

普鲁士蓝或联合血液灌流治疗急性铊中毒的疗效分析

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DOI: 10.3760/cma.j.issn.2095-4352.2018.07.016

【摘要】 **目的** 探讨普鲁士蓝(PB)或联合血液灌流(HP)治疗急性铊中毒的疗效。**方法** 选择2002年9月至2017年12月解放军第三〇七医院收治的资料完整的47例急性铊中毒患者,按中毒程度分为轻度中毒组(血铊 $<150\ \mu\text{g/L}$ 、尿铊 $<1000\ \mu\text{g/L}$)和中重度中毒组(血铊 $\geq 150\ \mu\text{g/L}$ 、尿铊 $\geq 1000\ \mu\text{g/L}$)。两组患者入院时均给予补钾、导泻、保护器官、营养神经、改善循环等对症支持治疗;同时,轻度中毒组口服PB $250\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$,中重度中毒组在口服PB的同时给予HP治疗(每次持续2~4 h),根据患者血、尿铊监测结果调整PB剂量或HP应用频数。收集两组患者的性别、年龄、疼痛分级(数字分级法, NRS)、临床表现、治疗前后血铊和尿铊水平以及住院时间和预后。**结果** 47例患者中,排除血、尿毒物检测数据不全及采用血浆置换、血液透析等治疗者,最终共29例患者纳入分析。① 29例患者中,男性20例,女性9例;中位年龄40.0(34.0, 49.0)岁;临床表现均以神经系统、脱发为主,部分患者出现消化系统症状。轻度中毒组13例(占44.8%),疼痛分级为无痛(0级)或轻度疼痛(1~3级),临床症状较轻,住院时间为17.0(14.2, 21.5)d;中重度中毒组16例(占55.2%),疼痛分级为中度疼痛(4~6级)或重度疼痛(7~10级),临床症状较重,住院时间为24.0(18.0, 29.0)d。② 治疗后轻度中毒组患者血铊和尿铊水平均较治疗前明显降低[$\mu\text{g/L}$: 血铊为0.80(0, 8.83)比60.00(40.00, 120.00),尿铊为11.30(0, 70.10)比370.00(168.30, 610.00),均 $P<0.01$];中重度中毒组血铊和尿铊水平也较治疗前明显降低[$\mu\text{g/L}$: 血铊为6.95(0, 50.50)比614.50(245.00, 922.00),尿铊为20.70(1.95, 283.00)比5434.00(4077.20, 10273.00),均 $P<0.01$]。29例患者无一例死亡,且临床症状均得到明显改善。随访半年后,27例患者预后良好,无后遗症;2例重度急性铊中毒患者遗留神经系统损伤。**结论** 针对急性铊中毒患者,在常规治疗基础上,轻度中毒者给予PB口服,中重度中毒者给予PB联合HP治疗均可获得满意疗效。

【关键词】 铊中毒; 血液灌流; 普鲁士蓝; 疗效分析

基金项目: 国家卫生和计划生育委员会公益性行业科研专项课题(201502043)

Efficacy analysis of prussian blue or its combination with hemoperfusion in the treatment of acute thallium poisoning Zhao Junxiu, Peng Xiaobo, Wang Chunyan, Bai Lili, Dong Jianguang, Lu Xiaoxia, Liu Yanqing, Feng Shufang, Long Jianhai, Qiu Zewu

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【Abstract】 **Objective** To investigate the efficacy of prussian blue (PB) or its combination with hemoperfusion (HP) in the treatment of acute thallium poisoning. **Methods** Forty-seven patients with acute thallium poisoning with complete data hospitalized in the 307th Hospital of PLA from September 2002 to December 2017 were enrolled, and they were divided into mild poisoning group (blood thallium $<150\ \mu\text{g/L}$, urinary thallium $<1000\ \mu\text{g/L}$) and moderate-severe poisoning group (blood thallium $\geq 150\ \mu\text{g/L}$, urinary thallium $\geq 1000\ \mu\text{g/L}$) according to the toxic degrees. All patients were given symptomatic supportive treatments such as potassium supplementation, catharsis, vital organ protections, neurotrophic drugs, and circulation support. The mild poisoning patients were given PB with an oral dose of $250\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, while moderate-severe poisoning patients were given PB combined HP continued 2-4 hours each time. The PB dose or frequency of HP application was adjusted according to the monitoring results of blood and urine thallium. Data of gender, age, pain grading (numeric rating scale NRS), clinical manifestations, blood and urine thallium before and after treatment, length of hospitalization and prognosis were collected. **Results** Of the 47 patients, patients with incomplete blood and urine test results, and used non-single HP treatment such as plasmapheresis and hemodialysis for treatment were excluded, and a total of 29 patients were enrolled in the analysis. ① Among 29 patients, there were 20 males and 9 females, median age of 40.0 (34.0, 49.0) years old; the main clinical manifestations were nervous system and alopecia, some patients had digestive system symptoms. There were 13 patients (44.8%) in the mild poisoning group with painless (grade 0) or mild pain (grade 1-3) with mild clinical symptoms, the length of hospitalization was 17.0 (14.2, 21.5) days. There were 16 patients (55.2%) in the moderate-severe poisoning group with moderate pain (grade 4-6) or severe pain (grade 7-10) with severe clinical symptoms, the length of hospitalization was 24.0 (18.0, 29.0) days.

