doi: 10.13241/j.cnki.pmb.2018.19.039

醒脑静联合古拉定对急性酒精中毒患者血清 H_2O_2、SOD、MDA 及 iNOS 水平的影响 *

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摘要 目的：探讨醒脑静联合古拉定治疗急性酒精中毒的疗效及对患者血清过氧化氢 (H_2O_2)、超氧化物歧化酶 (SOD)、丙二醛(MDA)和诱导型一氧化氮合酶(iNOS)水平的影响。**方法：**选取我院 2015 年 4 月至 2017 年 4 月收治的 80 例急性酒精中毒患者，采用随机数字表法分为两组。对照组 40 例，采用醒脑静治疗；观察组 40 例，采用醒脑静联合古拉定治疗。记录比较两组症状改善时间，治疗前后肝功能及血清学指标变化，临床疗效与不良反应的发生情况。**结果：**观察组血压与心率恢复正常及清醒时间均较对照组显著缩短(P＜0.01)。与治疗前相比，两组治疗后血清谷酰转肽酶(GGT)、谷草转氨酶(AST)和谷丙转氨酶(ALT)水平均显著下降(P＜0.01)，且观察组以上指标均显著低于对照组(P＜0.01)。治疗 4、8 h 后，两组血清 H_2O_2、MDA、iNOS 水平均较治疗前显著下降(P＜0.01)，血清 SOD 水平较治疗前显著升高(P＜0.01)，且观察组以上指标改善较对照组更显著(P＜0.01)。观察组治疗后总有效率达 97.50%，较对照组 (90.00%) 略高，但差异无统计学意义 (P＞0.05)。观察组苏醒后不适率为 27.50%，较对照组显著降低(67.50%，P＜0.01)。**结论：**采用醒脑静及古拉定治疗急性酒精中毒患者可更快速、有效消除临床症状，改善肝功能，减少患者不适感，疗效更显著，可能与其有效降低血清 MDA、iNOS 水平并升高血清 SOD 水平有关。

关键词：醒脑静；古拉定；急性酒精中毒；临床疗效；过氧化氢；超氧化物歧化酶；丙二醛；诱导型一氧化氮合酶
中图分类号：R595.6 **文献标识码：**A **文章编号：**1673-6273(2018)19-3772-05

Clinical Effect of Xingnaojing Combined with Gluthion on the Serum H_2O_2, SOD, MDA and iNOS Levels of Patients with Acute Alcoholism*

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ABSTRACT Objective: To explore the clinical effect of Xingnaojing combined with Gluthion on the acute alcoholism and influence on the levels of serum hydrogen peroxide (H_2O_2), superoxide dismutase (SOD), malonaldehyde (MDA), and inducible nitric oxide synthase (iNOS). **Methods:** 80 cases of patients with acute alcoholism admitted in our hospital from April 2015 to April 2017 were selected and randomly divided into two groups. 40 patients from the control group were treated with Xingnaojing, while the other 40 patients from the observation group were administrated with a combination of Xingnaojing and Gluthion. The time for improvement in symptoms, the liver function and changes of serological indicators before and after treatment, the clinical effect, and the incidence of adverse reactions were compared between the two groups. **Results:** The time to resume normal blood pressure, heart rate and consciousness of observation group were significantly shorter than those of the control group (P<0.01). The gamma-glutamyl transpeptidase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT) levels in both groups were evidently decreased as compared with those before treatment, and the above indexes in observation group were significantly lower than those in control group (P<0.01). For both groups, at 4, 8 h after treatment, the levels of H_2O_2, MDA and iNOS were dipped (P<0.01) and that of SOD jumped (P<0.01), and the improvement in the observation group was larger than that in the control group (P<0.01). The overall effective rate of observation group reached 97.50% which was slightly higher than 90.00% of the control group, but showed no statistical difference (P>0.05). The proportion of patients feeling uncomfortable after waking up was 27.5% in the observation group, which was much lower than 67.5% in the control group (P<0.01). **Conclusion:** Xingnaojing and Gluthion has better a clinical effect in treating patients with acute alcoholism by eliminating patients symptoms in a faster manner, improving their liver function and reducing their discomfor, which may be associated with its effect in reducing patients' serum MDA and iNOS lelves, and increasing their SOD levels as well.

