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双重血浆分子吸附联合低置换量血浆置换术与全量血浆置换术 治疗肝衰竭的疗效比较*

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摘要 目的:探讨双重血浆分子吸附术(DPMAS)联合低置换量血浆置换术(LPE)与全量血浆置换术(PE)治疗肝衰竭的临床疗效差异。**方法:**回顾性分析 2019 年 6 月至 2020 年 10 月在空军军医大学第二附属医院感染科治疗的 101 例肝衰竭患者的临床资料,分为双重血浆分子吸附联合低置换量血浆置换术(DPMAS+LPE)治疗组 51 例和全量血浆置换术(PE)治疗组 50 例。对首次治疗前及治疗后 24 h 的肝功能、凝血系列、血小板等实验室指标、不良反应等进行对比分析。**结果:**DPMAS+LPE 组与 PE 组治疗后两组血清总胆红素(TBIL)、谷丙转氨酶(ALT)、谷草转氨酶(AST)较治疗前均明显下降($P<0.05$),DPMAS+LPE 组对胆红素清除效果优于 PE 组,两组 TBIL 下降率分别为 $36.5\pm 17.1\%$ vs $25.2\pm 19.5\%$,差异有统计学意义($P<0.01$)。DPMAS+LPE 组治疗后凝血酶原时间(PT)、凝血酶原活动度(PTA)、活化部分凝血活酶时间(APTT)较治疗前无明显变化($P>0.05$),纤维蛋白原(FIB)、血浆白蛋白(ALB)较前有所降低($P<0.0001$),PE 组治疗后 PT、PTA、APTT 较治疗前有所改善($P<0.05$),纤维蛋白原(FIB)、血浆白蛋白(ALB)较治疗前无明显变化($P>0.05$)。两组血小板计数(PLT)较治疗前均有所降低($P<0.05$),但两组 PLT 下降率无统计学意义($P>0.05$)。两组治疗中及治疗后均未见明显不良反应。**结论:**双重血浆分子吸附联合低置换量血浆置换术,与全量血浆置换术比较,不仅在清除血清胆红素方面更有优势,且对凝血功能无明显影响,无明显不良反应,可节约血浆用量,是治疗肝衰竭有效、安全的方式,值得推广。

关键词: 双重血浆分子吸附术;低置换量血浆置换术;肝衰竭

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Comparison of the Efficacy of Double Plasma Molecular Absorb System Combined with Low-volume Exchange Plasma Exchange and Full-volume Plasma Exchange in the Treatment of Liver Failure*

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ABSTRACT Objective: To explore the clinical efficacy of double plasma molecular absorb system (DPMAS) combined with low-volume exchange plasma exchange(LPE) and full-volume plasma exchange (PE) in the treatment of liver failure. **Methods:** The clinical data of 101 patients with liver failure treated in the Department of Infectious Diseases, Second Affiliated Hospital of Air Force Military Medical University from June 2019 to October 2020 were retrospectively analyzed. Patients were divided into(DPMAS + LPE) treatment group with 51 cases and PE treatment group with 50 cases. The liver function, coagulation function, platelet parameters, and adverse reactions before the first treatment and 24 h after the treatment were compared and analyzed. **Results:** After treatment, the serum total bilirubin (TBIL), alanine aminotransferase(ALT) and aspartate transaminase (AST) in the DPMAS+LPE group and the PE group were significantly lower than before treatment ($P<0.05$). And the bilirubin clearance effect of DPMAS+LPE group was better than that of PE group ($P<0.05$). The reduction rate of TBIL in the two groups was $(36.5\pm 17.1)\%$ vs $(25.2\pm 19.5)\%$, and the difference was statistically significant ($P<0.01$). After treatment, the prothrombin time (PT), prothrombin time activity(PTA), and activated partial thromboplastin time (APTT) in the DPMAS+LPE group had no significant changes compared with those before treatment ($P>0.05$), and fibrinogen (FIB) and plasma albumin (ALB) were lower than before treatment ($P<0.0001$). After treatment, the PT, PTA, and APTT of the PE group were improved compared with those before treatment ($P<0.05$), and FIB and ALB had no significant changes compared with before treatment ($P>0.05$). The platelet counts (PLT) of the two groups were lower than before treatment ($P<0.05$), but the PLT reduction rate of the two groups was not statistically significant ($P>0.05$). There were no obvious adverse reactions during and after treatment in the two groups. **Conclusion:** Compared with PE, DPMAS combined with LPE has more advantages in clearing serum bilirubin, and it has no obvious effect on blood coagulation function and no obvious adverse reactions. At the same time, the amount of plasma can be saved, which is an

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effective and safe way to treat liver failure and is worthy of promotion.