② After treatment, the thallium concentrations in blood and urine in the mild poisoning group were significantly lower than those before treatment [$\mu\text{g/L}$: blood thallium was 0.80 (0, 8.83) vs. 60.00 (40.00, 120.00), urine thallium was 11.30 (0, 70.10) vs. 370.00 (168.30, 610.00), both $P < 0.01$], the thallium concentrations in blood and urine in the moderate-severe poisoning group were also significantly lower than those before treatment [$\mu\text{g/L}$: blood thallium was 6.95 (0, 50.50) vs. 614.50 (245.00, 922.00), urinary thallium was 20.70 (1.95, 283.00) vs. 5 434.00 (4 077.20, 10 273.00), both $P < 0.01$]. None of the 29 patients died, and their clinical symptoms were improved significantly. All the 27 patients had good prognosis without sequela in half a year follow-up, and 2 patients with severe acute thallium poisoning suffered from nervous system injury. **Conclusion** In the acute thallium poisoning patients, on the basis of general treatment, additional PB in mild poisoning group and PB combined with HP in moderate-severe poisoning group can obtain satisfactory curative effects.

【Key words】 Thallium poisoning; Hemoperfusion; Prussian blue; Efficacy analysis

Fund program: National Health and Family Planning Commission Public Welfare Industry Research Special Subject of China (201502043)

重金属铊多用于建筑、光学产业、珠宝、电子及摄影等行业。铊和铊化合物可经呼吸系统、消化系统、皮肤途径进入体内导致中毒^[1-2]。因铊盐无色、无味、易溶于水^[2-4],人体接触后不易被发现,加之中毒患者早期临床表现无特异性,常易被漏诊、延诊和误诊^[5]。重症患者铊中毒可出现昏迷,甚至死亡^[6]。收集本院急性铊中毒患者的临床资料,分析其临床特征,并利用前期基础实验结果和临床探索性治疗经验,对急性铊中毒患者实施普鲁士蓝(PB)或联合血液灌流(HP)治疗,获得满意疗效,报告如下。

1 资料与方法

1.1 研究对象:收集2002年9月至2017年12月在本院经血、尿毒物检测确诊为急性铊中毒并住院治疗的47例患者的临床资料。

1.1.1 纳入标准:采用7500ce型电感耦合等离子体质谱仪(美国Agilent公司)在血、尿中检测到重金属铊者。

1.1.2 排除标准:①血、尿物毒物检测结果资料不全者;②治疗时采用血浆置换、血液透析等非HP治疗者。满足以上任何一项即视为排除病例。

1.1.3 伦理学:本研究符合医学伦理学标准,并经医院伦理委员会批准(审批号:ky-2018-5-41),所有治疗及检测均获得患者或家属的知情同意。

1.2 分组及治疗:将入选患者按中毒程度分为轻度中毒组(血铊 $< 150 \mu\text{g/L}$ 、尿铊 $< 1000 \mu\text{g/L}$)和中重度中毒组(血铊 $\geq 150 \mu\text{g/L}$ 、尿铊 $\geq 1000 \mu\text{g/L}$)。入院时所有患者均常规静脉泵入氯化钾或口服氯化钾缓释片补钾,口服甘露醇导泻,静脉注射兰索拉唑抑酸+口服铝镁混悬液保护胃肠黏膜,静脉注射复方甘草酸苷+还原型谷胱甘肽保肝,肌肉注射鼠神经生长因子+静脉注射单唾液酸四己酸神经节苷脂钠营养神经,静脉注射丹参川芎嗪改善循环。轻度中毒组口服PB $250 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (PB胶囊 330 mg/粒 ,