* 基金项目：陕西省自然科学基金项目(2003C218)
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(收稿日期：2018-06-10 接受日期：2018-06-30)

Key words: Xingnaojing; Gluthion; Acute alcoholism; Clinical effect; Hydrogen peroxide; Superoxide dismutase; Malonaldehyde; Inducible nitric oxide synthase

Chinese Library Classification(CLC): R595.6 Document code: A

Article ID: 1673-6273(2018)19-3772-05

前言

急性酒精中毒为饮入过量乙醇引起的急诊常见病,表现为神经系统先出现兴奋,随后由于高浓度乙醇的麻醉作用转为抑制[1],部分患者可出现休克及呼吸抑制[2]。酒精具有直接的肝脏毒性,可造成肝损害甚至酒精性肝硬化,且急性酒精中毒为脑出血、心脏病、胰腺炎等疾病的诱因,症状严重可致死[3]。

醒脑静为临床治疗急性酒精中毒的常用注射液。含有冰片、郁金、麝香等成分,可醒脑通气、活血清毒,临床常用于治疗头痛昏迷、神志不清、酒精中毒等[4]。古拉定(还原型谷胱甘肽钠)在治疗酒精中毒及酒精性肝病中得到应用,是一种三肽物质,可与患者体内的自由基和乙醛发生作用[5]。研究表明过氧化氢(H_2O_2)、超氧化物歧化酶(SOD)、丙二醛(MDA)和诱导型一氧化氮合酶(iNOS)水平与患者酒精中毒程度及病情密切相关,可作为指导治疗的辅助指标和预后评估指标[6]。因此,本研究以我院 2015 年 4 月至 2017 年 4 月收治的急性酒精中毒患者为研究对象,探讨了联合采用醒脑静及古拉定治疗急性酒精中毒的疗效及对患者血清 H_2O_2、SOD、MDA、iNOS 水平的影响,现报道如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 4 月至 2017 年 4 月收治的 80 例急性酒精中毒患者,纳入标准:① 有饮酒史,呼气带酒精气味;② 年龄 18~60 岁;③ 出现异常兴奋或烦躁、神志不清、休克、无疼痛反应、四肢发冷、呼吸抑制等中毒表现;④ 患者或家属自愿参加本研究,并签署知情同意书。排除标准:① 合并严重电解质紊乱、肝肾功能不全或心律失常者;② 合并免疫系统疾病者;③ 合并代谢性病史者;④ 慢性酒精中毒者;⑤ 由药物等其他原因导致的昏睡[7];⑥ 临床资料不全者。

采用随机数字表法均分为两组。观察组 40 例,男 23 例,女 17 例;年龄 19~57 岁,平均(33.72± 6.18)岁;就诊时昏迷期 21 例, 兴奋期 8 例, 失调期 11 例; 饮酒量 310~620 mL, 平均(463.48± 53.16)mL;就诊时距离饮酒 1~5 h,平均(2.79± 0.61)h。对照组 40 例,男 21 例,女 19 例;年龄 18~59 岁,平均(34.21± 6.42)岁;就诊时昏迷期 23 例,兴奋期 7 例,失调期 10 例;饮酒量 280~610 mL, 平均 (452.04± 60.32)mL; 就诊时距离饮酒 1.5~5 h,平均(2.90± 0.64)h。两组基线资料相比差异无统计学意义(P>0.05),具有临床可比性。本研究经我院医学伦理委员会审查同意。