Key words: Double plasma molecular absorb system; Low-volume exchange plasma exchange; Liver failure

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前言

肝衰竭以严重的消化道症状、黄疸、凝血功能低下、肝性脑病和高病死率为特征^[1-3],而血浆置换(PE)作为人工肝支持最经典的模式,成为肝衰竭内科治疗的重要手段^[4-6]。但由于血源匮乏、用血安全及血浆置换模式的局限性等因素,单纯血浆置换已不能满足肝衰竭患者的临床救治需求。近年来双重血浆分子吸附(DPMAS)技术以其无需血浆、可清除中大分子肝毒性物质的同时又能特异性清除胆红素等优点,在血浆短缺时成为肝衰竭人工肝救治的有力武器。但又存在可能造成术后白蛋白、凝血因子丢失等风险^[7,8]。我科自2019年开展了DPMAS联合低置换量血浆置换术(LPE)应用于肝衰竭患者,相比于全量血浆置换术,取得了良好的治疗效果。现报道如下。

1 对象与方法

1.1 研究对象

回顾性分析2019年6月至2020年10月空军军医大学第二附属医院感染科收治的肝衰竭患者临床资料共101例,所有患者均在一般内科综合治疗的基础上给予人工肝治疗,收集入院后首次人工肝治疗前后的临床资料进行分析。其中DPMAS+LPE组51例,男39例,女12例;平均年龄(46.5±13.437)岁。其中慢性肝衰竭19例;亚急性肝衰竭7例;慢加急性肝衰竭16例;急性肝衰竭9例;PE组50例,男34例,女16例;平均年龄(44.72±14.698)岁。其中慢性肝衰竭14例;亚急性肝衰竭7例;慢加急性肝衰竭17例;急性肝衰竭12例。两组性别、年龄、治疗前肝功能等一般资料比较差异无统计学意义($P>0.05$),见表1。肝衰竭诊断均符合2018年中华医学会制定的《肝衰竭诊治指南(2018年版)》^[9],并经医院伦理委员会批准,所有治疗获得患者或家属知情同意。

表1 DPMAS+LPE组及PE组肝衰竭患者治疗前一般资料比较

Table 1 Comparison of general data of liver failure patients before treatment between DPMAS+LPE group and PE group

Groups	Age (years)	Gender (male/female)	TBIL($\mu\text{mol/L}$) (pre-treatment)	PTA(%) (pre-treatment)
DPMAS+LPE	46.500± 13.437	39/12	392.96± 159.30	31.24± 6.50
PE	44.720± 14.698	34/16	404.72± 122.00	32.15± 7.50
t	0.681	0.893	-0.558	-0.666
P	0.499	0.376	0.58	0.509

1.2 材料与方法

1.2.1 仪器与材料 采用膜式血浆分离、常规肝素抗凝及股静脉置管方法,分别采用PlasmaFlux P2 dry血浆分离器、一次性使用血浆胆红素吸附器BS330、中性大孔树脂血液灌流器HA330-II(健帆生物)。

1.2.2 操作方法 所有患者治疗前均给予静注地塞米松5 mg。血浆置换方法:按血浆置换模式连接管路,用含4%肝素钠盐水1000 mL对血浆分离器进行排气冲洗管路,常规使用肝素钠抗凝,肝素总量10-20 mg,血流速度100-150 mL/min,血浆分离速度20-30 mL/min。置换液采用新鲜冰冻血浆,血浆置换量3000 mL/次,每次治疗时间为3h。双重血浆分子吸附联合低置换量血浆置换术:分别用含4%肝素钠盐水1000 mL对血浆分离器、BS330胆红素吸附器、健帆HA330-II吸附器进行排气冲洗管路,并进行串连冲洗备用,常规使用肝素钠抗凝,肝素总量10-20 mg,血流速度100-150 mL/min,血浆分离速度20-30 mL/min。先行1000 mL血浆置换,之后行DPMAS治疗,血浆处置量为5000 mL(包含1000 mL血浆)。治疗时间4h。

