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献血者捐献单采血小板贮存期间血小板扩散功能的变化*

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摘要 目的:探讨献血者捐献单采血小板贮存期间血小板扩散功能的变化。**方法:**2017年8月到2020年6月选择在本血站参加单采血小板献血的献血者66例作为研究对象,每个献血者的单采血小板血液样本分为3管-A管、B管与C管,将产品置于血小板振荡保存箱22℃振荡保存,分别在贮存第1d(A管)、第3d(B管)、第5d(C管),检测血小板扩散功能的变化情况。**结果:**A管、B管与C管的Hct(Hematocrit,红细胞压积)、Hb(Hemoglobin,血红蛋白)、PDW(Platelet distribution width,血小板分布宽度)、WBC(leukocyte,白细胞)、RBC(Red blood cell,红细胞)、血小板(Platelets,PLT)、MPV(Mean platelet volume,平均血小板体积)对比差异无统计学意义($P>0.05$),B管与C管的P-LCR(platelet-larger cell ratio,大型血小板比例)值与血清白介素(Interleukin,IL)-1 β 、IL-6、肿瘤坏死因子(Tumor necrosis factor, TNF)- α 含量高于A管($P<0.05$),C管高于B管($P<0.05$)。B管与C管的血小板膜糖蛋白CD62p表达水平高于A管($P<0.05$),血小板最大聚集率低于A管($P<0.05$),C管与B管对比差异也都有统计学意义($P<0.05$)。A管、B管与C管的扩散后血小板合格率分别为97.0%、86.4%、77.3%,三组间对比差异有统计学意义($P<0.05$)。**结论:**献血者捐献单采血小板贮存时间可影响血小板扩散功能,导致炎症细胞因子释放量增加,可降低血小板血小板最大聚集率,提高血小板膜糖蛋白CD62p表达水平,从而降低输注疗效。

关键词:献血者;单采血小板;贮存时间;扩散功能;炎症因子;凝血功能;大型血小板比例

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Changes of Platelet Diffusion Function During Storage of Apheresis Platelets from Blood Donors*

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ABSTRACT Objective: To investigate the changes of platelet diffusion function during storage of apheresis platelets from blood donors. **Methods:** A total of 66 blood donors, who participated in platelet apheresis blood donation at blood centers in the region from August 2017 to June 2020, were selected as the research subjects. The platelet apheresis blood sample of each case was divided into 3 tubes-A tube, B tube and C tube, which were stored in a platelet incubator at 20 °C, tube A 1d after storage, tube B 3 d after storage, and tube C 5 d after storage were detected platelet diffusion functional changes. **Results:** There were not significantly differences in the Hct (Hematocrit), Hb (Hemoglobin), PDW (Platelet distribution width), WBC (leukocyte), RBC (Red blood cell), Platelets(PLT), and MPV (Mean platelet volume) among tube A, tube B and tube C($P>0.05$). The P-LCR (platelet-larger cell ratio), serum interleukin (IL)-1 β , IL-6, and tumor necrosis factor (Tumor necrosis factor, TNF)- α content of tube B and tube C were higher than those of tube A ($P<0.05$), tube C were higher than tube B ($P<0.05$). The expression levels of platelet membrane glycoprotein CD62p in tube B and tube C were higher than those in tube A ($P<0.05$), and the maximum platelet aggregation rate in tube B and tube C was lower than that in tube A ($P<0.05$), and the difference between tube C and tube B was also statistically significant ($P<0.05$). The platelet pass rate after diffusion of tube A, tube B and tube C were 97.0 %, 86.4 %, and 77.3 %, respectively, with statistically significant differences among the three groups ($P<0.05$). **Conclusion:** The storage time of apheresis platelets donated by blood donors may affect the platelet diffusion function, increase the release of inflammatory cytokines, can reduce the maximum platelet aggregation rate and increase the expression level of platelet membrane glycoprotein CD62p, thus reducing the efficacy of infusion.

Key words: Blood donors; Apheresis platelet; Storage time; Diffusion function; Inflammatory factor; Coagulation function; Platelet-larger cell ratio