1.2 治疗方法

两组患者经确诊后均采取常规治疗流程。包括:① 洗胃、催吐治疗,出现呼吸抑制的患者给予吸氧治疗;② 给予补液治疗,包括高渗葡萄糖、维生素、能量合剂、胰岛素、护肝药物等,补充营养,调节电解质及酸碱平衡;③ 监测血压、血氧、心率、心电等体征。对照组:在此基础上,给予醒脑静(河南天地药业,国药准字 Z41020665)治疗,具体为将 20 mL 醒脑静用 250 mL 的 5%葡萄糖溶液稀释后静脉滴注, 期间应结合该患者监测的血压、心率等指标对醒脑静实际应用剂量进行调整。观察组:在对照组基础上,给予古拉定(昆明积大制药,国药准字 J20120043)治疗, 具体为将 1.2 g 古拉定用 100 mL 的 5%葡萄糖溶液稀释后静脉滴注,期间密切关注患者体征监测状态,如有异常需及时调整。

1.3 观察指标

① 症状改善时间:观察记录两组患者的血压与心率恢复正常时间及清醒时间。② 肝功能指标检测:包括血清谷酰转肽酶(GGT)、谷草转氨酶(AST)和谷丙转氨酶(ALT)水平。③ 两组患者于治疗前及治疗后 4、8 h 各采集 5 mL/ 次的静脉血, 离心分离血清,H_2O_2 和 MDA 均应用活性比色法测定,SOD 和 iNOS 均应用酶联免疫吸附(ELISA)法测定,试剂盒均由南京森贝伽生物提供,各指标检测步骤严格参照配套说明书。④ 临床疗效:痊愈:体征稳定,神智恢复正常,表达清晰,各项功能无异;有效:体征稳定,神智有所恢复,表达基本清晰,但精神欠佳,反应速度偏慢;无效:未得到改善。总有效率 =(痊愈 + 有效)/ 总数×100%[8]。⑤ 苏醒后不适症状:包括头痛、呕吐、电解质紊乱等。

1.4 统计学分析

运用统计软件 SPSS19.0 处理数据, 计量资料以 ($\bar{x}$± s)表示,采取 t 检验,计数资料以(%)表示,应用 x^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组症状改善时间的比较

观察组血压与心率恢复正常及清醒时间均较对照组显著缩短(P<0.01),见表 1。

表 1 两组症状改善时间的比较($\bar{x}$± s, min)

Table 1 Comparison of the symptoms improvement time between two groups($\bar{x}$± s, min)

Groups	n	Blood pressure and heart rate returned to normal time	Awake time
Control group	40	79.42± 10.07	261.54± 28.05
Observation group	40	40.17± 8.94	148.93± 17.60
P		0.000	0.000

2.2 两组治疗前后肝功能指标的比较

与治疗前相比，两组治疗后血清 GGT、AST 和 ALT 水平均显著下降(P＜0.01)，且观察组血清 GGT、AST 和 ALT 水平显著低于对照组(P＜0.01)，见表 2。

表 2 两组治疗前后肝功能指标的比较($\bar{x}\pm s$, U/L)

Table 2 Comparison of the liver function indexes between two groups before and after treatment($\bar{x}\pm s$, U/L)

Groups	Time	GGT	AST	ALT
Control group (n=40)	Before treatment	35.11± 3.84	34.71± 4.04	29.26± 3.42
	After treatment	28.42± 3.26[1)]	28.05± 3.32[1)]	24.89± 3.10[1)]
Observation group (n=40)	Before treatment	35.24± 3.79	34.46± 3.97	29.15± 3.38
	After treatment	23.17± 2.89[1)2)]	22.87± 3.01[1)2)]	20.74± 2.81[1)2)]

Note: compared with the same group before treatment, [1)]P<0.01; compared with the control group after treatment; [2)]P<0.01.

