·脑静脉系统疾病和脑小血管病·

# 三七总皂苷对急性缺血性卒中患者重组组织型纤溶酶原激活物静脉溶栓疗效及出血性转化的影响

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【摘要】 **目的** 探讨三七总皂苷对急性缺血性卒中患者重组组织型纤溶酶原激活物(rt-PA)静脉溶栓疗效和出血性转化的影响。**方法** 共200例急性(发病至入院时间<4.50 h)缺血性卒中患者采用随机数字表法随机分为常规rt-PA静脉溶栓组(对照组,100例)和rt-PA静脉溶栓联合三七总皂苷治疗组(治疗组,100例),分别于治疗前、静脉溶栓后24 h和14 d检测缺血-再灌注损伤指标[丙二醛(MDA)、超氧化物歧化酶(SOD)]、出血性转化指标[基质金属蛋白酶-9(MMP-9)、纤维连接蛋白(FN)]和神经功能指标[美国国立卫生研究院卒中量表(NIHSS)、Barthel指数(BI)],观察静脉溶栓后14 d药物不良反应和出血性转化发生率,评价静脉溶栓后12个月预后(病死率和BI评分)。**结果** 治疗组患者血清SOD($P=0.000$)和BI评分($P=0.000$)高于,血清MDA($P=0.001$)和MMP-9($P=0.001$)、血浆FN($P=0.000$)和NIHSS评分($P=0.006$)低于对照组。rt-PA静脉溶栓联合三七总皂苷治疗后24 h,血清MDA($P=0.000$)和MMP-9($P=0.000$)、BI评分($P=0.000$)升高,NIHSS评分降低($P=0.000$);治疗后14 d,血清MDA($P=0.000$)和MMP-9($P=0.000$)反而降低,血清SOD($P=0.000$)和BI评分($P=0.000$)持续升高,血浆FN($P=0.000$)和NIHSS评分($P=0.000$)持续降低。静脉溶栓后14 d,治疗组患者出血性转化发生率低于对照组[9例(9%)对19例(19%);$\chi^2=4.153$,$P=0.042$)],药物不良反应发生率组间差异无统计学意义[14例(14%)对11例(11%);$\chi^2=0.411$,$P=0.521$]。静脉溶栓后12个月,两组病死率差异无统计学意义[5例(5%)对1例(1%);$\chi^2=1.546$,$P=0.241$],而治疗组生存患者BI评分高于对照组(88.51±11.49对84.47±9.83;$t=2.451$,$P=0.015$)。**结论** 三七总皂苷可以减轻急性缺血性卒中患者rt-PA静脉溶栓后缺血-再灌注损伤,降低出血性转化发生率,改善患者预后,且安全性良好。

【关键词】 卒中; 脑缺血; 三七皂甙; 组织型纤溶酶原激活物; 脑出血

## Effect of panax notoginseng saponins on efficacy and hemorrhagic transformation of rt-PA intravenous thrombolysis in patients with acute ischemic stroke

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【Abstract】 **Objective** To study the effect of panax notoginseng saponins (PNS) on the efficacy and hemorrhagic transformation (HT) of recombinant tissue-type plasminogen activator (rt-PA) intravenous thrombolysis in patients with acute ischemic stroke. **Methods** A total of 200 patients with early acute ischemic stroke (the length of time between attack and hospital admission < 4.50 h) were divided into 2 groups according to random number table method: treatment group (N = 100) and control group (N = 100). The control group was treated with routine rt-PA intravenous thrombolysis treatment, and the treatment group was treated with rt-PA intravenous thrombolysis plus PNS injection. The ischemia-reperfusion injury index [malondialdehyde (MDA) and superoxide dismutase (SOD)], hemorrhagic transformation prediction index [matrix metalloproteinase-9 (MMP-9) and fibronectin (FN)] and nerve function index [National Institutes of Health Stroke Scale (NIHSS) and Barthel Index (BI)] were measured and compared before treatment, 24 h after thrombolysis and 14 d after thrombolysis. Adverse drug reactions and hemorrhagic transformation rate were observed 14 d after thrombolysis, and the prognosis (mortality and BI) was