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前言

随着医疗卫生事业的不断发展,临床用血量呈显著上升趋势^[1]。特别是内外因素导致血小板功能异常、血小板计数降低引起的严重出血者,在临床输血量中多对血小板的需求量更多^[2,3]。血小板(Platelets, Plt)是人类身体中重要的血液成分,当机体血小板数量减少或出现功能异常时,就会导致机体出血^[4]。单采血小板(Apheresis platelets)是使用血细胞分离机在完全封闭的条件下,献血者血液中的血小板自动分离并悬浮于一定量血浆内的单采成分血。单采血小板由单个供血者提供,具有血小板浓度高、纯度高、输注剂量易于掌握等特点^[5,6]。并且其可降低发生人类白细胞抗原(human leukocyte antigen, HLA)同种免疫反应输血不良反应的风险^[7,8]。并且捐献单采血小板后献血者体内红细胞(Red blood cell, RBC)和白细胞(White blood cell, WBC)的损失量较少,机体短期内很快代偿恢复,对献血者造血及凝血系统的影响比较小^[9,10]。单采血小板一般在采集后 2~5 d 发至临床应用,血小板在贮存期可能导致血小板形态与功能变化,影响血小板的质量稳定性,造成临床血小板使用质量下降,输血后,可能导致血小板相关的并发症,包括轻、中度不良反应(发热、炎症)以及危及患者的生命^[11,12]。因此,本文具体探讨了献血者捐献单采血小板贮存期间血小板扩散功能的变化,希望在一定程度上杜绝血液安全隐患,对临床输血的安全性和有效性具有重要意义。

1 资料与方法

1.1 研究对象

2017 年 8 月到 2020 年 6 月选择在本血站参加单采血小板献血的献血者 66 例作为研究对象,纳入标准:年龄 55~60 岁,具有献血指征;献血前体检结果符合“献血者健康检查要求”;2 次献血时间间隔≥1 个月;自愿参加本研究;献血前 14 d 内未服用任何影响血小板功能及代谢的药物者;上肢静脉充盈度良好。排除标准:高血压、糖尿病献血者;合并免疫系统异常者;合并肿瘤献血者;合并炎症性疾病献血者等。

其中男 36 例,女 30 例;年龄最小 55 岁,最大 60 岁,平均年龄 57.47±2.15 岁;平均体质指数 23.18±2.11 岁;平均献血次数 2.41±0.18 次,均为再次献血者。

1.2 单采血小板与贮存方法

全自动血凝仪(Sysmex CA7000,日本 Sysmex 公司)、全自动血浆速冻机(MBF-21,美国多美达公司)、低温离心机(捷安公司)、冰冻血浆解冻箱(苏州医用仪器厂)、流式细胞仪(EPICS-XL 型)、血液细胞自动分析仪(MICROS-60 型)。

选择血细胞分离机用于单次机采血小板,每个献血者的血液样本分为 3 管-A 管、B 管与 C 管,都依靠重力进行分离,分离速率 80~100 mL/min。将产品置于血小板振荡保存箱 22℃振荡保存。3 管血液样本分别在贮存第 1 d(A 管)、第 3 d(B 管)、第 5 d(C 管)后处理。

1.3 检测指标

(1)检测 3 管血液样本的常规血常规参数指标,包括 Hct(Hematocrit,红细胞压积)、P-LCR(platelet-larger cell ratio,大型血小板比例)、Hb(Hemoglobin,血红蛋白)、PDW(Platelet distribution width,血小板分布宽度)、WBC(leukocyte,白细胞)、RBC(Red blood cell,红细胞)、血小板(Platelets, PLT)、MPV(Mean platelet volume,平均血小板体积)等。(2)取 3 管血液样本,3000 r/min 离心 10 min,取血清组织,采用酶联免疫法检测血清 IL-1β、IL-6、TNF-α 含量,检测试剂盒购自上海生物工程有限公司,严格按照说明书进行测定。(3)取 3 管血小板样本,采用流式细胞检测血小板膜糖蛋白 CD62p 表达水平,同时进行血小板聚集试验,观察血小板最大聚集率。(4)扩散后血小板合格率标准:ALT 值≤50 U/L,150×10⁹/L≤血小板计数<450×10⁹/L, HCT≥0.36,4.0×10⁹/L≤WBC≤10.0×10⁹/L,男性 Hb≥120 g/L,女性 Hb 值≥115 g/L,HBsAg 阴性、HIV、HCV、TP 均为阴性,血浆外观呈淡黄色、透明。

1.4 统计方法

采用 SPSS 25.00,计数数据以(%)表示,两两对比为卡方 χ^2 检验;计量数据以均数±标准差($\bar{x} \pm s$)表示,两两对比为独立样本 t 检验,计数数据与计量数据的多组间对比为方差 F 检验,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 常规血液学指标对比

A 管、B 管与 C 管的 Hct、Hb、PDW、WBC、RBC、PLT、MPV 值对比差异无统计学意义($P>0.05$),B 管与 C 管的 P-LCR 值高于 A 管($P<0.05$),C 管的 P-LCR 值高于 B 管($P<0.05$),见表 1。

表 1 三管常规血液学指标对比($\bar{x} \pm s$)

