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ORIGINAL ARTICLE

Artificial Liver, Pancreas

A comparison among three different apheretic techniques for treatment of hyperbilirubinemia

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Abstract Liver failure is associated to high mortality due to the accumulation of protein-bound metabolites, such as bilirubin, not removed by conventional hemodialysis. Different methods can efficiently remove them, such as the molecular adsorbent recirculating system (MARS), plasma exchange (PEX), and bilirubin or plasma adsorption perfusion (PAP). No direct comparison exists between MARS, PEX and PAP, and current guidelines do not specify which method (and when) to use. We have retrospectively evaluated MARS, PEX and PAP in their effectiveness in lowering plasma bilirubin concentration, and their effects on liver and kidney function. A total of 98 patients have been recruited, which comprised 68 patients treated with PAP (177 sessions), 16 patients with PEX (41 sessions) and 11 patients with MARS (21 sessions). Bilirubin, creatinine, liver enzymes were analyzed before and after the first treatment with each technique. The three methods did not differ for bilirubin lowering efficiency, with MARS showing only slightly less effective reductions. Finally, the three techniques did not differ in the amount of change of cholinesterase, but a lower reduction in AST was found using PAP. Our retrospective observation is one of the largest case series of hepatic failure treated with bilirubin absorption. The choice of the technique cannot be based on the desired reduction in bilirubin concentration. Based on costs and duration of treatment, we suggest that PAP could be considered as a first-line approach. In case of kidney involvement, MARS remains a valuable option.

Keywords Hyperbilirubinemia · Liver failure · Molecular adsorbent recirculating system · Plasma exchange · Bilirubin adsorption · Plasma adsorption perfusion

Introduction

The high mortality associated with liver failure has been attributed to the accumulation of several metabolites, such as bile acids and bilirubin. These metabolites, normally removed by the liver, would lead to the dysfunction of the brain (hepatic encephalopathy), kidney (hepatic-renal syndrome) and, eventually, the death.

Although bilirubin removal is unlikely to affect liver failure (and the data in the present communication support incidentally this view), it may be important to prevent the failure of other organs and, in general, as an index of removal of other protein-bound toxins such as bile acids. In fact, bilirubin may be a toxic substance under specific concentrations and conditions: for example, in newborns, when the blood brain barrier is not yet developed, it may cause a degeneration of basal nuclei of the brain (kernikterus) [1]. Conversely, in adults, the brain effects are milder and only associations with acute and transient psychotic disorders have been described [2]. Moreover, in adults hyperbilirubinemia may cause damage to the kidney (bile casts, acute tubular necrosis) [3]. Elevated blood bilirubin levels are accompanied by an increased risk for death under specific

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circumstances [4]. Finally, the presence of high levels of bilirubin may compromise other organs particularly when a surgical approach is necessary: in this case a preoperative preparation is essential for renal failure prophylaxis [5]. Therefore, methods for bilirubin removal might be useful both to reduce the risk of organ damage and as an indirect marker of efficiency of removal of other protein-bound toxins.

Unfortunately, bilirubin, bile acids and other toxins are tightly bound to albumin and hence cannot be removed by conventional hemodialysis or hemofiltration. However, bilirubin removal can be increased up to sixfold if albumin is added to the dialysate as a binder [6]. This principle is behind several systems of extracorporeal albumin dialysis (ECAD) devised to reduce endogenous albumin-bound toxic agents, and hence to function as bridging therapy to liver transplant [7].

Several ECAD systems have been devised such as (1) the molecular adsorbent recirculating system (MARS) [8], (2) the single pass albumin dialysis (SPAD), (3) the fractionated plasma separation and adsorption (e.g. PROMETHEUS) [9].

In addition, the plasma exchange (PEX), by which virtually all plasma constituents can be removed, has the potential to eliminate all relevant substances, albeit in a rather unspecific manner. In addition, since hyperbilirubinemia severity is related to prognosis in advanced liver failure, the bilirubin adsorption (plasma adsorption perfusion—PAP, being the technique) has also been proposed as symptomatic therapy for intractable jaundice in a number of hepatic diseases [10–12].

