

Clinical Observation of Danshen Ligustrazine Injection in the Treatment of aPL Positive Recurrent Spontaneous Abortion

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Abstract

Objective: To observe the efficacy and safety of Danshen Ligustrazine Injection (DLI) in aPL-positive recurrent abortion women. **Methods:** 180 cases of selected outpatients were included in this experiment: 90 cases in the control group and 90 cases in the treatment group. Blood D-dimer (D-Di), platelet aggregation rate (PAR) and uterine artery RI and PI values of patients in the control group (heparin + dydrogesterone + folic acid) and the treatment group (DLI + heparin + dydrogesterone + folic acid) were detected. And the live birth rate, preterm birth rate and other adverse events were observed and calculated. **Results:** The overall live birth rate of the treatment group was higher than that of the control group ($P < 0.05$). The incidence of preeclampsia, vaginal bleeding and drug-induced liver injury in the treatment group was lower than that in the control group ($P < 0.05$). There was no significant difference in the incidence of premature birth rate and fetal malformation between the two groups ($P > 0.05$). D-Di, platelet aggregation rate, bilateral uterine artery RI, and PI values showed a downward trend after treatments in two groups, but the treatment group showed a more significant decrease ($P < 0.05$). **Conclusion:** DLI can improve the hypercoagulability of patients, improve the uterine hemodynamics during pregnancy, promote the maintenance of pregnancy, increase the live birth rate, and reduce the incidence of pre-pregnancy. In combination with heparin, it can enhance heparin anti-coagulation and anti-abortion effects, reduce the incidence of heparin drug-induced liver injury and does not increase the incidence of adverse events, such as premature delivery, fetal malformation and vaginal bleeding. The medication during pregnancy is safe and effective.

Keywords

Traditional Chinese Medicine, Danshen Ligustrazine Injection, Recurrent Spontaneous Abortion, Low Molecular Weight Heparin

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丹参川芎嗪针治疗aPL阳性复发性流产的临床观察

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摘要

目的: 观察丹参川芎嗪针对aPL阳性复发性流产女性中的保胎疗效及安全性。**方法:** 收集有效门诊病历180例; 对照组与治疗组各90例, 观察对照组(肝素 + 地屈孕酮 + 叶酸干预)与治疗组(在对照组基础上加用丹参川芎嗪针)患者血D二聚体(D-Di)、血小板聚集率及患者双侧子宫动脉RI、PI指标变化, 并通过回访了解各组活产率、早产率及其它不良事件发生率。**结果:** 治疗组总体活产率高于对照组($P < 0.05$)。治疗组子痫前期、阴道出血发生率及药物性肝损伤发生概率低于对照组($P < 0.05$)。两组早产率、胎儿畸形发生率无统计学意义($P > 0.05$)。两组治疗后D-Di、血小板聚集率、双侧子宫动脉RI、PI值均呈下降趋势, 且治疗组下降更明显($P < 0.05$)。**结论:** 丹参川芎嗪针能改善患者高血凝状态, 改善患者妊娠期子宫血流动力学指标, 促进妊娠的维持, 增加活产率, 降低子痫前期的发生。配合肝素使用, 增强肝素抗凝及保胎作用, 减轻肝素药物性肝损伤发生概率, 不增加早产、胎儿畸形、阴道出血不良事件发生率。孕期用药安全性高。

关键词

中药, 丹参川芎嗪针, 复发流产, 低分子肝素

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1. 引言

发生连续 2 次及以上的自然流产, 称为复发性流产(RSA), 其病因病机复杂, 育龄期妇女发病率达 1%~3% [1]。抗磷脂抗体(antiphospholipid antibodies aPL)是一组异质性的自身抗体, 可在 0%~5%人群中被检出[1] [2], 它与复发性流产、死胎[3] [4] [5] [6] [7]、先兆子痫、胎儿宫内生长受限、早产[4] [7] [8] [9] [10]、动静脉血栓形成[11] [12] [13] [14]等疾病发生有关。其中超过 40%的女性可出现复发性流产、死胎[3] [4] [5] [6] [7]。aPL 能与 β_2 糖蛋白(β_2 -GPI) [15]结合, 激活血小板, 损伤血管内皮, 激活补体系统, 促进大量促凝因子的产生、胎盘血管血栓的形成, 导致流产、妊娠期子痫前状态的发生。抗凝抗血小板药成为治疗 APS 复发性流产的重要药物。基于凝血亢进与 APS 不良妊娠间的联系, 及丹参川芎嗪针的改善血供及组织代谢的药理作用, 我们展开了对丹参川芎嗪针对 aPL 阳性复发性流产患者妊娠结局影响的临床研究。

