 1: Rat Liver Oxidative Stress after Fe and Cu Overloads.[a]

	----------Fe----------			----------Cu----------		
Property	**Effect (%)[b]**	**$t_{1/2}$ (h)**	**C_{50} (μg Fe/g)[c]**	**Change (%)**	**$t_{1/2}$ (h)**	**C_{50} (μg Cu/g)[c]**
Rat survival	(-) 10	About 240	140	(-) 40	About 120	120
Metal content	(+) 40	4	60	(+) 1000	5	80
Liver chemiluminescence	(+) 200	4	115	(+) 100	4	42
Lipoperoxidation	(+) 200	6.5	130	(+) 100	7	45
Protein oxidation	(+) 60	4	116	(+) 40	5.5	50
Hydrophilic antioxidant	(-) 60	5	118	(-) 75	4	42
Hydrophobic antioxidant	(-) 50	5	120	(-) 50	5	52
GSH content	(-) 58	4	116	(-) 79	4	40
GSH/GSSG ratio	(-) 50	2	108	(-) 50	2	30
SOD1 activity	(+) 57	8	114	(+) 127	8.5	42
Catalase activity	(+) 65	8.5	110	(-) 26	8	44
GPx activity	(-) 39	4.5	120	(-) 22	5	48

[a]Adapted from references. (1-3): [b]in % of increased (+) or decreased (-) property compared with control rats; [c]determined by atomic absorption.

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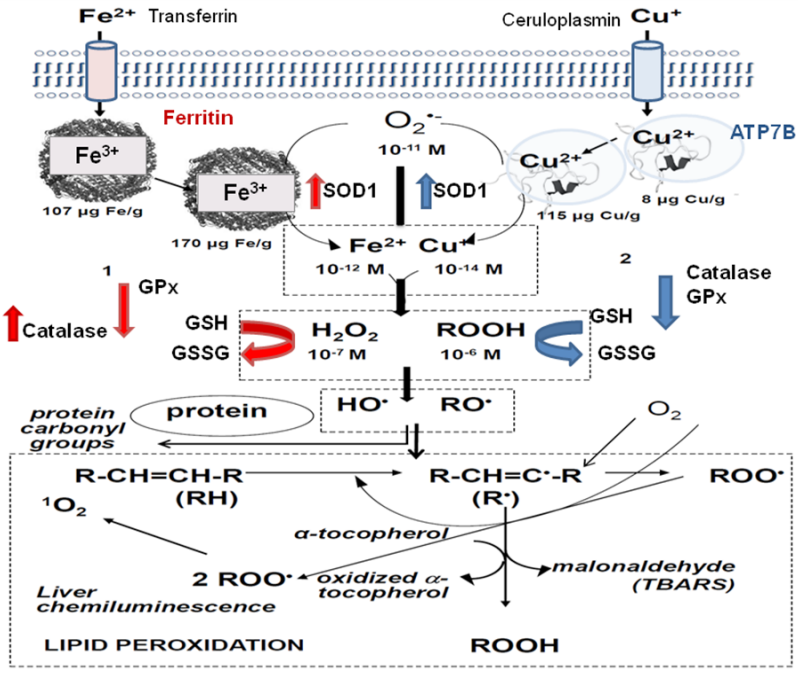

Figure 1: Scheme of the Biochemical Process in Fe and Cu Liver Toxicity.[1]

In red, effects of Fe toxicity and in Blue, effects of Cu toxicity.

(SOD1), catalase, and glutathione peroxidase (GPx).

Rat liver antioxidant defenses were affected by Fe and Cu overloads. Hydrophilic antioxidants were decreased, measured either as a pool, or as GSH concentration. Similarly, hydrophobic antioxidants were diminished. The decrease of both types of antioxidants indicates antioxidant consumption, consistent with an increased rate of liver oxidative free-radical reactions. Antioxidant consumption exhibited similar $t_{1/2}$, coincident with the idea that the observed oxidative damage is due to a common free-radical mediated mechanism.