由军事医学科学院放射与辐射医学研究所研制,批准文号:军药准字×2001006);中重度中毒组患者如无HP禁忌证,于征得患者及家属知情同意后,在口服PB的基础上,给予HP治疗(健帆JF-800A型一次性使用血液灌流器HA330),每次持续2~4h。入院早期每日1次,连续应用3~5d;根据患者血、尿铊监测结果调整PB剂量或HP的应用频数。

1.3 资料收集:收集患者的性别、年龄、疼痛分级、临床表现,入院24h内和治疗后血、尿铊水平,以及住院时间和预后。

1.4 统计学分析:使用SAS 9.0软件进行数据分析,对计量资料进行Shapiro-Wilk正态性检验,均不符合正态分布,以中位数(四分位数)[$M(Q_L, Q_U)$]表示,采用Kruskal-Wallis秩和检验。计数资料采用 χ^2 检验或Fisher精确概率法。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般情况(表1):47例患者中,排除血、尿毒物检测数据不全及血浆置换、血液透析等治疗者,共纳入急性铊中毒患者29例,其中男性20例,女性9例;年龄3~68岁,中位年龄40.0(34.0, 49.0)岁。轻度中毒组13例,男性10例,女性3例;中位年龄37.0(32.0, 46.0)岁;数字分级法(NRS)疼痛分级为无痛(0级)或轻度疼痛(1~3级);临床症状较轻,所有患者均出现神经系统症状,8例出现消化系统症状,12例出现脱发。中重度中毒组16例,男性10例,女性6例;中位年龄40.5(36.0, 53.0)岁;疼痛分级为中度疼痛(4~6级)或重度疼痛(7~10级),临床症状较重,所有患者均出现神经系统症状和脱发,13例出现消化系统症状。

2.2 疗效及预后(表2):两组治疗后血、尿铊水平均较治疗前明显下降(均 $P < 0.01$),且临床症状均得到明显改善。29例患者无一例死亡。随访半年后,

表1 不同中毒程度两组急性铊中毒患者一般情况及临床特征

组别	例数 (例)	性别(例)		年龄 [岁, $M(Q_L, Q_U)$]	疼痛分级 [级, $M(Q_L, Q_U)$]	临床表现(例)			住院时间 [d, $M(Q_L, Q_U)$]
		男性	女性			神经系统	消化系统	脱发	
轻度中毒组	13	10	3	37.0(32.0, 46.0)	2.00(1.25, 2.75)	13	8	12	17.0(14.2, 21.5)
中重度中毒组	16	10	6	40.5(36.0, 53.0)	6.50(5.00, 8.00)	16	13	16	24.0(18.0, 29.0)

表2 不同中毒程度两组急性铊中毒患者治疗前后血、尿铊水平变化及预后

组别	例数 (例)	血铊 [$\mu\text{g/L}$, $M(Q_L, Q_U)$]		尿铊 [$\mu\text{g/L}$, $M(Q_L, Q_U)$]		出院时预后 良好(例)
		治疗前	治疗后	治疗前	治疗后	
轻度中毒组	13	60.00(40.00, 120.00)	0.80(0, 8.83) ^a	370.00(168.30, 610.00)	11.30(0, 70.10) ^a	7
中重度中毒组	16	614.50(245.00, 922.00)	6.95(0, 50.50) ^a	5434.00(4077.20, 10273.00)	20.70(1.95, 283.00) ^a	7

注:轻度中毒组给予普鲁士蓝(PB)口服,中重度中毒组给予PB联合血液灌流(HP)治疗;与本组治疗前比较,^a $P < 0.01$

27例患者预后良好,无后遗症;2例重度急性铊中毒患者遗留神经系统损伤,表现为记忆力减退、反应迟钝、肢体无力、肌肉萎缩等。

3 讨论

铊曾用来治疗淋病、梅毒、肺结核、癣等,甚至作为脱毛剂去除多余的头发;铊也被用作杀鼠剂,但由于可致人中毒,于1965年被禁止家庭使用^[4]。目前职业性铊中毒少见,中毒原因多为误食或投毒。1995至2005年,美国毒物数据中心报道了830例铊中毒患者,其中包括1例死亡报道^[7],近年来每年约有20例铊中毒新发病例^[8]。1965至2017年,国内文献报道铊中毒患者共319例,其中90%以上的中毒案例发生在1994年清华大学朱令铊中毒案例之后;本院中毒救治中心在近3年内就收治了数起群体性铊中毒患者。