2. 资料与方法

2.1. 资料

2.1.1. 一般资料

收集 2014 年 3 月至 2017 年 3 月首次就诊我科的有连续流产 2 次及以上流产经历的女性共 180 人; 其中流产 2 次者 100 人; 流产 3 次者 60 人; 流产 4 次及以上者 20 人。通过随机数字法将其随机均分入对照组及治疗组中。本研究 2013 年得到机构伦理委员会的道德批准, 所有参与本研究的女性均获得知情同意。

2.1.2. 纳入标准

1) 符合第 8 版《妇产科学》及中华医学会妇产科学分会 2016 年发布的 RSA 诊治指南中相关标准; 2) 具有以下一项及以上指标阳性: D-二聚体(D-Di) > 0.5 mg/L, 抗心磷脂抗体(anticardiolipin antibody, ACA)阳性, 抗 β_2 糖蛋白(β_2 GP-I)阳性, 狼疮抗凝物(LA)阳性, 血小板聚集率(PAgT) > 69%。

2.1.3. 排除标准

1) 夫妇双方有一方及以上染色体异常; 2) 男方精液常规异常; 3) 有肝素使用禁忌症者; 或因早孕反应严重服药困难者。4) 有子宫畸形, 宫腔粘连、子宫肌瘤、子宫内膜异位症及盆腔炎者。5) 排除内分泌疾病: 糖尿病、甲亢等内分泌疾病患者。除 ACA、 β_2 GP-I、LA 外有其它自身抗体阳性者。6) 有生殖道急性感染者。7) 夫妻双方一方及以上具有抽烟或酗酒史。

2.2. 方法

2.2.1. 治疗方法

从备孕前 3 个月开始, 所有受试对象开始常规服用叶酸 400 μ g/d; 自 B 超确定宫内妊娠起, 两组均口服地屈孕酮片(苏威制药生产) 10 mg po bid; 并予低分子肝素(葛兰素史克有限公司) 4100IU IH q12h; 治疗组在对照组基础上加用 5%葡萄糖 250 ml 配丹参川芎嗪 3 ml ivgtt qd。一般患者常规保胎至 12 周, 若患者 D-Di、凝血功能等指标检测项目恢复正常, 胎儿生长发育良好, 与孕周相符, 患者未出现阴道流血、腰酸腹痛症状可考虑提前停药, 停药后仍每月复查凝血指标及胎儿 B 超, 必要时重新用药。

2.2.2. 监测指标

所有受试者规律检测排卵, 排卵同房后 10 日每日抽血检查 β HCG, 判断患者是否妊娠。从确定妊娠后放入 D1 天开始用药, 患者用药后每 14 d 空腹测查血清 D-Di 浓度、肝功能指标, 血小板聚集率; 盆腔 B 超检查患者双侧子宫动脉 RI、PI 值。治疗期间记录患者不良反应。并通过回访了解各组活产率、早产率及其它不良事件发生率。

2.2.3. 统计方法

采用 SPSS22.0 进行数据统计分析, 计量资料以 $\bar{x} \pm s$ 表示, 治疗前后比较采用配对 t 检验; 组间比较采用随机区组设计方差分析, 并用 SNK-q 法进行多个样本均数之间的两两比较。计数资料用百分比表示, 组间比较采用卡方检验, 所有实验均以 $P < 0.05$ 为水准进行统计学分析。重复检测资料采用拟合广义线性混合效应模型(MIXED)进行统计学分析。

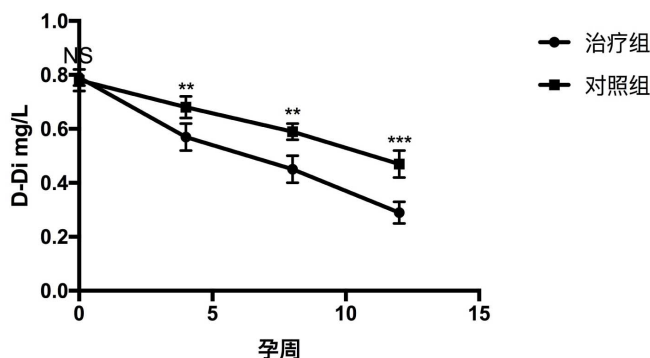
3. 结果

比较孕前、孕 4 周、孕 8 周、孕 12 周患者血液各指标的变化。实验过程中治疗组缺失 2 人, 对照组缺失 1 人。

3.1. 凝血指标

3.1.1. 血 D-Di 水平变化

如图 1 所示, 相同孕周治疗组与对照组各指标进行比较, 重复检测资料通过拟合广义线性混合效应模型(MIXED)进行统计学分析。药物干预后, 对照组与治疗组 D-Di 平均值均呈下降趋势(时间 $P < 0.05$), 且治疗组的下降趋势较对照组更明显(处理因素 $P < 0.01$)。