1.3 观察指标

(1)术中及术后不良反应发生情况:发热、皮疹、血压下降、头晕、恶心等症状、体征;(2)肝功能:血清总胆红素(TBIL)、谷

丙转氨酶(ALT)、谷草转氨酶(AST)、血浆白蛋白(ALB)、纤维蛋白原(FIB);(3)凝血功能:凝血酶原时间(PT)、凝血酶原活动度(PTA)、活化部分凝血活酶时间(APTT)、血小板(PLT)。

1.4 统计学处理

采用SPSS20.0统计软件进行统计学分析,计量资料以均数±标准差表示,两组间比较采用独立样本t检验。组内治疗前后的比较采用配对t检验。 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组治疗前后肝功能及凝血功能指标比较

DPMAS+LPE组与PE组治疗后两组血清总胆红素(TBIL)、谷丙转氨酶(ALT)、谷草转氨酶(AST)较治疗前均明显下降($P<0.05$),见表2。DPMAS+LPE组对胆红素清除效果优于PE组,两组TBIL下降率分别为36.5±17.1% vs 25.2±19.5%,差异有统计学意义($P<0.01$),见表3及图1。DPMAS+LPE组治疗后凝血酶原时间(PT)、凝血酶原活动度(PTA)、活化部分凝血活酶时间(APTT)较治疗前无明显变化($P>0.05$),纤维蛋白原(FIB)、血浆白蛋白(ALB)较前有所降低($P<0.01$),PE组治疗后PT、PTA、APTT较治疗前有所改善($P<0.05$),纤维蛋白原(FIB)、血浆白蛋白(ALB)较治疗前无明显

显变化($P>0.05$)。两组血小板计数较治疗前均有所降低($P<0.05$),但两组 PLT 下降率相比无统计学意义($P>0.05$),见表 2 及表 3。

表 2 DPMAS+LPE 与 PE 两组肝功能、凝血指标、血小板治疗前及治疗 24 h 后的比较

Table 2 Comparison of liver function, coagulation index, platelet before and after 24 h of treatment between DPMAS+LPE and PE groups

Inspection items	DPMAS+LPE(n=51)					PE(n=50)				
	pretreatment	posttreatment	t	P		pretreatment	posttreatment	t	P	
TBIL μ mol/L	392.96 $\pm$ 159.30	254.37 $\pm$ 108.44	11.236	<0.001**		404.72 $\pm$ 122.00	301.13 $\pm$ 116.93	8.133	<0.001**	
ALT U/L	409.26 $\pm$ 784.00	295.09 $\pm$ 718.24	3.818	<0.001**		227.38 $\pm$ 491.80	114.52 $\pm$ 191.02	2.485	0.017*	
AST U/L	297.31 $\pm$ 333.38	183.93 $\pm$ 219.24	4.203	0.000**		158.02 $\pm$ 273.85	93.38 $\pm$ 123.58	2.81	0.007**	
ALB g/L	34.12 $\pm$ 5.03	31.20 $\pm$ 4.06	3.692	0.001**		34.40 $\pm$ 5.94	34.33 $\pm$ 3.90	0.078	0.938	
PT sec	21.70 $\pm$ 9.25	22.93 $\pm$ 10.77	-0.968	0.338		22.23 $\pm$ 8.83	18.15 $\pm$ 5.76	4.768	<0.001**	
PTA %	31.24 $\pm$ 6.50	29.41 $\pm$ 6.83	1.833	0.073		32.15 $\pm$ 7.50	38.42 $\pm$ 10.47	-4.603	<0.001**	
FIB g/L	1.46 $\pm$ 0.72	1.20 $\pm$ 0.50	3.993	<0.001**		1.38 $\pm$ 0.53	1.39 $\pm$ 0.45	-0.152	0.88	
APTT sec	44.77 $\pm$ 11.67	49.17 $\pm$ 18.99	-1.648	0.107		45.45 $\pm$ 16.56	39.61 $\pm$ 17.45	2.348	0.023*	
PLT $\times 10^9$ /L	104.63 $\pm$ 54.22	94.05 $\pm$ 52.57	2.13	0.039*		101.81 $\pm$ 94.62	89.88 $\pm$ 77.96	2.773	0.008**	

Note: * $P<0.05$; ** $P<0.01$.

