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神经节苷脂联合咪达唑仑治疗重症颅脑损伤的临床疗效及对患者血清 MMP-9、GFAP、MBP、NSE 水平的影响 *

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摘要 目的:探讨神经节苷脂联合咪达唑仑治疗重症颅脑损伤的临床疗效及对患者血清基质金属蛋白酶-9(MMP-9)、胶质纤维酸性蛋白(GFAP)、髓鞘碱性蛋白(MBP)、神经元特异性烯醇化酶(NSE)水平的影响。**方法:**选择2016年3月到2017年9月于我院进行治疗的85例重症颅脑损伤患者,将其按随机数表法分为观察组(n=45)和对照组(n=40),对照组使用神经节苷脂治疗,观察组采用神经节苷脂联合咪达唑仑治疗。比较两组治疗后疗效及血清GFAP、中枢神经特异蛋白(S100β)、NSE、MMP-9、MBP、C反应蛋白(CRP)、白细胞介素-6(IL-6)、肿瘤坏死因子α(TNF-α)水平、格拉斯哥昏迷评分(Glasgow Coma Scale, GCS)评分的变化及不良反应的发生情况。**结果:**治疗后,观察组临床疗效总有效率(93.33%)显著高于对照组(75.00%, $P<0.05$);两组血清GFAP、S100β、NSE、MMP-9、MBP、CRP、IL-6及TNF-α水平均较治疗前明显下降,且观察组以上指标均显著低于对照组($P<0.05$);观察组GCS评分明显高于对照组($P<0.05$),且不良反应发生率明显低于对照组(6.67% vs. 30.00%, $P<0.05$)。**结论:**神经节苷脂联合咪达唑仑治疗重症颅脑损伤患者的临床效果显著,明显优于单用神经节苷脂治疗,可能与其有效改善患者血清MMP-9、GFAP、MBP、NSE水平及抑制炎症因子的生成有关。

关键词:神经节苷脂;咪达唑仑;重症颅脑损伤;基质金属蛋白酶-9;胶质纤维酸性蛋白;髓鞘碱性蛋白;神经元特异性烯醇化酶
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Curative Efficacy of Ganglioside Combined with Midazolamin in the Treatment of Severe Craniocerebral Injury and Its Effect on the Serum MMP-9, GFAP, MBP, NSE Levels*

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ABSTRACT Objective: To study the curative efficacy of ganglioside combined with midazolamin in the treatment of severe craniocerebral injury and its effect on the serum matrix metalloproteinase-9 (MMP-9), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), neuron-specific enolase (NSE) levels. **Methods:** 85 cases of patients with severe craniocerebral injury treated in our hospital from March 2016 to September 2017 were selected, they were divided into the observation group (n=45) and the control group (n=40) according to the random number table. The control group was treated by ganglioside, and the observation group was treated by ganglioside combined with midazolamin. After treatment, the curative effect, changes of serum GFAP, CNS, MMP-9, MBP, c-reactive protein (CRP), interleukin-6 (IL-6), TNF-α, Glasgow Coma Scale (GCS) levels before and after treatment and incidence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate (93.33%) of observation group was significantly higher than that of the control group (75.00%) ($P<0.05$); the serum GFAP, S100 aspirate, NSE, MMP-9, MBP, CRP, IL-6 and TNF-α were significantly decreased in the two groups compared with those before treatment, and the above indicators in the observation group were significantly lower than those in the control group ($P<0.05$); The GCS score of observation group was significantly higher than that of the control group ($P<0.05$). The incidence of adverse reactions in the observation group was significantly lower than that in the control group (6.67% vs. 30.00%, $P<0.05$). **Conclusion:** The clinical effect of ganglioside combined with midazolamin was more effective than ganglioside alone in the treatment of patients with severe craniocerebral injury, it may be related to the effective decrease of serum levels of MMP-9, GFAP, MBP, and NSE.

Key words: Ganglioside; Midazolamin; Severe craniocerebral injury; Matrix metalloproteinase-9; Glial fibrillary acid protein; Myelin basic protein; Neuron-specific enolase

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前言

头部遭受直接或间接暴力作用所引起的颅脑组织损伤称为颅脑损伤,是一种常见的外伤,根据病情的严重程度可分为轻、中、重、特重四型,多伴有感染、癫痫、脑梗死等,严重者还会出现昏迷,其病死率和致残率居高不下^[1,2]。近年来,随着院前急救措施的急症医疗条件的改进,重型颅脑损伤患者死亡率明显下降,但由于患者神经功能受到损伤,其致残率仍较高^[3,4]。如何提高患者神经康复治疗的效果并降低疾病的致残率仍是神经外科学者所关注的重点。