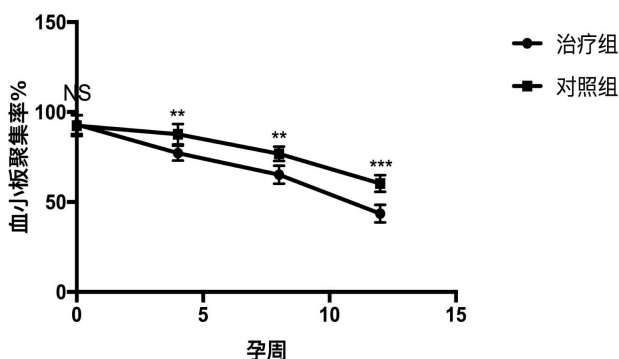


注: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ 。

Figure 1. Comparison of D-Di blood level between the treatment group and the control group
图 1. 治疗组、对照组 D-Di 含量比较

3.1.2. 血液血小板聚集率变化

如图 2 所示, 相同孕周治疗组与对照组各指标进行比较, 重复检测资料通过拟合广义线性混合效应模型(MIXED)进行统计学分析。药物干预后, 对照组与治疗组血小板聚集率平均值均呈下降趋势(时间 $P < 0.05$), 且治疗组的下降趋势较对照组更明显(处理因素 $P < 0.05$)。



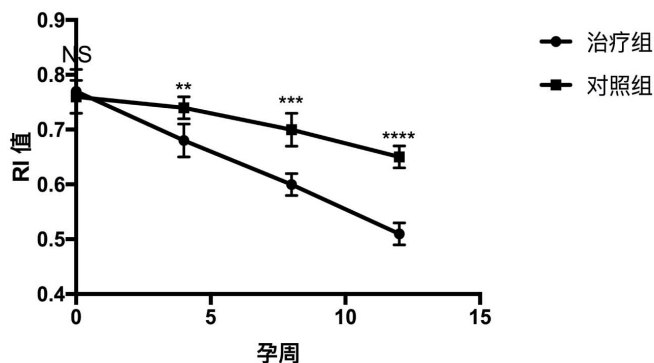
注: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ 。

Figure 2. Comparison of platelet aggregation rate between the treatment group and the control group
图 2. 治疗组、对照组血小板聚集率含量比较

3.2. 子宫动脉血流参数指标

3.2.1. 子宫动脉 RI 值变化

如图 3 所示, 相同孕周治疗组与对照组各指标进行比较, 重复检测资料通过拟合广义线性混合效应模型(MIXED)进行统计学分析。药物干预后, 对照组与治疗组子宫动脉 RI 平均值均呈下降趋势(时间 $P < 0.01$), 且治疗组的下降趋势较对照组更明显(处理因素 $P < 0.01$)。



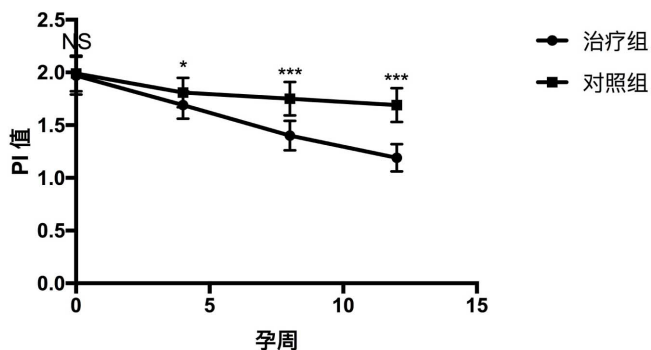
注: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ 。RI 值取双侧子宫动脉的平均值。

Figure 3. Comparison of uterine artery RI value between the treatment group and the control group
图 3. 治疗组、对照组子宫动脉 RI 值比较

3.2.2. 子宫动脉 PI 值变化

如图 4 所示, 相同孕周治疗组与对照组各指标进行比较, 重复检测资料通过拟合广义线性混合效应模型(MIXED)进行统计学分析。药物干预后, 对照组与治疗组子宫动脉 PI 平均值均呈下降趋势(时间 $P < 0.01$), 且治疗组的下降趋势较对照组更明显(处理因素 $P < 0.01$)。