The MARS system has been developed in 1993 and comprises three compartments or circuits: (1) the blood circuit, based on a veno-venous access (double-lumen catheter) and a high-flux, non-albumin-permeable serum dialysis against exogenous human serum albumin; (2) a system of two adsorption columns (a charcoal filter and an anion exchanger in series), to regenerate the albumin dialysate after it has absorbed toxins from the patient's blood; (3) a circuit similar to a standard hemodialysis system, to remove water-soluble toxins from the albumin dialysate; the cleaned albumin is then re-circulated to the semi-permeable membrane in contact with the patient's blood [13, 14].

The advantage of MARS is the absence of exposure to exogenous plasma/albumin, hence having low risk of allergies and infections. Moreover, MARS has interesting features for the renal function [13, 15, 16]. However, this system is quite complex, with long set up times, and it is a costly procedure, in the range of about 2000€ for a 7-h treatment.

The PEX method consists in the removal of bilirubin-saturated albumin in exchange of fresh, bilirubin-free albumin, using a plasma separator. Its advantage is its simplicity, since it requires only a plasma separation column and then the reinfusion of exogenous albumin in place of the plasma removed from the patient. However, the amount of fresh human albumin required makes the technique rather expensive and exposes patients to possible reactions to human blood-derived products. Another disadvantage is that clotting factors are lost if albumin is selected as substitute of the plasma extracted from the patient; moreover, drugs are also usually lost from the bloodstream after the treatment.

The PAP is a technique of therapeutic apheresis which exploits a bilirubin-adsorbing column. PAP has been established, in the last 15 years, as a treatment for hyperbilirubinemia in several conditions such as pre- and post-liver transplant, in the chronic liver failure [12] and in cardiac cirrhosis [17].

The main advantage of PAP is its simplicity: the plasma is separated on a first column and then filtered on a bilirubin-binding column before its reinfusion into the patient. Therefore, it does not require exogenous plasma or albumin infusion, thus being most cost-effective compared to PEX. Moreover, it allows the preservation of clotting factors or drugs. The column allows to treat large plasma volumes (up to 7 l), with an efficient removal of bilirubin.

A very limited amount of information is yet available about the optimal technique for bilirubin removal and no direct comparison exists between MARS, PEX and PAP.

Due to the complexity of liver functions, the creation of a liver support system to simulate an artificial liver has been less successful than for other organ support therapies. However, there are two main categories of disease in which liver support system may be useful. The first is to treat reversible liver disease, in which the system would allow time for recovery and regeneration. The second is in the management of irreversible liver disease in which it may be used as a bridge to transplantation or to control symptoms, such as pruritus, in patients not suitable for transplant.

In this respect, MARS seems to have more extensive detoxification capacities than PAP and PEX. However, in the RELIEF study, no survival benefit could be demonstrated despite physiological improvement [18]. The reasons for this are in part due to our incomplete understanding of the liver pathophysiology that results in multiorgan failure and eventually death.

However, due to the fact that bilirubin and the biliary salts are toxic under many respects, their removal is essential in severe cases of hyperbilirubinemia and predict short-term mortality in these patients. So, our mission was to remove as much bilirubin as possible. Having the three different systems (PAP, PEX and MARS), we compared the common denominator of bilirubin removal, aiming at evaluating the differences among them.

In the present study we have retrospectively evaluated MARS, PEX and PAP in their effectiveness in bilirubin

removal, and in their possible beneficial effects on liver and kidney function.