神经节苷、轴突生长及神经再生具有促进作用,但是关于重型颅脑损伤患者接受神经节苷脂治疗后炎症因子表达和神经体液情况的变化仍不完全明确^[5,6]。咪达唑仑是重症加强治疗病房常规镇痛药物之一,可抑制炎症因子的表达和分泌,起到保护大脑的作用^[7,8]。因此,本研究主要探讨了神经节苷脂联合咪达唑仑治疗重症颅脑损伤患者使用的临床疗效,并观察其对患者血清 MMP-9、GFAP、MBP、NSE 水平的影响,旨在为临床治疗提供依据,现报道如下。

1 资料与方法

1.1 一般资料

选择 2016 年 3 月到 2017 年 9 月于我院进行治疗的 85 例重症颅脑损伤患者进行研究。通过随机数表法分为 2 组,观察组男 24 例,女 21 例;年龄 23~69 岁,平均(44.85±8.62)岁;其中交通伤 24 例,坠落伤 13 例,混合伤 5 例,其余 3 例。对照组男 25 例,女 15 例;年龄 21~70 岁,平均(46.13±7.95)岁;致伤原因:交通伤 22 例,坠落伤 10 例,混合伤 6 例,其余 2 例。两组患者性别($\chi^2=0.729$, $P=0.393$)、年龄($t=0.709$, $P=0.481$)等一般资料比较差异不显著,具有可比性。

纳入标准:(1)存在明确外伤,CT 检查确诊为颅脑损伤;(2)有不同程度的意识障碍;(3)未合并精神障碍者。排除标准:(1)单纯硬膜外血肿;(2)合并严重心、脑、肾等器官疾病者;(3)妊娠期妇女。

1.2 治疗方法

两组均给予降颅内压、维持水电解质平衡、止血、抗感染等

常规治疗措施。对照组给予神经节苷脂(规格 40 mg,厂家:哈尔滨医大药业股份有限公司,国药准字 H20080502)10 mL+5%葡萄糖注射液 250 mL 静脉滴注,1 d 1 次。观察组在对照组的基础上加用咪达唑仑(规格 5 mL: 5 mg,厂家:江苏恩华药业股份有限公司,国药准字 H20031071)0.2~0.3 mg/(Kg·h),持续静脉泵入 10 min。

1.3 观察指标

于治疗前及治疗后,采集清晨空腹血 8 mL,室温下静置 1 h 后,以 3000 r·min⁻¹ 离心 15 min 后,提取上层血清,置于冷冻箱内储存以备检测,血清 GFAP、S100 β 、NSE、MMP-9、MBP、CRP、IL-6、TNF- α 的测定采用双抗体夹心酶联免疫吸附法(ELISA),试剂盒购于深圳晶美生物工程有限公司,所有操作均严格按照仪器及试剂盒说明书进行;采用格拉斯哥昏迷量表(GCS)对患者入院时和治疗后进行评分;记录术后不良反应发生情况。

格拉斯哥量表评分标准^[9]:(1)5 分:良好,正常生活,有轻度缺陷;(2)4 分:轻度残疾,独立生活,参加工作在保护状态下进行;(3)3 分:重度残疾,有清醒的意识,无法独立生活,需要人照顾;(4)2 分:只有最小的反应(如清醒的时候眼睛能睁开)或死亡,分值越低,病情越重。

疗效评定标准^[10]:显效:颅内血肿、昏迷等症状完全消失,功能缺损功能评分减少 >46%;有效:生命体征及临床症状明显改善,功能缺损功能评分减少 18%~45%;无效:功能缺损功能评分减少 <18%,生命体征及临床症状无明显改善。显效 + 有效 = 总有效率。

1.4 统计学分析

本实验的数据使用 SPSS19.0 进行处理,计量资料表示为($\bar{x} \pm s$),组间比较采用 t 检验,计数资料表示为[例(%)],组间比较选用 χ^2 检验,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组总有效率显著高于对照组(93.33% vs. 75.00%, $P < 0.05$),见表 1。

表 1 两组患者临床疗效的比较[例(%)]

Table 1 Comparison of the efficacy between the two groups[n(%)]

Groups	n	Effective	Valid	Invalid	Total effective rate
Observation group	45	24(53.33)	18(40.00)	3(6.67)	42(93.33)
The control group	40	16(40.00)	14(35.00)	10(25.00)	30(75.00)
P value					0.019

2.2 两组患者治疗前后血清 GFAP、S100 β 及 NSE 水平比较

两组患者治疗前血清 GFAP、S100 β 及 NSE 水平比较无明显差异;治疗后,两组血清 GFAP、S100 β 及 NSE 水平均较治疗前明显下降,且观察组血清 GFAP、S100 β 及 NSE 水平显著低于对照组($P < 0.05$),见表 2。