2.3 两组治疗前后血清学指标的比较

治疗前，两组血清 H_2O_2、SOD、MDA、iNOS 水平相比差异均无统计学意义 (P＞0.01)；治疗 4、8 h 后，两组血清 H_2O_2、MDA、iNOS 水平均较治前显著下降(P＜0.01)，血清 SOD 水平较治疗前显著提高(P＜0.01)，且观察组以上指标改善较对照组更显著(P＜0.01)，见表 3。

表 3 两组治疗前后血清学指标的比较($\bar{x}\pm s$)

Table 3 Comparison of the serological indicators between two groups before and after treatment($\bar{x}\pm s$)

Groups	Time	H_2O_2(mmol/gprot)	SOD(U/L)	MDA(mg/L)	iNOS(%)
Control group (n=40)	Before treatment	91.57± 15.46	87.14± 13.67	9.56± 1.43	92.11± 14.27
	4 h after treatment	74.59± 13.11[1)]	95.64± 14.08[1)]	7.69± 1.24[1)]	77.15± 11.41[1)]
	8 h after treatment	44.18± 7.08[1)]	108.91± 15.34[1)]	5.74± 1.16[1)]	58.83± 10.01[1)]
Observation group (n=40)	Before treatment	90.40± 15.27	86.49± 13.42	9.62± 1.47	91.87± 14.14
	4 h after treatment	55.38± 9.14[1)2)]	112.15± 16.54[1)2)]	5.79± 1.20[1)2)]	59.48± 9.85[1)2)]
	8 h after treatment	30.46± 6.12[1)2)]	134.58± 17.87[1)2)]	4.38± 0.94[1)2)]	43.15± 8.07[1)2)]

Note: compared with the same group before treatment, [1)]P<0.01; compared with the control group after treatment; [2)]P<0.01.

2.4 两组临床疗效的比较

观察组治疗后总有效率达 97.50%(39/40)，较对照组[90.00%(36/40)]略有上升，但差异无统计学意义(P＞0.05)，见表4。

表 4 两组临床疗效的比较[n(%)]

Table 4 Comparison of the clinical effect between two groups[n(%)]

Groups	n	Cure	Effective	Invalid	Total effective rate
Control group	40	17(42.50)	19(47.50)	4(10.00)	36(90.00)
Observation group	40	26(65.00)	13(32.50)	1(2.50)	39(97.50)
P					0.166

2.5 两组苏醒后不适症状的比较

观察组苏醒后不适率为 27.50%，较对照组显著下降(67.50%，P＜0.01)，但两组症状均较轻微，及时给予对症治疗后得到改善，且均未见死亡病例。见表 5。

表 5 两组苏醒后不适症状的比较[n(%)]

Table 5 Comparison of the discomfort symptoms after wake up between two groups

Groups	n	Headache and vomiting	Electrolyte disturbances	Total
Control group	40	21(52.50)	6(15.00)	27(67.50)
Observation group	40	9(22.50)	2(5.00)	11(27.50)
P				0.000

3 讨论

急性酒精中毒的发病机制为短期内摄入过量乙醇超过肝脏负荷能力，未被代谢的乙醇可生成具脂溶性的乙醛，进入大脑细胞膜与多巴胺结合[9]，生成阿片状物质作用于机体脑内的受体，使患者神经系统兴奋[10]，随即对呼吸中枢、延髓、皮层下

中枢出现抑制作用,出现休克、四肢发冷、无疼痛反应等临床表现[11],甚至可发生呼吸衰竭,故患者多出现先兴奋后抑制的症状[12]。过量乙醇会显著提高机体内乳酸水平,引发酸中毒;未能代谢的乙醇可与酶合成大量的强破坏性氧自由基,且可导致脂质过氧化损害细胞功能[13];乙醇浓度过高还导致NO大量生成,损伤细胞结构[14]。近来,随着人们交际活动增加、生活压力增大等原因,饮酒比例显著增加,急性酒精中毒发病率也明显上升,成为我国急性中毒的主要发病原因[15,16]。