Materials and methods

Study design

The study was designed as a single-center-retrospective study comparing the efficacy of MARS, PAP and PEX. We retrieved data pertaining to 103 patients recovered in the Cotugno Hospital with a diagnosis of hyperbilirubinemia from acute liver failure or acute-on-chronic liver failure. These patients have been treated, in the years 2002–2015, with one of the following systems: PEX or PAP or MARS. All causes of acute liver failure have been considered for the study. Some patients have been excluded from further analysis due to the of lack of complete data and a single case was also excluded due to the very complex pathology with very high levels of plasma liver enzymes (ALT >2600) largely greater than other patients.

A total of 95 patients corresponded to the selection criteria: 66 patients treated with PAP, 15 patients treated with PEX and 14 patients treated with MARS.

The anthropometric and hematologic characteristics of these patients are reported in Table 1 and were not significantly different among the three groups.

According to the department's standard operating procedure, an extracorporeal liver support (ELS) was considered when patients with a pertinent diagnosis showed plasma bilirubin level >20 mg/dl, or an increase in bilirubin level of more than 2 mg/dl per day for 4 consecutive days [12]. Analyses were conducted retrospectively using deidentified patient data; this study was approved by institutional review board. We adhered to the Declaration of Helsinki; informed consent was not required.

Extracorporeal liver support procedure and blood sampling

The vascular access was obtained via a double-lumen hemodialysis catheter (Mahurkar, Covidien™, USA), introduced into the femoral, jugular or subclavian vein.

Blood anti-coagulation was controlled using unfractionated heparin (final activated clotting time of 140–200 s).

In the MARS device (Gambro, Lund, Sweden), using a standard hemodialysis machine Dialog+ (BBraun Medical, Germany) performing the procedure, the following parameters were set:

- blood flow rate: 100–150 ml/min,
- albumin flow rate (roller pump of MARS monitor) equalized to blood flow rates,
- duration 6 h,
- dialysis flow rate 2000 ml/h.

In the PEX device, using Plasmaflo OP-0.5W (Asahi-Kasai Medical, Japan) as plasma filter, and Diapact CRRT system (BBraun Medical, Germany) as machine performing the procedure, the following parameters were set:

- albumin solution 4%,
- blood flow rate 100–150 ml/min,
- plasma flow rate 25–30 ml/min,
- average amount of plasma treated 1–1.5 volumes,
- average duration of treatment 2–3 h.

In the PAP device, using Plasmaflo OP-0.5W (Asahi-Kasai Medical, Japan) as plasma filter; Plasorba BR-350 (Asahi-Kasei Medical, Japan) as bilirubin absorption column and Diapact CRRT system (BBraun Medical, Germany) as machine performing the procedure, the following parameters were set:

- blood flow rate 100–150 ml/min,

Table 1 Group characteristics, baseline values

	PAP	PEX	MARS	*p*
n	66	15	14	
F/M	21/45	3/12	1/13	0.14
Age (years)	49.2 ± 15.9	45.8 ± 18.6	49 ± 20	0.80
Bilirubin (mg/dl)	31 ± 7.7	29.7 ± 9.2	30 ± 15	0.84
AST (mg/dl)	203 ± 287	304 ± 350	465 ± 711	0.07
ALT (mg/dl)	203 ± 363	322 ± 461	466 ± 728	0.12
PT %	56 ± 30	38 ± 11	34 ± 21	0.11
aPTT (sec)	53 ± 26	61 ± 13	49 ± 11	0.72
Total plasma proteins (g/dl)	6.0 ± 1.2	6.3 ± 1.1	6.0 ± 1.6	0.91
CHE (mg/dl)	2698 ± 1599	2558 ± 1193	1851 ± 1015	0.33
eGFR (CKD-EPI; ml/min)	61.9 ± 39	66.4 ± 34	44.5 ± 50.6	0.30

- plasma flow rate 25–30 ml,
- average amount of plasma treated 6000 ml,
- average duration of treatment 3 h.

Depending on the reduction of the bilirubin levels and clinical conditions, patients have been treated with one or up to five treatment sessions, usually every other day. To gain further insight into the differences in plasma bilirubin level after each treatment, data have also been analyzed by pooling all apheretic sessions and treating them as independent samples.