注: RI、PI 值均取双侧子宫动脉的平均值。



注: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ **** $P < 0.0001$ 。PI 值取双侧子宫动脉的平均值。

Figure 4. Comparison of uterine artery PI value between the treatment group and the control group
图 4. 治疗组、对照组子宫动脉 PI 值比较

3.3. 活产率及不良事件发生率

3.3.1. 畸形发生率

两组观察病例中均未及有明显胎儿外观及超声下畸形者。

3.3.2. 活产、早产、子痫前期、阴道出血、药物性肝损伤发生率

如表 1 所示, 治疗组活产率明显高于对照组($P < 0.05$); 早产率、畸胎发生率间无明显差异($P > 0.05$); 治疗组较对照组子痫前期、阴道出血及药物性肝损伤发生率明显低于对照组($P < 0.05$)。

4. 讨论

目前抗凝、抗血小板药仍是治疗 APS 复发性流产的主要药物。低分子肝素被证实是治疗 APS 复发性

流产的有效药物[16] [17] [18], 肝素单独或联合小剂量阿司匹林是血栓前状态复发性流产的一线治疗方案[19] [20]。

Table 1. Live birth, premature delivery, preeclampsia, vaginal bleeding, drug-induced liver injury rates between the treatment group and the control group

表 1. 治疗组与对照组活产、早产、子痫前期、阴道出血、药物性肝损伤发生率的比较

	治疗组	对照组	RR 值(95% IC)	P 值
	部分/总体(率)	部分/总体(率)		
活产	78/88 (88.6)	70/89 (78.7)	0.32 (0.13~0.80)	0.01
早产	7/88 (8.0)	9/89 (10.1)	1.30 (0.46~3.66)	0.62
子痫前期	5/88 (5.7)	14/89 (15.9)	3.10 (1.07~9.01)	0.03
阴道出血	10/88 (11.4)	21/89 (23.6)	2.41 (1.06~5.47)	0.03
药物性肝损伤	11/88 (12.5)	25/89 (28.1)	2.73 (1.25~5.98)	0.01

然而仍有近 30% [21]的女性对单纯抗凝治疗缺乏敏感。中药及中成药的开发运用逐渐受到人们的关注。丹参川芎嗪针从传统中药丹参及川芎中提取而来, 主要药效成分为丹参素及盐酸川芎嗪。研究表明丹参中的有效成分丹参素具有保护血管内皮细胞[22]、减轻内皮炎症损伤[23]、抗脂质过氧化[24]、改善微循环、清除氧自由基[25] [26]、改善血循环中红细胞的聚集现象、减少血流阻力[27]的作用。川芎嗪是一种 TXA₂ (血栓烷 A₂)合成酶抑制剂, 具有抑制血小板磷脂酶 A₂ 活性、减少内源性花生四烯酸的释放及 TXA₂ 的合成, 从而抑制血小板激活的作用[27]。川芎嗪还通过抑制炎症信号通路的激活[28], 减轻炎症介导的组织损伤。同时川芎嗪还具有抗血栓形成[29] [30]、保护血管内皮细胞[31]的作用, 这些都有利于改善病变组织的血供。

丹参川芎嗪针因具有改善组织血供, 促进组织代谢, 安全, 高效而被广泛用于多种血栓性疾病的治疗。丹参川芎嗪针在心脑血管疾病中的研究较多, 然而在 aPL 阳性复发性流产中的临床运用相关研究较少。观察丹参川芎嗪针在 aPL 阳性所致复发性流产女性中的保胎疗效及安全性对拓展丹参川芎嗪针的临床适用范围具有重要的意义。

本实验通过临床研究发现, 丹参川芎嗪针能改善 aPL 阳性患者高凝状态, 增加患者妊娠期子宫胎盘血供, 以促进妊娠的维持, 增加 aPL 阳性患者活产率, 降低子痫前期发生率。配合肝素使用, 能增强肝素抗凝作用, 减轻肝素药物性肝损伤发生概率, 不增加早产、胎儿畸形、阴道出血等不良事件发生率, 孕期用药安全性高。丹参川芎嗪注射液在脑血管上的运用历史悠久、价格低廉。相较肝素皮下注射方式, 丹参川芎嗪针的静脉注射方式对患者造成的痛苦更小, 接受度更高, 是治疗血栓前状态复发性流产的潜力药。然而丹参川芎嗪注射液在血栓前状态复发性流产的运用处于初始阶段, 还需要更多临床及实验研究进一步证实其孕期用药的安全性及治疗的有效。

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