The two main antioxidant enzymes, SOD and catalase, evolved with aerobic life in bacteria.[15] Animal biochemistry kept this ancestral defense mechanism and SOD1 and catalase decreased activities have been associated with pathological conditions in mammals and humans.[6,16] The adaptive response of increased SOD1 and catalase activities in mammalian organs was early reported in neonatal rabbit lung,[17] and recognized as a strategy of antioxidant defense in mammals[18] and in humans.[19] In Fe overload, there was an increase in SOD1 and catalase activities in response to oxidative stress. In Cu toxicity, a different response was observed in the two enzymes: SOD activity increased but catalase activity decreased. GPx activity was decreased after Fe and Cu overloads, it is likely that increased phospholipid peroxidation would include high levels of ROO• (peroxyl radical) that binds to the enzyme and inactivates the reaction center.

The adaptive response involving the described increased enzyme activities is likely to be mediated by the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor that appears as responsive to increases in ROOH intracellular levels.[5]

The mitochondrial respiration of rat liver mitochondria isolated from Cu-overloaded rats showed significant decreases in the active ATP-forming state 3, but not in the resting state 4. With malate-glutamate as substrate, state 3 respiration was 36% diminished, and with succinate, O_2 uptake was 25% decreased (Table 2).

CONCLUSION

Rats exposed to Fe and Cu overloads develop liver oxidative stress in which cells may adapt to the situation or succumb with eventual cell death. The adaptation includes the up-regulation of SOD1 and catalase synthesis and of enzymes involved in GSH conjugation and in GSH synthesis. The apparent purpose of the adaptive response is to overcome the oxidative challenge and to restore reactive oxygen species to levels compatible with cell life. The molecular mechanisms underlying cell adaptation are at present not fully understood. However, in recent years some transcription factors, as Nrf2, have emerged as master regulators of the adaptive response. Decreased liver GSH, consequence of Fe and Cu accumulation and the ensuing oxidative stress, trigger downstream signaling as an attempt to keep the normal composition of membranes and proteins. Given its high

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Table 2: Oxygen Uptake of Rat Liver Mitochondria after Cu Overload.[a]

	Oxygen uptake (ng-at O/min × mg protein)	
	Control	**Cu treated**
Substrate: 5 mM malate, 5 mM glutamate		
State 3	47±2	30±3*
State 4	6.4±0.4	5.0±0.3
Respiratory control	7.3±0.1	6.0±0.2
Substrate; 10 mM succinate		
State 3	64±3	48±3*
State 4	11.4±0.6	10.2±0.5
Respiratory control	4.5±0.1	4.7±0.1

[a]Rats received 25.5 mg/kg of cupric sulfate/kg rat, corresponding to 6.5 mg of Cu element /kg rat, 6 h before rat sacrifice. *p<0.05.

intracellular concentration in liver (5-7 mM), GSH defines the cellular redox potential and protects cells against oxidative stress. The whole process of metal toxicity is constituted by oxidative biochemical processes with $t_{1/2}$ of 4.6±0.5 h for Fe and of 4.9±0.6 h for Cu, that encompass increased free-radical mediated oxidations and decreased GSH contents, superimposed with the adaptive response of the antioxidant enzymes. Altogether, this set of biochemical changes appears to indicate an oxidative stress situation where cells are unable to control the enhanced production of oxidative species.

DECLARATION OF INTEREST

The authors declare that they have no competing interests.