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evaluated 12 months after thrombolysis. **Results** Compared with control group, serum SOD ($P = 0.000$) and BI ($P = 0.000$) in treatment group were significantly higher, while serum MDA ($P = 0.001$), MMP-9 ($P = 0.001$), plasma FN ($P = 0.000$) and NIHSS score ($P = 0.006$) were significantly lower. In treatment group, 24 h after rt-PA intravenous thrombolysis plus PNS injection, serum MDA ($P = 0.000$), MMP-9 ($P = 0.000$) and BI ($P = 0.000$) were significantly increased, while NIHSS score ($P = 0.000$) was significantly decreased; 14 d after treatment, serum MDA ($P = 0.000$) and MMP-9 ($P = 0.000$) were decreased, serum SOD ($P = 0.000$) and BI ($P = 0.000$) were continuously increased, plasma FN ($P = 0.000$) and NIHSS score ($P = 0.000$) were continuously decreased. On the 14th day after thrombolysis, hemorrhagic transformation rate of treatment group was lower than that of control group [9 cases (9%) vs 19 cases (19%); $\chi^2 = 4.153$, $P = 0.042$]. There was no significant difference in the incidence of adverse drug reactions between 2 groups [14 cases (14%) vs 11 cases (11%); $\chi^2 = 0.411$, $P = 0.521$]. Twelve months after thrombolysis, there were 5 cases of death (5%) in control group and one case (1%) of death in treatment group. There was no significant difference in the incidence of mortality between 2 groups ($\chi^2 = 1.546$, $P = 0.241$). The BI of treatment group was significantly higher than that of control group (88.51 ± 11.49 vs 84.47 ± 9.83; $t = 2.451$, $P = 0.015$). **Conclusions** PNS reduces ischemia-reperfusion injury after rt-PA intravenous thrombolysis in patients with acute ischemic stroke. It can reduce the rate of hemorrhagic transformation after rt-PA intravenous thrombolysis and improve the prognosis with good safety.

**【Key words】** Stroke; Brain ischemia; Sanchinoside; Tissue plasminogen activator; Cerebral hemorrhage

重组组织型纤溶酶原激活物(rt-PA)静脉溶栓治疗发病3小时内急性缺血性卒中疗效明显,已获美国食品与药品管理局(FDA)审核批准[1]。但仍有高达10%~40%的急性缺血性卒中患者静脉溶栓后发生出血性转化(HT),病残率较高[2-3],出血性转化的风险限制了临床早期施行静脉溶栓且不利于患者预后[4]。因此,寻找一种药物既能治疗缺血性卒中又能预防出血性转化,成为神经科关注的热点。动物实验证实,三七总皂苷可以抑制缺血性卒中大鼠静脉溶栓后基质金属蛋白酶-9(MMP-9)的表达,减少血-脑屏障破坏和出血性转化的发生[5];然而关于三七总皂苷能否安全有效地降低急性缺血性卒中患者rt-PA静脉溶栓后出血性转化风险的研究较少。鉴于此,本研究旨在探讨三七总皂苷降低急性缺血性卒中患者rt-PA静脉溶栓后出血性转化发生率的可能性及其作用机制。

## 资料与方法

一、临床资料

1. 纳入标准 (1)急性缺血性卒中的诊断符合《中国急性缺血性脑卒中诊治指南2014》[6]。(2)年龄18~80岁,首次发病,发病至入院时间<4.50 h,存在局灶性中枢神经系统定位体征,症状持续时间>0.50 h,瘫痪肢体肌力0~3级。(3)头部CT未见与局灶性中枢神经系统定位体征相对应的梗死灶;MRI扩散加权成像(DWI)可见与中枢神经系统定位体征相对应的高信号影,即缺血半暗带区,表观扩散系数(ADC)呈现低信号影且ADC值降低。(4)不存在MRI检查和静脉溶栓治疗禁忌证。(5)能够配合检查和治疗。(6)本研究经河南省信阳市中心医院道德伦理委员会审核批准,所有患者或其家属均知情同意并签署知情同意书。