醒脑静为传统治疗急性酒精中毒的药物,是由安宫牛黄丸提取制得的中药,对急性酒精中毒的治疗机制为:① 其作为一种强抗氧化剂,对氧自由基可起强力清除作用[17];② 醒脑静中的麝香酮可通过血脑屏障有效作用于中枢神经,解除对其的抑制作用,其中的冰片可双向调节,起到促醒及定神作用,其中的郁金可凉血醒神,有效催醒开窍,促进意识恢复[18];③ 可抑制脑部钠离子含量,其中的山栀可缓解脑水肿情况,释放神经递质,改善血脑循环,并可清热泻火,促进通气[19];④ 是一种阿片受体拮抗剂,可减少β内啡呔,保护脑组织[20];⑤ 醒脑静具有抗炎作用,降低炎性因子活性;⑥ 对抑制性氨基酸(EAAs)起到有效抑制,降低其兴奋毒性;⑦ 醒脑静可起到有效的抑制细胞凋亡作用。动物实验显示[18]醒脑静可通过对抑制性神经递质和兴奋性氨基酸类神经递质及受体的表达进行调控,起到有效的促醒作用。大量研究也已表明[21,22]醒脑静对急性酒精中毒具有良好疗效,且具有作用温和、安全性好的优点。

古拉定为治疗酒精中毒和酒精性肝硬化的常用药物,是一种还原型谷胱甘肽,研究[23]显示古拉定具有良好的解毒排解作用,对保护机体肝功能可起到较好的效果。有文献[24,25]显示古拉定可显著降低患者体内乙醇浓度,并可促进消化道对脂溶性维生素的吸收及体内蛋白质、脂肪等代谢,促进患者恢复。有研究表明[26]古拉定可有效保护血管细胞,促进细胞恢复。近年来,关于醒脑静和古拉定分别用于治疗酒精中毒的研究较多,但两者联合治疗的相关研究较少,本研究主要探讨了醒脑静联合古拉定治疗对急性酒精中毒,以期指导临床治疗。

本研究结果显示:联合古拉定组的血压与心率恢复正常及清醒时间均显著提前,其原因可能为古拉定可激活体内巯基酶,促进代谢,加快缓解细胞损伤,因此与单纯使用醒脑静相比,联合古拉定可对急性酒精中毒患者起到更快速、有效的治疗作用。本研究中,联合古拉定组GGT、AST、和ALT水平均显著更低,原因可能为古拉定中的谷氨酸等可参与机体内反应,促进解毒排毒,有效保护肝脏,故而可更显著的起到改善肝功、保护肝脏的作用。有研究显示H_2O_2、SOD、MDA和iNOS均在急性酒精中毒的发病及病情发展中起到重要作用。iNOS是机体氮自由基产生的催化酶,具有神经毒性,对体内细胞结构有严重损害。H_2O_2为酒精中毒产生的氧自由基,具有很强的破坏性,是发生过氧化反应、损害细胞功能的重要因素;而MDA为脂质过氧化的分解产物,毒性高,可生成反应性醛危害细胞膜,可造成细胞凋亡,故其水平可体现肝脏损害情况,并可间接体现自由基对机体的损害,水平越高损害越重;SOD为体内的抗氧化物质,为体内氧自由基浓度及氧化反应平衡程度的重要评价指标,可有效清除自由基,修复受其损伤的细胞,但MDA水平的提高可引发SOD水平降低。H_2O_2、SOD、MDA、iNOS体现急性酒精中毒患者体内氧化反应及细胞受损程度,可作为治疗疗效的评价指标。本研究中,与单纯醒脑静组同期对比,联合古拉定组H_2O_2、MDA、iNOS水平均显著更低,SOD水平显著更高,原因为古拉定可与乙醇的毒性代谢物及生成的自由基结合,对脂质过氧化反应起抑制作用,本文研究进一步证实古拉定对清除自由基,恢复氧化反应平衡,保护机体细胞功能,促进患者恢复具有良好疗效。本研究中,两组均有较好的治疗效果,但联合古拉定组要略优,且联合组患者苏醒后不适症状显著减少,可见两者联合使用能明显降低患者不适感。

综上所述,采用醒脑静及古拉定治疗急性酒精中毒患者可更快速、有效消除临床症状,改善肝功能,减少患者不适感,疗效更显著,可能与其有效降低血清MDA、iNOS水平并升高血清SOD水平有关。但对于两者联合的具体作用机制及安全性,仍有待更多大样本、多中心、大规模的长期研究加以验证。

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