铊中毒机制至今尚未完全阐明,目前主要认为:

- ① 铊对钾离子的竞争性抑制导致细胞内铊积聚而产生中毒效应;
- ② 铊与含巯基的蛋白酶结合,干扰其生物活性,影响三磷酸腺苷(ATP)生成,使神经系统受损^[9];
- ③ 铊可结合核黄素,形成不溶性复合物,减少核黄蛋白合成,使生物氧化受到影响,从而阻滞能量代谢的产生^[10];
- ④ 铊可抑制组织细胞有丝分裂,造成细胞代谢功能紊乱,从而影响DNA合成^[11];
- ⑤ 铊的脂质过氧化作用使神经系统受到损伤。

目前铊中毒治疗包括3个方面,即增加尿液排出、增加粪便排出及血液净化^[12-14]。1955年, Fretwurst 和 Lochmann 提出通过利尿促进铊盐排泄; Lameijer 和 van Zwieten^[15]研究表明,25 mg 依地尼酸的促排作用最为显著,排出量约为正常量的3倍;1971年 Kamerbeek 等^[16]提出PB是促进粪便排泄铊盐的唯一途径,可有效阻断铊盐的肝肠循环,促进粪便铊盐的排出。Kuroda^[17]及 Sojaková^[18]等也提出铊中毒患者应早期使用PB进行驱铊治疗。美国

食品与药物监督管理局(FDA)已批准PB用于急性铊中毒的治疗^[19]。PB与铊的结合涉及离子捕获、离子交换、物理吸附等多种机制^[20]。目前有单用PB、血液净化以及二者联合使用取得一定效果的个案报道^[1, 6, 21-26],国外也仅有数例采用PB联合血液净化治疗铊中毒的报道^[13, 27]。由于铊中毒在临床上属于相对罕见的疾病,且其发病无规律性,至今国内外有关急性铊中毒患者的详细病例资料研究较少,更缺乏针对急性铊中毒患者治疗的基础实验和临床系统研究。

本研究中29例铊中毒患者均伴有不同程度的肢体麻木、疼痛、无力等神经系统表现;21例出现腹胀、腹痛、恶心、呕吐等不同程度的胃肠道反应;28例患者在中毒后1~3周脱发。本研究结果与文献报道的铊中毒典型特征为神经系统症状、胃肠道症状及脱发一致^[1, 3, 28-29]。在治疗过程中发现,肝损伤患者在轻度中毒组和中重度中毒组分别为2例、8例;此外,在中重度中毒组中还出现呼吸衰竭、中毒性脑病、肠梗阻、代谢性酸碱中毒各2例,心肌损伤1例。

HP可稳定、高效地清除血中的铊^[25]。Ghannoum 等^[8]提出铊中毒24~48 h内进行血液净化具有明显疗效,建议停止血液净化指标为血铊 $< 100 \mu\text{g/L}$,同时间断性HP对铊中毒的治疗有效;但因其证据等级均为D级(较低的证据水平),需要统计学数据分析进一步支持。本组13例轻度中毒患者经单纯PB治疗均取得较好的疗效,16例中重度中毒患者经PB+HP治疗效果亦显著。本课题组前期进行了家兔急性硝酸亚铊中毒半数致死量测定和毒代动力学研究^[12],并基于毒代动力学研究结果,对PB、HP及PB联合HP治疗比格犬急性铊中毒的效应进行了系列研究^[21];同时探讨了不同治疗方案对铊中毒比格犬脑内多种氨基酸神经递质的影响^[30]。结

果均提示 PB、HP 都是治疗急性铊中毒的有效措施,且两者联合使用具有“1+1>2”的治疗效应,尤其适合中重度急性铊中毒患者的早期急救^[21]。以上基础实验研究对本次临床资料进行了有力的诠释。

综上所述,在临床上患者突发对称性四肢远端麻木,且对痛觉过敏,并伴有胃肠道症状和脱发时,应高度警觉铊中毒的可能,尽早留取患者血、尿标本进行毒物鉴定,尽早明确诊断。对于血、尿铊水平较低且症状相对较轻的铊中毒患者,单纯应用 PB 治疗即可获得较好疗效;PB+HP 是中重度急性铊中毒患者的有效治疗措施,可最大程度减轻组织器官损伤,降低重症铊中毒患者的致死致残率。

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