表 3 DPMAS+LPE 与 PE 两组肝功能、凝血指标、血小板治疗前及治疗 24 h 后下降率的比较

Table 3 Comparison of liver function, coagulation index, platelet decrease rate before treatment and 24 h after treatment between DPMAS+LPE group and PE group

Decrease rate of inspection items	TBIL%	ALT%	AST%	ALB%	PTA%	FIB%	PLT%
DPMAS+LPE	36.5 $\pm$ 17.1	25.8 $\pm$ 27.1	26.9 $\pm$ 28.2	7.9 $\pm$ 13.1	1.1 $\pm$ 30.5	17.7 $\pm$ 37.4	10.3 $\pm$ 20.6
PE	25.2 $\pm$ 19.5	29.2 $\pm$ 29.3	23.2 $\pm$ 38.5	-1.2 $\pm$ 15	-24.8 $\pm$ 45.3	0.2 $\pm$ 39.7	0.4 $\pm$ 57.3
t	2.676	-0.588	0.501	2.836	4.036	2.374	0.954
P	0.010*	0.56	0.619	0.007**	<0.001**	0.022*	0.347

Note: * $P<0.05$; ** $P<0.01$.

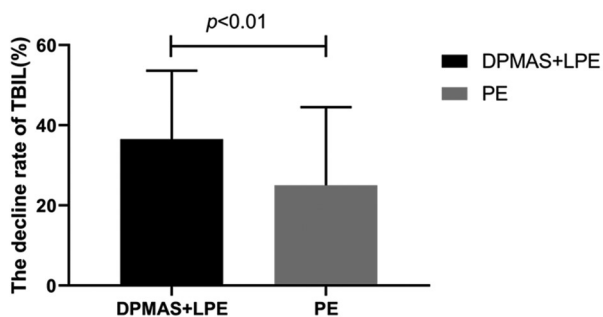


图 1 DPMAS+LPE 与 PE 两组总胆红素治疗前及治疗 24 h 后下降率的比较

Fig. 1 Comparison of the decrease rate of total bilirubin between DPMAS+LPE group and PE group before treatment and 24 h after treatment

2.2 不良反应

两组患者治疗中及治疗 24 h 后均未见发热、皮疹、血压下降、头晕、恶心等症状,未见破膜、管路堵塞等情况发生。

3 讨论

能有效清除肝衰竭时患者体内水溶性毒素、蛋白结合毒素

及代谢产物等,是人工肝技术发挥肝衰竭临床救治作用的关键^[10,11],其中血浆置换术作为最经典的人工肝治疗手段已广泛应用于肝衰竭患者的临床救治,但其治疗模式单一不能完全满足清除各类毒素的需求,还面临血浆短缺的限制^[10,12-15]。近年来双重血浆分子吸附术以其无需血浆、能有效吸附肝毒性物质等优势,成为肝衰竭人工肝治疗的后起之秀,但也存在影响凝血功能等隐患^[16,17]。将两者联合应用是否能达到取长补短的作用成为临床研究的热点^[18,19]。本研究回顾性分析了双重血浆分子吸附联合低置换量血浆置换术与单纯全量血浆置换术用于慢加急性肝衰竭患者的临床疗效,发现两者均可明显降低 TBIL、ALT、AST 等水平,DPMAS+LPE 组在清除血清胆红素方面更有优势,且对 PT、PTA、APTT 影响不大,无明显不良反应,可节约血浆用量,是治疗肝衰竭有效、安全的方式,值得临床推广。