2. 排除标准 (1)出血倾向疾病:未控制的严重高血压[收缩压≥180 mm Hg(1 mm Hg=0.133 kPa)和(或)舒张压≥110 mm Hg]、血液系统疾病、凝血功能障碍、血小板计数减少(<$100\times10^9$/L)、颅内动脉瘤、颅内动-静脉畸形(AVM)、恶性肿瘤和既往有颅内出血史。(2)严重心、肺、肝、肾等脏器功能障碍,近期感染,自身免疫性疾病。(3)妊娠期或哺乳期女性。

3. 一般资料 选择2015年3-12月在河南省信阳市中心医院神经内科住院治疗且符合上述纳入与排除标准的急性缺血性卒中患者共200例,男性129例,女性71例;年龄46~80岁,平均(65.23±11.93)岁;体重指数(BMI)20.94~29.47 kg/m$^2$,平均(25.20±2.87) kg/m$^2$;发病至入院时间2.34~4.47 h,平均(3.37±0.88) h;既往有高血压97例(48.50%)、糖尿病55例(27.50%)、冠心病87例(43.50%)、心房颤动20例(10%),吸烟83例(41.50%)、饮酒68例(34%)。所有患者按照随机数字表法随机分为常规rt-PA静脉溶栓组(对照组)和rt-PA静脉溶栓联合三七总皂苷治疗组(治疗组)。(1)对照组:100例患者,

**表1** 两组患者一般资料的比较

**Table 1.** Comparison of general data between 2 groups

| Item | Control (N = 100) | Treatment (N = 100) | $\chi^2$ or $t$ value | $P$ value |
|---|---|---|---|---|
| Sex [case (%)] | | | 0.197 | 0.658 |
| Male | 63 (63.00) | 66 (66.00) | | |
| Female | 37 (37.00) | 34 (34.00) | | |
| Age ($\bar{x} \pm s$, year) | 64.95 ± 12.27 | 65.48 ± 11.64 | -0.314 | 0.754 |
| BMI ($\bar{x} \pm s$, kg/m$^2$) | 25.10 ± 2.73 | 25.30 ± 3.12 | -0.479 | 0.633 |
| Onset time ($\bar{x} \pm s$, h) | 3.31 ± 0.84 | 3.45 ± 0.96 | -1.127 | 0.261 |
| Hypertension [case (%)] | 50 (50.00) | 47 (47.00) | 0.180 | 0.671 |
| Diabetes [case (%)] | 26 (26.00) | 29 (29.00) | 0.226 | 0.635 |
| Coronary heart disease [case (%)] | 45 (45.00) | 42 (42.00) | 0.183 | 0.669 |
| Atrial fibrillation [case (%)] | 9 ( 9.00) | 11 (11.00) | 0.222 | 0.637 |
| Smoking [case (%)] | 40 (40.00) | 43 (43.00) | 0.185 | 0.667 |
| Drinking [case (%)] | 35 (35.00) | 33 (33.00) | 0.089 | 0.765 |

Two-independent-sample $t$ test for comparison of age, BMI and onset time, and $\chi^2$ test for comparison of others。BMI, body mass index,体重指数

男性63例,女性37例;年龄46~80岁,平均(64.95±12.27)岁;体重指数20.94~29.47 kg/m$^2$,平均为(25.10±2.73) kg/m$^2$;发病至入院时间2.35~4.47 h,平均(3.31±0.84) h;既往有高血压50例(50%)、糖尿病26例(26%)、冠心病45例(45%)、心房颤动9例(9%),吸烟40例(40%)、饮酒35例(35%)。(2)治疗组:100例,男性66例,女性34例;年龄47~79岁,平均(65.48±11.64)岁;体重指数21.27~28.95 kg/m$^2$,平均(25.30±3.12) kg/m$^2$;发病至入院时间2.34~4.45 h,平均(3.45±0.96) h;既往有高血压47例(47%)、糖尿病29例(29%)、冠心病42例(42%)、心房颤动11例(11%),吸烟43例(43%)、饮酒33例(33%)。两组患者性别、年龄、体重指数、发病至入院时间和既往史比较,差异均无统计学意义($P$>0.05,表1),均衡可比。