Quantification of hematological parameters

Blood samplings were carried out no more than 30 min before or after ELS, respectively. Blood samples for routine laboratory parameters were immediately sent to the clinical laboratory for measurement. Plasma samples for non-routine measurements were immediately centrifuged (4700 U/min, 4 °C) for 10 min. Serum samples were centrifuged (4700 U/min, 4 °C) for 10 min after 30 min of resting. All samples were kept frozen at −80 °C until evaluation.

Statistics

Data are reported as mean ± SD. Comparisons among the three groups was conducted using separate ONE-way ANOVA for different variables. Unplanned comparisons between groups were done using the LSD post-hoc test. Modifications in plasma values after apheretic techniques compared to pre-treatment values were done using paired samples *t* test. Correlations between amount of plasma bilirubin reduction and bilirubin levels, eGFR and AST levels were calculated using the Pearson correlation coefficient. eGFR was calculated using the CKD-EPI formula. The association between treatment (PEX, PAP or MARS) and frequency of exitus, type of underlying liver disease, acute or chronic liver disease were tested by Chi square.

The software used was SPSS 13.0 (SPSS Inc). The level of probability taken as significant was $p = 0.05$ or less.

Results

The effect of the three apheretic techniques on plasma bilirubin concentration (as absolute value or as percent of basal value) after the first session is reported in Table 2. All techniques determined a significant reduction of the plasma bilirubin of about 27% the basal value. MARS showed smaller reductions in bilirubin levels, compared to other techniques, although this difference did not reach the statistical significance level. Assuming that the percent of bilirubin removed does not depend on previous apheretic sessions, we also analyzed all apheretic sessions (including repeated treatments on the same subject), treating them as independent data, in order to increase the sample size. Using this approach, it was evident a smaller reduction in bilirubin levels after MARS treatment, compared to the other techniques (change in bilirubin concentration compared with pre-apheresis values: PAP 30 ± 12%, PEX 35 ± 13%, MARS 24 ± 14%, $F(2,235) = 5.66$, $p = 0.04$).

PAP and PEX also led to a significant improvement in eGFR, with no differences between the two techniques. Liver function tests also showed some differences between the three techniques: cholinesterases (CHE) significantly increased above the baseline only with PAP and PEX, but not with MARS, without significant differences between the three techniques. Aspartate transaminase (AST) and alanine transaminase (ALT) were not affected by PAP, whereas AST was decreased by PEX and ALT by MARS, with significant

Table 2 Comparison of PAP, PEX and MARS on the modifications of blood parameters

	PAP	PEX	MARS	Differences among techniques, *p* (one-way ANOVA)
Relative reduction of plasma bilirubin concentration (percent of initial value)	30 ± 13.9%**	27 ± 26.6%**	26 ± 16%**	0.64
Percent improvement in filtration rate/eGFR (%)	11 ± 76%	27 ± 29%**		0.4 (Student's *t* test)
Percent increase in cholinesterases (%)	17 ± 39%**	29 ± 27%*	8 ± 22%	0.67
Percent decrease in plasma proteins (%)	4.1 ± 17.2*	Not applicable	–2.7 ± 24.1	0.34
Percent decrease in AST (%)	**−8 ± 46% ($p = 0.034$ vs PEX; $p = 0.009$ vs MARS)**	20 ± 43%*	25 ± 29%	**0.009**
Percent decrease in ALT (%)	**6.8 ± 23% ($p = 0.002$ vs PEX)**	35 ± 33%	17 ± 23% *	**0.005**
Percent decrease in PT	10 ± 62	15 ± 41	27 ± 46	0.77
Percent decrease in aPTT	−10.9 ± 38	−7.9 ± 44	0.1 ± 18	0.48

Bold indicates significant differences. eGFR has been considered only for PAP and PEX because MARS has also dialytic properties. Asterisks indicate significant differences, for a specific technique, between pre- and post-dialysis values by paired samples *t* test (*$p < 0.05$, **$p < 0.01$)

differences between the three techniques. Finally, no significant effect was found on prothrombin time (PT) or activated partial thromboplastin time (aPTT).