2.3 两组患者治疗前后血清 MMP-9、MBP 水平比较

两组患者治疗前 MMP-9、MBP 水平比较无明显差异;治

疗后,两组血清 MMP-9、MBP 水平均较治疗前明显下降,且观察组血清 MMP-9、MBP 水平显著低于对照组($P < 0.05$)。

2.4 两组患者治疗前后血清 CRP、IL-6 及 TNF- α 水平比较

两组患者治疗前血清 CRP、IL-6 及 TNF- α 水平比较无明显差异;治疗后,两组 CRP、IL-6 及 TNF- α 水平均较治疗前显著降低,且观察组血清 CRP、IL-6 及 TNF- α 水平均显著低于对照组($P < 0.05$)。

表 2 两组患者治疗前后血清 GFAP、S100 β 及 NSE 水平比较($\bar{x} \pm s$)Table 2 Comparison of the serum GFAP, S100 and NSE levels before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	GFAP(pg/mL)		S100 β (ng/mL)		NSE(ng/mL)	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group	45	5.73 $\pm$ 0.78	1.76 $\pm$ 0.21	0.59 $\pm$ 0.07	0.15 $\pm$ 0.02	38.59 $\pm$ 5.52	14.51 $\pm$ 1.80
The control group	40	5.81 $\pm$ 0.71	2.43 $\pm$ 0.28	0.61 $\pm$ 0.08	0.28 $\pm$ 0.04	39.11 $\pm$ 5.83	19.39 $\pm$ 2.26
t value		0.492	12.564	1.229	19.269	0.422	11.067
P value		0.624	0.000	0.222	0.000	0.674	0.000

2.5 两组患者治疗前后 GCS 评分比较

后, 观察组 GCS 评分明显高于对照组($P < 0.05$), 见表 3。

治疗前, 两组 GCS 评分比较差异不显著($P > 0.05$); 治疗

表 3 两组患者治疗前后 GCS 评分比较($\bar{x} \pm s$)Table 3 Comparison of the GCS score before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	Before the treatment	After treatment
Observation group	45	6.82 $\pm$ 2.11	12.53 $\pm$ 3.81
The control group	40	6.27 $\pm$ 2.23	9.62 $\pm$ 4.27
t value		1.168	3.321
P value		0.246	0.001

2.6 两组患者不良反应发生情况比较

治疗期间, 观察组不良反应总发生率为 6.67%, 显著低于对照组(30.00%, $P < 0.05$)。

3 讨论

重症颅脑损伤是常见急危重症, 病情复杂且病情发展快。在患者受伤后, 机体可出现氧自由基大量释放、能量代谢障碍、微循环障碍、缺氧、细胞凋亡等一系列复杂的病理和生理改变, 致使脑组织发生不同的变性、坏死等症状^[11,12]。曾有报道指出重症颅脑损伤病情进展与局部神经细胞破坏、血管通透性升高、炎症因子释放等因素相关^[13,14]。

神经节苷脂是新发展起来的具有神经修复作用的药物, 能够促进毒副代谢产物的清除、减轻神经功能的持续损伤^[15]。有研究表明神经节苷脂在脑神经再生发育的过程中神经生长因子发挥了重要作用。在形成新的神经网络时, 脑神经的再次发育因为神经节苷脂介导的神经生长因子的活性增加了几十倍而得到修复^[16,17]。在重症颅脑损伤治疗中, 咪达唑仑作为苯二氮受体激动剂, 有一定的特异性, 具有明显的镇静、肌松、抗惊厥、抗焦虑等作用, 且对脑损伤患者具有一定的脑保护^[18,19]。

本研究结果显示使用神经节苷脂联合咪达唑仑治疗的总有效率为 93.33%, 明显高于使用沙丁胺醇治疗的患者, 提示联合用药治疗重症颅脑损伤效果显著。MMP-9 是以酶原的形式从胞内分泌到胞外, 主要是降解和重塑细胞外基质的动态平衡的; GFAP 是星形胶质细胞活化的标志物, 主要分布于中枢神经系统的星形胶质细胞, 参与细胞骨架的构成并维持其张力强度; MBP 是一种单链灵活的多肽, 位于致密的髓鞘与髓核中, 能用作少突细胞、施万细胞和施万细胞瘤的标记物; NSE 有多种二聚异构体, 由三种亚单位 α 、 β 和 γ 组成^[20,21]。联合用药的