二、研究方法

1.治疗方法 治疗组患者入院后即予三七总皂苷(血塞通注射液,规格:400 mg,黑龙江珍宝岛药业股份有限公司)400 mg加入5%葡萄糖溶液500 ml中静脉滴注(1次/d),对照组患者予维生素C注射液0.25 g加入5%葡萄糖溶液500 ml中(安慰剂)静脉滴注(1次/d),余治疗方法一致,均行rt-PA静脉溶栓治疗。(1)静脉溶栓:阿替普酶(爱通立,规格:25 mg,德国Boehringer Ingelheim公司)按照0.90 mg/kg计算总剂量,最大剂量≤90 mg。先将总剂量的10%于1 min内缓慢静脉注射,余90%溶入50 ml生理盐水中于60 min内静脉泵注。(2)脱水降低颅内压:予20%甘露醇注射液250 ml/次、1~2次/d静脉滴注,连续1~3 d,治疗剂量和疗程根据病情调整。(3)抗血小板聚集:静脉溶栓后24 h予阿司匹林100 mg/d口服,连续12个月。(4)抗凝:静脉溶栓后24 h后予低分子量肝素5000 IU/12 h于脐周腹壁皮下注射,连续7 d。(5)控制血压、血糖、血脂,预防感染,维持水电解质平衡。(6)出血性转化的治疗:一旦出现出血性转化,立即停用抗血小板药、抗凝药和扩血管药,密切监测和控制血压、血糖,交替予甘露醇和白蛋白增加血浆胶体渗透压以减轻脑水肿。头部CT显示单个较大血肿,经内科保守治疗无好转或有持续性颅内高压症状且能够耐受手术者,可以考虑行去骨瓣减压术和钻孔引流术。两组患者均治疗1个疗程(14 d)。糖尿病患者可以生理盐水替代葡萄糖溶液。

2.评价指标 (1)血液生化指标:两组患者均于入院时、静脉溶栓后24 h和14 d晨起空腹采集肘静脉血6 ml,于1000×$g$离心15 min,分离血清和血浆,置-80 ℃冻存备用。采用硫代巴比妥酸比色法检测血清丙二醛(MDA)水平(试剂盒购自南京聚力生物医学工程研究所),化学比色法检测血清超氧化物歧化酶(SOD)水平(试剂盒购自上海恒远生物科技有限公司),双抗体夹心酶联免疫吸附试验(ELISA)检测血清MMP-9水平(试剂盒购自上海森雄科技实业有限公司),ELISA法检测血浆纤维连接蛋白(FN)水平(试剂盒购自美国Uscn公司),操作步骤严格按照试剂盒说明书进行。(2)神经功能评价量表:两组患者分别于入院时、静脉溶栓后24 h和14 d由同一位神经内科医师盲法采用美国国立卫生研究院卒中量表(NIHSS)和Barthel指数(BI)评价神经功能。①NIHSS量表。用于评价神经功能缺损程度,共包含11项内容、13个向度,分别为意识状态、回答问题能力、遵从指令能力、眼球运动、视野、面瘫、上肢运动功能、下肢运动功能、肢体协调能力、感觉功能、言语功能、构音障碍、感觉忽视,总评分42分,评分越高、神经功能缺损程度越严重。②BI量表。用于评价日常生活活动能力(ADL),共包含10项内容,分别为进食、床椅转移、修饰、进出厕所、洗澡、平地行走、上下楼梯、穿衣、大便控制、小便控制,每项内容根据是否需要他人帮助及帮助程度分