本研究 DPMAS+LPE 组及 PE 组均能有效降低总胆红素水平,DPMAS+LPE 组治疗前及治疗 24 小时后 TBIL 分别为 392.96 $\pm$ 159.30 μ mol/L vs 254.37 $\pm$ 108.44 μ mol/L, $P<0.001$;PE 组治疗前及治疗 24 小时后 TBIL 分别为 404.72 $\pm$ 122.00 μ mol/L vs 301.13 $\pm$ 116.93 μ mol/L, $P<0.001$ (见表 2),且 24 小时总胆红素下降率 DPMAS+LPE 组明显优于单纯 PE 组治疗,分别为 36.5 $\pm$ 17.1% vs 25.2 $\pm$ 19.5%, $P<0.01$, (见表及图 1)。这

与近期 Yao 等^[7] 研究结果一致, 该研究对比观察了单纯 PE (2200-2400 mL 血浆) 77 例及 DPMAS 联合半量血浆置换 (1100-1200 mL 血浆) 54 例对肝功能指标和 28 天生存率的影响, 结果表明 24 小时和 72 小时总胆红素下降率 DPMAS 联合半量 PE 明显优于单纯 PE 治疗, 中晚期患者 28 天生存率 DPMAS 加半量 PE 组明显优于单纯 PE 组 (57.4% vs 41.7%, $P=0.043$)。

本研究两组患者在治疗中及治疗后均未见发热、寒战、血压变化等不良反应发生。在对凝血功能的影响方面, 尽管 DPMAS+LPE 组在治疗 24 小时后 FIB 下降, 分别为 1.46 ± 0.72 g/L vs 1.20 ± 0.50 g/L, $P<0.001$, 但 PT、PTA、APTT 在 DPMAS+LPE 组治疗 24 小时后无变化, 表明 DPMAS+LPE 的模式未对凝血功能造成明显影响。相比而言, 单纯全量 PE 组在提升凝血功能方面确有优势^[6,20], 虽然在治疗 24 小时后 FIB 并无变化, 但可见 PT、PTA、APTT 在 PE 组治疗 24 小时后明显改善。此外, PE 组治疗 24 小时后白蛋白无变化, 但 DPMAS+LPE 组治疗 24 小时后有所下降, 分别为 34.12 ± 5.03 g/L 31.20 ± 4.06 g/L, P 值为 0.001 (见表 2)。这就提示我们在 DPMAS+LPE 治疗后仍需输注白蛋白加强支持治疗, 必要时可输注 FIB。由于血浆短缺严重, 本研究 DPMAS+LPE 组采用的血浆量为 1000 mL, 对于凝血功能严重低下的患者, 在进行 DPMAS 联合 PE 治疗时, 可考虑适当增加血浆用量以改善凝血功能。需注意的是, 两组治疗 24 小时后均可见血小板较前降低 (见表 2), 但两组相对对血小板的影响无统计学差异 (见表 3), 其降低原因可能与血液流经血浆分离器或血液管路时血小板机械损伤、破坏或吸附等造成^[21,22]。

既往研究表明大量 PE 可提高急性肝衰竭生存率^[23-27], 同时可补充体内缺乏的白蛋白和凝血因子等^[28-30], 但由于血浆供应短缺, 采用全量的新鲜冻干血浆进行 PE 治疗受到很大限制, 而 DPMAS 无需血浆, 在对分离的血浆持续经过大孔径 HA330-II 和离子交换柱 BS330 吸附后, 可高效清除中大分子和蛋白结合毒素, 特异性清除胆红素, 但其存在部分凝血因子及白蛋白被吸附丢失的弱点。本研究表明了两组联合方案时采用 1000 mL 血浆, 一方面大大节约了血浆, 一方面相较于单纯 PE 对于胆红素的清除能力大大提升, 且未对凝血功能造成明显影响, 两种模式联合可互相取长补短^[31-35], 不失为肝衰竭人工肝治疗的较好选择。

本研究为回顾性研究, 研究数据也较少, 对于双重血浆分子吸附术联合低置换量血浆置换术对肝衰竭患者的有效性、安全性及生存率影响等尚需进一步前瞻性研究以证实。

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