We then explored whether the reduction of bilirubin after the first treatment session was dependent on the initial concentration of bilirubin. As shown in Table 3, the reduction in bilirubin concentration was strictly correlated on the initial concentration of bilirubin and this linear relation was similar among the three techniques.

Furthermore, we analyzed whether liver or kidney function was affected by the amount of bilirubin removed. As shown in Table 3, the amount of bilirubin removed did not affect the kidney function; Similarly, the amount of bilirubin removed did not correlate with the modifications in CHE or with AST levels.

The type of technique used (PAP, PEX or MARS) was not significantly associated to the time of onset of the disease (acute or chronic: $p=0.29$, Chi square test), the type of liver disease (toxic, HCV, HAV, HBV, other conditions; $p=0.53$), the gender ($p=0.136$), and the exitus ($p=0.927$, Pearson Chi-Square).

Discussion

In liver failure, the use of techniques of therapeutic apheresis, such as MARS, PAP and PEX, has still insufficient evidence to clarify risk/benefit [19].

However, in liver failure, the short-term mortality depends on high levels of bilirubin [20]. Indeed, low levels of bilirubin could facilitate hepatocyte regeneration [21], whereas high levels of bile acids may induce apoptosis and cell necrosis of hepatocytes and retard hepatic regeneration [22]. The hyperbilirubinemia itself does not cause multiple organ failure, but may represent an important cofactor potentiating other insults, such as infection, rejection, or operative complications. In addition bilirubin has neurotoxic and encephalopathic effects [23].

For the aforementioned reasons, the removal of bilirubin and bile acids seems to be a plausible therapeutic target.

Our report is one of the largest case series of patients with hepatic failure treated with bilirubin absorption. As in other experiences, the ultimate goal of bilirubin adsorption was to detoxify the body at the time of liver failure, to allow the native liver to recover or for a transplant organ to become available [22].

The use of PEX and PAP for bilirubinemia treatment was established in our center before MARS became available. Afterwards, we have used the three techniques in an alternating fashion. Therefore, our clinical data allowed us to directly compare the three techniques.

When comparing the three techniques, we observe that the absolute and relative amount of bilirubin removed is not significantly different among the three techniques, although on average MARS has lower removal ability (22%) compared to PEX and PAP (30%). Although this difference was not significant in our hands, a previous study also suggested that MARS has inferior bilirubin removal capacity compared to PEX [24]. MARS has received greater attention than other ELS in the scientific literature and has already been compared to other approaches e.g. Prometheus [25, 26] and PEX [24, 27].

It has been speculated that MARS should have limited clearance capacity due to the 20-fold higher molar ratio of serum bilirubin to albumin compared to the respective dialysate [24, 28] and to the loss of albumin with time due to its binding to the filter [29].

Indeed, any system designed to remove albumin-binding toxins should consider the following rate limiting factors: (1) plasma ion strength and (2) pH [28], (3) the possible loss of albumin due to its binding to the absorber columns [29] and (4) the molar ratio of bilirubin to albumin [30].

The latter is possibly the most influential factor because we find that, independently from the technique (MARS, PEX and PAP), the absolute amount of bilirubin removal is strictly dependent on the initial amount of bilirubin and that the percent of removal is, by contrast, constant (22–30%). To explain these data, the large distribution volume of bilirubin must be considered. Being mainly present in the extravascular and intracellular compartments, a constant re-rise in bilirubin levels is observed already during the extracorporeal treatments, for the bilirubin redistribution [12]. Our data would suggest that this effect is so important that any improvement in the technique actually would lead on to a marginal optimization of bilirubin removal. Therefore, the choice of the technique (PAP, PEX or MARS) cannot be based on the amount of bilirubin to remove. As expected, all the techniques seemed to improve