Table 1 Comparison of conventional hematology indexes of 3 tubes ($\bar{x} \pm s$)

Index	A pipe (n=66)	B pipe (n=66)	C pipe (n=66)	F	P
Hct(%)	0.43±0.04	0.44±0.03	0.43±0.02	0.123	0.899
Hb(g/L)	142.57±11.39	143.02±12.00	142.76±12.57	0.349	0.765
PDW(%)	10.45±1.58	10.55±2.10	10.47±1.57	0.233	0.856
WBC(×10 ⁹ /L)	6.31±0.22	6.32±0.45	6.29±0.73	0.299	0.812
RBC(×10 ¹² /L)	4.82±0.32	4.83±0.27	4.82±0.33	0.102	0.923
PLT(×10 ⁹ /L)	230.76±10.44	231.65±8.82	230.92±10.00	0.093	0.956
MPV(fl)	8.92±0.71	8.93±0.65	8.99±0.71	0.388	0.713
P-LCR(%)	0.18±0.02	0.21±0.02*	0.24±0.02*#	6.555	0.021

Note: Compared with tube A, * $P<0.05$; compared with tube B, # $P<0.05$.

2.2 炎症因子指标对比 ($P<0.05$), C 管的血清 IL-1 β 、IL-6、TNF- α 含量高于 B 管 ($P<0.05$), 见表 2。
B 管与 C 管的血清 IL-1 β 、IL-6、TNF- α 含量高于 A 管

表 2 三管血清炎症因子指标对比(pg/mL, $\bar{x} \pm s$)

Table 2 Comparison of serum inflammatory factors of 3 tubes (pg/mL, $\bar{x} \pm s$)

Index	A pipe (n=66)	B pipe (n=66)	C pipe (n=66)	F	P
IL-1 β	6.22 $\pm$ 0.14	7.17 $\pm$ 0.22*	7.98 $\pm$ 0.87**	7.013	0.014
IL-6	4.09 $\pm$ 0.27	5.13 $\pm$ 0.28*	6.09 $\pm$ 0.33**	8.275	0.005
TNF- α	22.47 $\pm$ 3.11	25.09 $\pm$ 2.56*	28.76 $\pm$ 3.11**	7.444	0.010

Note: Compared with tube A, * $P<0.05$; compared with tube B, ** $P<0.05$.

2.3 血小板膜糖蛋白 CD62p 表达水平与血小板最大聚集率对比 ($P<0.05$), 血小板最大聚集率低于 A 管 ($P<0.05$), C 管与 B 管对比差异也都有统计学意义 ($P<0.05$), 见表 3。

B 管与 C 管的血小板膜糖蛋白 CD62p 表达水平高于 A 管

表 3 三管血小板膜糖蛋白 CD62p 表达水平与血小板最大聚集率对比($\bar{x} \pm s$)

Table 3 Comparison of coagulation indexes of 3 tubes of blood sample ($\bar{x} \pm s$)

Index	A pipe (n=66)	B pipe (n=66)	C pipe (n=66)	F	P
Platelet membrane glycoprotein CD62p	32.32 $\pm$ 9.81	16.02 $\pm$ 2.17*	2.33 $\pm$ 0.31**	18.022	0.000
Maximum platelet aggregation rate(%)	18.00 $\pm$ 0.22	6.49 $\pm$ 0.58*	2.24 $\pm$ 0.24**	9.113	0.001

Note: Compared with tube A, * $P<0.05$; compared with tube B, ** $P<0.05$.

2.4 3 管扩散后血小板合格率的对比 86.4 %、77.3 %, 三组间对比差异有统计学意义 ($P<0.05$), 见表 4。
A 管、B 管与 C 管的扩散后血小板合格率分别为 97.0 %、

表 4 三管扩散后血小板合格率对比

Table 4 Comparison of platelet qualification rate after 3 tubes of diffusion

Groups	n	Qualification	Qualification rate
A pipe	66	64	97.0 %
B pipe	66	57	86.4 %*
C pipe	66	51	77.3 %**
F			11.246
P			0.004

Note: Compared with tube A, * $P<0.05$; compared with tube B, ** $P<0.05$.