**表2** 两组患者不同观察时间点各项临床指标的比较($\bar{x} \pm s$)

**Table 2.** Comparison of each clinical index at different time points between 2 groups ($\bar{x} \pm s$)

| Group | N | Before treatment (1) | 24 h after thrombolysis (2) | 14 d after thrombolysis (3) | Group | N | Before treatment (1) | 24 h after thrombolysis (2) | 14 d after thrombolysis (3) |
|---|---|---|---|---|---|---|---|---|---|
| MDA (nmol/ml) | | | | | FN (μg/L) | | | | |
| Control | 100 | 9.45 ± 1.84 | 11.30 ± 2.33 | 7.15 ± 1.47 | Control | 100 | 6.55 ± 2.33 | 7.99 ± 2.63 | 4.34 ± 1.39 |
| Treatment | 100 | 9.18 ± 1.90 | 10.43 ± 2.16 | 6.70 ± 1.54 | Treatment | 100 | 6.32 ± 2.53 | 6.78 ± 2.44 | 3.32 ± 1.23 |
| SOD (U/ml) | | | | | NIHSS (score) | | | | |
| Control | 100 | 65.00 ± 17.69 | 54.97 ± 19.43 | 95.06 ± 21.54 | Control | 100 | 16.01 ± 4.12 | 11.42 ± 3.54 | 5.53 ± 1.54 |
| Treatment | 100 | 62.49 ± 19.96 | 63.75 ± 20.46 | 110.22 ± 27.33 | Treatment | 100 | 16.60 ± 4.01 | 10.07 ± 2.78 | 4.07 ± 1.37 |
| MMP-9 (μg/L) | | | | | BI | | | | |
| Control | 100 | 191.23 ± 70.80 | 323.81 ± 85.88 | 176.90 ± 50.25 | Control | 100 | 48.59 ± 3.81 | 56.98 ± 6.75 | 80.59 ± 7.66 |
| Treatment | 100 | 205.58 ± 75.97 | 285.99 ± 82.58 | 142.41 ± 45.84 | Treatment | 100 | 48.28 ± 3.87 | 58.73 ± 8.84 | 87.64 ± 9.46 |

MDA，malondialdehyde，丙二醛；SOD，superoxide dismutase，超氧化物歧化酶；MMP-9，matrix metalloproteinase-9，基质金属蛋白酶-9；FN，fibronectin，纤维连接蛋白；NIHSS，National Institutes of Health Stroke Scale，美国国立卫生研究院卒中量表；BI，Barthel Index，Barthel指数。The same for tables below

为0、5、10和15分共4级，总评分100分，评分越低、日常生活活动能力越差。(3)安全性评价：于静脉溶栓后14 d观察患者药物不良反应。(4)预后评价：于静脉溶栓后12个月记录患者病死率和评价日常生活活动能力。

3. 出血性转化的判定标准　根据欧洲合作组急性脑卒中研究Ⅱ(ECASSⅡ)标准[7]，将出血性转化患者头部CT表现分为出血性梗死(HI)和脑实质血肿(PH)，其中，出血性梗死进一步细分为：HI1，沿梗死灶边缘的小点状出血，无占位效应；HI2，梗死灶内多个融合的点片状出血，无占位效应。脑实质血肿进一步细分为：PH1，出血灶≤30%的梗死灶并有轻微占位效应；PH2，出血灶>30%的梗死灶并有明显占位效应或远隔梗死灶出血。

三、统计分析方法

采用SPSS 22.0统计软件进行数据处理与分析。计量资料以均数±标准差($\bar{x} \pm s$)表示，两组患者不同观察时间点临床指标的比较采用重复测量设计的方差分析，两两比较行LSD-$t$检验；两组患者预后的比较采用两独立样本的$t$检验。计数资料以相对数构成比(%)或率(%)表示，采用$\chi^2$检验。以$P \leq 0.05$为差异具有统计学意义。

## 结　果

一、临床疗效

治疗组患者血清SOD($P = 0.000$)和BI评分($P = 0.000$)均高于，血清MDA($P = 0.001$)和MMP-9($P = 0.001$)、血浆FN($P = 0.000$)和NIHSS评分($P = 0.006$)均低于对照组(表2，3)。与治疗前相比，予以rt-PA联合三七总皂苷的患者治疗后24 h血清MDA($P = 0.000$)和MMP-9($P = 0.000$)、BI评分($P = 0.000$)升高，NIHSS评分降低($P = 0.000$)；治疗后14 d血清MDA($P = 0.000$)和MMP-9($P = 0.000$)反而降低，血清SOD($P = 0.000$)和BI评分($P = 0.000$)持续升高，血浆FN($P = 0.000$)和NIHSS评分($P = 0.000$)持续降低(表2，4)。