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Short Communication

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Pediatric Acute Liver Failure: Current Perspectives

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It is well known that acute liver failure (ALF) in children is rare but potentially a life-threatening disorder. Its true incidence in the pediatric population is undetermined but is responsible for 10-15% of all pediatric liver transplantations.[1] Unlike adults, a specific cause of pediatric ALF is not identified in almost half of the cases,[2] and the etiology is classified as indeterminate in 18-47% of all patients.[1] The etiology is important because the survival rate and need for liver transplantation vary depending on the diagnosis. Spontaneous recovery is better in children with toxic etiology and worst for those with indeterminate or other causes.[1,2] There is no specific treatment for most ALF cases, and the mainstay of medical care is to minimize complications and to limit additional morbidity.[3] ALF can be associated with rapidly progressive multiorgan failure and high mortality rates. One of the leading causes of death is cerebral edema and intracranial hypertension (ICH), responsible for about 20-25% of all deaths.[3] From that perspective, it is desirable to develop new therapies/technologies for diagnostic investigation and interventions.

The use of transcranial Doppler (TCD) is an important component in the assessment of cerebral edema, which should be monitored. Some centers use invasive intracranial pressure (ICP) monitoring; however, non-invasive monitoring of cerebral arterial flow is becoming a useful tool to identify ICH.[1] Two relevant articles[4,5] tried to demonstrate the usefulness of TCD to characterize the cerebral hemodynamics patterns in patients diagnosed with ALF. TCD is becoming an important tool since there is no risk of complications like bleeding or infection, which can occur in the use of invasive ICP monitoring.[4,6] The complication risk is around 20%, and there are limited therapeutic options for ICH,[6] which should be taken into consideration to indicate invasive procedures. Besides that, Aggarwal et al[6] studied whether TCD waveform features could be used to differentiate ALF patients with respect to ICP or cerebral perfusion pressure (CPP) levels. They concluded that TCD could provide information about the dynamic state of the intracranial circulation and perfusion with clinical complications.

Another issue is the use of continuous renal replacement therapy (CRRT) on pediatric ALF.[7] As mentioned before, the pediatric ALF is a dramatic clinical syndrome in which children has rapid deterioration of hepatic function and can evolve to multiorgan failure and cerebral edema. As found by Deep et al[7] patients who benefited most from CRRT were those with toxic cause unlike the patients with metabolic causes. Therefore, clinicians should be careful in the selection of patients who underwent CRRT, as the cause of pediatric ALF is determinant for prognosis. That is important to consider because of the possible complications related to CRRT. Santiago et al[8] found in their study that CRRT-complications are common in children and some are potentially serious, the majority were problems of venous catheterization, hypotension on connection to CRRT, electrolytes disturbances and clinically significant hemorrhage. Probably this can be diminished by ultrasound-guided catheter placement, as well as the choice to use prostacyclin instead of regional citrate anticoagulation, and standardized service practices.[9]

Despite these two useful tools, another relevant resource to be used by intensivists is the ammonia level. It is well known that the ammonia level is an independent risk factor for the development of severe hepatic encephalopathy and ICH. Bernal et al[10] demonstrated that

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a level greater than 100 µmol/L predicted the onset of severe hepatic encephalopathy (HE) and ICH developed in 55% of ALF patients with a level higher than 200 µmol/L. That raises 2 important questions: what is more important on the indication of early CRRT, the absolute value of ammonia or the increasing curve? First, it is important to ensure effective control of ammonia levels through a therapeutic strategy focusing on the determinants of ammonia metabolism and neurotoxicity before indication of CRRT. However, a consistent increase in ammonia levels is an indicator of poor prognosis and should be taken into account when indicating CRRT. And how ammonia level can be correlated with TCD? There are no publications that correlate levels of ammonia and TCD directly, although TCD has a good correlation with ICH. TCD can be used serially to follow the response to treatment of ICH.

Almost all the work in the intensivist field is to allow the liver to regenerate or, if it is unlikely, to allow enough time to find a suitable organ for transplantation. Therapeutic possibilities are scarce[11] and, in this context, it is always important to explore new diagnostic and treatment options.

As a future goal, since TCD and CRRT are valuable tools, it is desirable to make them available in specialized centers as we still have a high mortality in ALF, and new therapies could improve survival rates.

CONFLICTS OF INTEREST

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