Table 3 Correlations between bilirubin removal and other clinically relevant variables

	PAP	PEX	MARS
Correlation between reduction of bilirubin levels and baseline values	$R=0.501$; $p<0.01$	$R=0.575$; $p=0.016$	$R=0.593$; $p=0.025$
Correlation between amount of bilirubin removed and % change in eGFR	$R=0.12$; $p=0.328$	$R=0.28$; $p=0.307$	
Correlation between amount of bilirubin removed and % change in CHE	$R=0.319$; $p=0.058$	$R=0.734$; $p=0.158$	$R=0.882$; $p=0.118$
Correlation between amount of bilirubin removed and % change in AST	$R=0.022$; $p=0.087$	$R=0.163$; $p=0.594$	$R=0.55$; $p=0.05$

the kidney function, but this effect was much more remarkable with MARS, due to the associated dialysis.

A corollary would be that the damage of kidney function in presence of hyperbilirubinemia does not seem to be dependent on the amount of circulating bilirubinemia.

Overall, since the three techniques here compared do not differ regarding the efficiency in bilirubin removal, other criteria should be taken into consideration in the decisional process regarding the choice of a specific technique.

MARS is more expensive than PEX (4185$ vs 957$) and requires a much longer time (6 vs 1.5 h) [23]. Moreover, according to the data published by the Institute for Health Care Management, University of Duisburg-Essen, the average costs for MARS treatment alone were €14,631 per patient treated. Patients of the intervention group received, on average, 5.4 treatments which brought the average costs for a single MARS therapy to approximately €2900. According to published information, the cost of a seven-hour treatment with MARS adds up to €2165 [31].

At our institution, the average cost per treatment for MARS, PEX and PAP are as follows: MARS 3330€, PEX 610€, PAP 930€. Overall, PEX is less expensive, whereas MARS exceeds the others being 4–5 times more expensive.

In contrast, bilirubin adsorption is a safe and easy treatment modality for a team with expertise in extracorporeal therapy and can be combined with haemodialysis sessions in concomitant renal failure [12]. Moreover, when compared to PEX, PAP does not require the administration of blood products. These features may enhance both safety as well as cost-effectiveness of bilirubin absorption [12]. Moreover, there are some adverse effects that accompany PEX such as hypernatremia, metabolic alkalosis, citrate poisoning and abrupt changes in colloid osmotic pressure [32].

In addition, PEX presents risk of viral infections and depression of specific immunity [33]. Summarizing, on the basis of cost and technique simplicity, we suggest that PAP could be considered a first-line approach for patient with hyperbilirubinemia.

In the case of a kidney involvement, MARS is probably more indicated, unless a concomitant dialysis is associated to PAP treatment.

One major limitation of this study is that it cannot be excluded that each technique here considered (PAP, PEX and MARS) is set in a suboptimal condition under the current guidelines and therefore might give substantial improvements using different operating conditions. At the best, all the conclusions apply only when using exactly the conditions used in the present communication. However, we believe that, given the importance of the issue, these data will serve both as a basis for a more rigorous benchmark to compare, in the future, different bilirubin-removal techniques and to foster research in this field.

There are several points that await further investigation: which subsets of patients with liver failure would benefit the most from each type of liver support devices; when the most optimal time is for initiation of such therapy and which is the best duration of treatment [22]. Further studies are needed to explore whether organ support and patient survival could be improved using a more intensive treatment, higher dosage, and/or different schedules and also if appropriate patient selection can improve the results [34].

Conclusions

The present report discusses one of the largest case series of hepatic failure treated with bilirubin absorption, MARS or plasma exchange. The choice of the technique cannot be based on the desired concentration of plasmatic bilirubin as all three techniques are similar, with similar final outcome (exitus). Based on costs and duration of treatment, we suggest that PAP could be considered as a first-line approach. In case of kidney involvement, MARS is more indicated.

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