二、出血性转化

静脉溶栓后14 d，对照组19例(19%)发生出血性转化，包括HI1型8例、HI2型6例、PH1型3例、PH2型2例；治疗组9例(9%)发生出血性转化，包括HI1型4例、HI2型3例、PH1型1例、PH2型1例。治疗组患者出血性转化发生率低于对照组($\chi^2 = 4.153$，$P = 0.042$)，表明三七总皂苷能够有效抑制rt-PA静脉溶栓后出血性转化。

三、药物不良反应

静脉溶栓后14 d，对照组11例患者(11%)出现药物不良反应，主要表现为头痛1例、皮肤黏膜出血2例、胸闷2例、咽干1例、便秘1例、血小板计数减少2例、肝功能轻度异常2例；治疗组14例患者(14%)出现药物不良反应，表现为头晕2例、皮肤黏膜出血3例、皮疹2例、心悸2例、恶心1例、肝功能轻度异常4例。两组药物不良反应均较轻微且发生率差异无统计学意义($\chi^2 = 0.411$，$P = 0.521$)，经对症处理或停药后均恢复正常，未影响继续用药，表明三七总皂

**表3** 两组患者不同观察时间点各项临床指标的重复测量设计方差分析表

**Table 3.** ANOVA of repeated measurement design for clinical index at different time points between 2 groups

| Source of variation | *SS* | df | *MS* | *F* value | *P* value | Source of variation | *SS* | df | *MS* | *F* value | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| MDA | | | | | | FN | | | | | |
| Treatment | 42.241 | 1 | 42.241 | 12.031 | 0.001 | Treatment | 33.812 | 1 | 33.812 | 21.394 | 0.000 |
| Time | 1 573.659 | 2 | 786.830 | 215.178 | 0.000 | Time | 1 354.345 | 2 | 677.172 | 145.049 | 0.000 |
| Treatment × time | 9.299 | 2 | 4.650 | 1.272 | 0.282 | Treatment × time | 26.970 | 2 | 13.485 | 2.888 | 0.057 |
| Error between groups | 695.171 | 198 | 3.511 | | | Error between groups | 312.931 | 198 | 1.580 | | |
| Error within group | 1 448.035 | 366 | 3.954 | | | Error within group | 1 848.752 | 385 | 4.800 | | |
| SOD | | | | | | NIHSS | | | | | |
| Treatment | 8 385.829 | 1 | 8 385.829 | 19.559 | 0.000 | Treatment | 81.645 | 1 | 81.645 | 7.835 | 0.006 |
| Time | 232 565.204 | 2 | 116 282.602 | 249.923 | 0.000 | Time | 13 235.882 | 2 | 7 757.003 | 722.808 | 0.000 |
| Treatment × time | 8 839.106 | 2 | 4 419.553 | 9.499 | 0.000 | Treatment × time | 133.120 | 2 | 78.016 | 7.270 | 0.000 |
| Error between groups | 84 891.337 | 198 | 428.774 | | | Error between groups | 2 063.291 | 198 | 10.421 | | |
| Error within group | 184 248.071 | 385 | 478.464 | | | Error within group | 3 625.726 | 342 | 10.595 | | |
| MMP-9 | | | | | | BI | | | | | |
| Treatment | 18 663.764 | 1 | 18 663.764 | 12.200 | 0.001 | Treatment | 399.502 | 1 | 399.502 | 23.022 | 0.000 |
| Time | 2 262 678.270 | 2 | 1 131 339.135 | 221.539 | 0.000 | Time | 136 783.509 | 2 | 68 391.755 | 1386.833 | 0.000 |
| Treatment × time | 85 308.459 | 2 | 42 654.229 | 8.353 | 0.000 | Treatment × time | 1 444.892 | 2 | 722.446 | 14.650 | 0.000 |
| Error between groups | 302 914.074 | 198 | 1 529.869 | | | Error between groups | 3 435.939 | 198 | 17.353 | | |
| Error within group | 2 022 260.998 | 360 | 5 605.375 | | | Error within group | 19 528.765 | 342 | 57.126 | | |