3 讨论

由于受工作环境、交通运输、生活环境、饮食习惯等因素的影响, 严重性创伤、血液病和恶性肿瘤发生率逐年升高, 使得对单采血小板制品的需求日益增加^[13,14]。单采血小板由单个供血者提供, 具有纯度高、输血相关不良反应少、输注剂量易于掌控、白细胞和红细胞污染率低等优点, 其可精确测得血小板的最终数目, 从而可大量应用于临床, 也可节约血液资源^[15,16]。但是贮存对血液质量有一定的负面影响, 且单采的血小板存在血液保存环节, 可能消耗部分凝血因子^[17,18]。本研究显示 A 管、B 管与 C 管的 Hct、Hb、PDW、WBC、RBC、PLT、MPV 值对比差异无统计学意义, B 管与 C 管的 P-LCR 值高于 A 管, C 管的 P-LCR 值高于 B 管, 表明献血者单采血小板贮存期的绝大多

数血液指标如 WBC、RBC、PLT 等都在正常参考范围内^[19]。与张进萍^[20]的研究类似, 讨不同储存时间对少白细胞单采血小板 (leukocyte-reduced apheresis platelet, LRA-Plt) 中外泌体 (exosome, EXO) 释放及内容物的影响, 结果显示储存早期 (储存 d 1、2), LRA-Plt 来源 EXO 的粒径较小, 分布多在 30-40 nm; 蛋白和 RNA 含量较低, 2 组间粒径分布, 蛋白和 RNA 含量无显著差异。储存中晚期, LRA-Plt 来源 EXO 的粒径较储存早期大, 分布多在 130-200 nm, 蛋白和 RNA 含量较早期显著上升; 与储存早期相比, 储存中晚期 LRA-Plt 中 EXO 在粒径分布, 蛋白和 RNA 含量上均出现显著上升。说明在于单采血液样本具有强大的自我调节功能, 同时献血者只要遵守体检标准并按照规定时限内捐献单采血小板, 常规外周血指标能较快恢复正常生理水平, 不会影响献血者的身体健康^[21]。不过贮存时间可能提高

大型血小板比例,从而影响血小板紊乱,导致输注者可能出现血小板功能紊乱^[22,23]。

血小板作为成分输血的重要组成部分受到广泛关注,单采血小板指的是对献血者使用血液成分单采机进行血小板采集,其在保存可能多具有很高的安全性,减少同种免疫反应以及输血造成的传染疾病,也能够增加血小板储存以及气体交换的面积^[24,25]。不过血液经过保存后血清中存在着大量细胞因子,包括 IL-1 β 、IL-6、TNF- α 等,这些细胞因子随血液保存时间的延长而增多^[26]。上述细胞因子的大量表达可刺激温度感应神经元调定点上移,导致输注者出现寒战和发热^[27]。本研究显示 B 管与 C 管的血清 IL-1 β 、IL-6、TNF- α 含量高于 A 管, C 管的血清 IL-1 β 、IL-6、TNF- α 含量高于 B 管。表明血小板随保存时间延长, IL-1 β 、IL-6、TNF- α 含量明显增加。与蔡红军^[28]的研究类似,该学者探究血小板贮存期间血小板扩散功能和炎症介质的变化,结果显示与第 1 d 比较,第 3、5 d 血小板的扩散能力下降,第 5 d 血小板的扩散能力低于第 3 d; 与第 1 d 比较,第 3、5 d 的血栓素 B2 (TXB2),前列腺素 E2(PGE2),血小板因子 4(PF4),可溶性 CD40L (SCD40L),CD62P 等炎症因子均增加,第 5 d 的 TXB2,CD62P 和 ROS 均高于第 3 d。

活化的血小板可释放出趋化因子、血管收缩物质、凝血因子等,促进凝血酶生成、血管痉挛^[29,30];并且活化的血小板形态发生变化,使其表面的糖蛋白 CD62p 表达水平增加,使血小板之间形成交叉连接,使得血小板最大聚集率降低^[31-33]。有学者研究显示细胞松弛素 B 可以维持长期低温保存血小板膜的完整性,从而提高血小板的存活率,但长期低温保存的血小板输入体内后会被很快清除,导致止血功能下降^[34,35]。研究显示 B 管与 C 管的血小板膜糖蛋白 CD62p 表达水平高于 A 管,血小板最大聚集率低于 A 管, C 管与 B 管对比差异也都有统计学意义。同时本研究显示 A 管、B 管与 C 管的扩散后血小板合格率分别为 97.0 %、86.4 %、77.3 %, 三组间对比差异有统计学意义,其中血小板不合格的主要原因为血小板计数下降、HCT 下降、ALT 值升高、WBC 值不合格等。本研究也存在一定的不足,纳入的血液样本数量比较少,且观察的时间点比较短,将在后续研究中进行探讨。

总之,献血者捐献单采血小板贮存时间可影响血小板扩散功能,导致炎症细胞因子释放量增加,可降低血小板血小板最大聚集率,提高血小板膜糖蛋白 CD62p 表达水平,从而降低输注疗效。

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