**表4** 同一组别患者不同观察时间点各项临床指标的两两比较

**Table 4.** Paired comparison of clinical index at different time points in the same group

| Paired comparison | Control | | Treatment | | Paired comparison | Control | | Treatment | |
|---|---|---|---|---|---|---|---|---|---|
| | *t* value | *P* value | *t* value | *P* value | | *t* value | *P* value | *t* value | *P* value |
| MDA | | | | | FN | | | | |
| (1) : (2) | 5.849 | 0.000 | 10.178 | 0.000 | (1) : (2) | 4.441 | 0.000 | 1.329 | 0.187 |
| (1) : (3) | 9.222 | 0.000 | 10.898 | 0.000 | (1) : (3) | 8.077 | 0.000 | 10.529 | 0.000 |
| (2) : (3) | 17.163 | 0.000 | 13.455 | 0.000 | (2) : (3) | 11.320 | 0.000 | 12.322 | 0.000 |
| SOD | | | | | NIHSS | | | | |
| (1) : (2) | 3.929 | 0.000 | 0.436 | 0.664 | (1) : (2) | 9.226 | 0.000 | 13.748 | 0.000 |
| (1) : (3) | 11.122 | 0.000 | 13.772 | 0.000 | (1) : (3) | 9.246 | 0.000 | 29.807 | 0.000 |
| (2) : (3) | 14.233 | 0.000 | 13.040 | 0.000 | (2) : (3) | 0.120 | 0.905 | 19.810 | 0.000 |
| MMP-9 | | | | | BI | | | | |
| (1) : (2) | 10.930 | 0.000 | 7.316 | 0.000 | (1) : (2) | 11.743 | 0.000 | 10.745 | 0.000 |
| (1) : (3) | 1.701 | 0.092 | 7.083 | 0.000 | (1) : (3) | 37.039 | 0.000 | 40.806 | 0.000 |
| (2) : (3) | 14.646 | 0.000 | 14.840 | 0.000 | (2) : (3) | 22.808 | 0.000 | 22.096 | 0.000 |

苷并未增加药物不良反应，安全性较好。

四、预后

静脉溶栓后12个月，对照组失访1例（1%），死亡5例（5%），分别为急性心肌梗死2例，再发大量颅内出血1例，缺血性卒中后遗症（吞咽障碍、吸入性肺炎、呼吸衰竭）1例，褥疮致败血症1例；治疗组失访1例（1%），死亡1例（1%），为急性心肌梗死。两组患者病死率差异无统计学意义（$\chi^2 = 1.546$，$P = 0.214$）。对照组94例生存患者BI评分64.37～93.60，平均84.47±9.83；治疗组98例生存患者BI评分51.26～97.03，平均88.51±11.49；治疗组患者BI评分高于对照组（$t = 2.451$，$P = 0.015$），表明rt-PA静脉溶栓联合三七总皂苷治疗急性缺血性卒中的预后优于常规rt-PA静脉溶栓。

## 讨 论

脑组织缺血-再灌注损伤是rt-PA静脉溶栓后发生出血性转化的关键因素[8]。缺血-再灌注损伤可以引起灌注氧骤然增加，产生大量氧自由基，磷脂降解破坏，诱发细胞膜不饱和脂肪酸发生过氧化反应，继发细胞毒性和离子性脑水肿，内皮细胞肿胀引起细胞骨架重新排列，缺氧激活转录程序使缺血核心区血管通透性增加，导致血-脑屏障损伤，毛细血管壁完整性破坏和血液外渗进入脑实质，最终导致出血性转化[9]。缺血-再灌注损伤发生时，脂质过氧化物如MDA表达水平明显升高，作为氧自由基与生物膜不饱和脂肪酸发生脂质过氧化反应的代谢产物，MDA水平反映氧自由基水平，间接反映神经细胞损伤程度[10]；而SOD是一种金属蛋白酶，能够清除氧自由基、抗氧化和拮抗氧自由基损伤，其表达水平间接反应机体清除氧自由基能力[11]。此时，梗死灶内多种蛋白水解酶活性均明显增强，在本研究中，我们选择与出血性转化密切相关的2个代表性指标：(1)MMP-9是一种内源性锌离子依赖性中性蛋白水解酶，通过降解和重塑细胞外基质(ECM)，使毛细血管间紧密连接和基底膜破坏，导致血浆和红细胞外渗，诱发血管源性脑水肿和出血性转化[12-13]。故MMP-9水平升高与静脉溶栓后出血性转化的发生密切相关，对预测静脉溶栓后出血性转化的发生和评价患者预后有重要价值[14-17]。MMP-9降解血管基底膜，使外周血FN表达水平也有所升高[18]。(2)FN是一种具有重要生物学活性的非胶原糖蛋白，也是基底膜的一种组成成分。当基底膜受损时，由内皮细胞合成和分泌的FN释放进入血浆，促进细胞与细胞、细胞与基质的粘连，参与上皮组织修复、排列规律化、增殖分化、促凝血、免疫调控以及诱导神经元和神经胶质细胞分化等多种生理学活动。已有研究显示，FN表达变化是缺血性卒中出血性转化的独立预测因素[19]。

在本研究中，与治疗前相比，rt-PA静脉溶栓后24小时两组患者血清MDA和MMP-9、血浆FN升高，而对照组血清SOD下降，表明缺血-再灌注损伤产生大量氧自由基，介导细胞膜中多种不饱和脂肪酸的过氧化反应，使SOD消耗量增加，氧自由基酶性清除系统损伤。与对照组相比，治疗组患者血清SOD升高，而血清MDA和MMP-9、血浆FN降低，表明三七总皂苷能够减轻急性缺血性卒中患者rt-PA静脉溶栓后缺血-再灌注损伤的炎症反应。静脉溶栓后14天，治疗组患者出血性转化发生率低于对照组，而药物不良反应发生率与对照组无明显差异。其机制可能是，三七总皂苷是从三七根部提纯的，含多种有效活性成分，包括人参皂苷$Rb_1$、$Rg_1$、$Rg_2$、黄酮苷、黄酮等，这些有效成分具有多个治疗靶点，其药理学机制为：(1)清除氧自由基。人参皂苷$Rb_1$和$Rg_1$是氧离子($O^{-2}$)的天然清除剂，避免缺氧时游离脂肪酸的堆积；抑制黄嘌呤氧化酶形成，保护内源性过氧化酶活性，对黄嘌呤氧化酶氧化黄嘌呤产生的氧自由基也具有清除作用[20]。本研究也证实三七总皂苷可以升高SOD水平、降低MDA水平，从而具有清除氧自由基的作用。(2)抗脂质过氧化反应。一方面通过抗炎症作用，减少白细胞释放氧自由基，另一方面通过激活抗氧化酶SOD活性，抑制氧自由基，降低脂质过氧化物水平[21]。(3)改善微循环。三七总皂苷为神经元钙离子拮抗剂，通过阻止细胞外钙离子内流和细胞内钙离子释放，以防止细胞内钙离子超载，抑制血管内皮收缩，促进微动脉和微静脉扩张，增加缺血半暗带区脑组织侧支循环的血流灌注量，改善缺血半暗带区代谢，促进神经功能恢复，从而抑制缺血性连锁反应，防止缺血-再灌注后迟发性神经元损伤[22]。三七总皂苷通过降低红细胞比容(HCT)和纤维蛋白原水平降低血液黏滞度，增快血流速度。三七总皂苷通过抑制血小板合成和聚集，抑制血栓形成[23]。(4)促进血管内皮细胞生成，保持内皮细胞完整性，降低毛细血管和神经细胞通透性，减轻间质性脑水肿，促进神经功能恢复[24]。(5)保护神经元。抑制Caspase-3 mRNA转录和Caspase-3蛋白裂解活化，减少细胞凋亡，促进脑出血后前脑神经元存活和损伤修复[25]。

综上所述，三七总皂苷能够有效预防和治疗脑组织缺血-再灌注损伤，保护神经细胞，减少静脉溶栓后出血性转化的发生，在抗凝治疗的同时不增加颅内出血风险，可以作为静脉溶栓治疗急性缺血性卒中后预防出血性转化的安全、有效药物。

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