患者血清 GFAP、S100 β 、NSE 水平、MMP-9 及 MBP 水平明显低于使用神经节苷脂治疗的患者。联合咪达唑仑治疗的患者血清中各项指标改善程度明显比单纯使用神经节苷脂的患者更具有优势。有研究显示炎症反应在重症颅脑损伤中起着重要作用, 颅脑损伤后造成的继发性颅脑损伤与炎症细胞的相互作用有关^[22]。本研究结果显示使用神经节苷脂联合咪达唑仑治疗的患者 CRP、IL-6 及 TNF- α 水平明显低于使用神经节苷脂的患者, 提示, 联合用药能抑制炎症相关因子的分泌、减少炎症反应所造成的神经功能二次损伤。分析是因为咪达唑仑是苯二氮受体激动剂, 能有效抑制血清炎症因子的各项表达和分泌, 降低脑氧代谢。本次研究结果还显示联合用药治疗的患者 GCS 评分明显高于使用神经节苷脂治疗的患者, 说明联合用药能更加明显的促进重症颅脑损伤患者的神经功能恢复。此外, 神经节苷脂联合咪达唑仑治疗后患者的不良反应总发生率明显低于单纯使用神经节苷脂的患者, 提示联合用药安全性更高。

综上所述, 神经节苷脂联合咪达唑仑治疗重症颅脑损伤患者的临床效果显著, 明显优于单用神经节苷脂治疗, 可能与其有效改善患者血清 MMP-9、GFAP、MBP、NSE 水平及抑制炎症因子的生成有关。

参考文献(References)

- [1] Caughlin S, Maheshwari S, Agca Y, et al. Membrane-lipid homeostasis in a prodromal rat model of Alzheimer's disease: Characteristic profiles in ganglioside distributions during aging detected using MALDI imaging mass spectrometry [J]. Biochim Biophys Acta, 2018, 1862 (6): 1327-1338
- [2] Benktander J, Barone A, Johansson MM et al. Helicobacter pylori SabA binding gangliosides of human stomach [J]. Virulence, 2018, 9(1): 738-751
- [3] Sasaki N, Itakura Y, Toyoda M. Ganglioside GM1 contributes to extra-

- cellular/intracellular regulation of insulin resistance, impairment of insulin signaling and down-stream eNOS activation, in human aortic endothelial cells after short- or long-term exposure to TNF α [J]. *Oncotarget*, 2017, 9(5): 5562-5577
- [4] Iwasawa T, Zhang P, Ohkawa Y, et al. Enhancement of malignant properties of human glioma cells by ganglioside GD3/GD2 [J]. *Int J Oncol*, 2018, 52(4): 1255-1266
- [5] Barrientos RC, Zhang Q. Isobaric Labeling of Intact Gangliosides toward Multiplexed LC-MS/MS-Based Quantitative Analysis [J]. *Anal Chem*, 2018, 90(4): 2578-2586
- [6] Klehmet J, Marschenz S, Ruprecht K, et al. Analysis of anti-ganglioside antibodies by a line immunoassay in patients with chronic-inflammatory demyelinating polyneuropathies (CIDP)[J]. *Clin Chem Lab Med*, 2018, 56(6): 919-926
- [7] Martinez-Thompson JM, Snyder MR, Ettore M, et al. Composite ganglioside autoantibodies and immune treatment response in MN and MADSAM[J]. *Muscle Nerve*, 2018, 57(6): 1000-1005
- [8] Vantaku V, Donepudi SR, Ambati CR, et al. Expression of ganglioside GD2, reprogram the lipid metabolism and EMT phenotype in bladder cancer[J]. *Oncotarget*, 2017, 8(56): 95620-95631
- [9] Bousquet PA, Sandvik JA, Jeppesen Edin NF, et al. Hypothesis: Hypoxia induces de novo synthesis of NeuGc gangliosides in humans through CMAH domain substitute[J]. *Biochem Biophys Res Commun*, 2018, 495(1): 1562-1566
- [10] Shah PA, Shah AM. A Sibling Pair with Autosomal Recessive Charcot-Marie-Tooth Disease Due to Novel Ganglioside-induced Differentiation-associated Protein 1 Mutation[J]. *Ann Indian Acad Neurol*, 2017, 20(4): 434-435
- [11] Gupta MK, Mondkar JA, Hegde D. Paradoxical Reaction to Midazolam in Preterm Neonates: A Case Series [J]. *Indian J Crit Care Med*, 2018, 22(4): 300-302
- [12] Dey S, Kumar M. Comparison of pretreatment with dexmedetomidine with midazolam for prevention of etomidate-induced myoclonus and attenuation of stress response at intubation: A randomized controlled study[J]. *J Anaesthesiol Clin Pharmacol*, 2018, 34(1): 94-98
- [13] Paleti S, Prasad PK, Lakshmi BS. A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section[J]. *J Anaesthesiol Clin Pharmacol*, 2018, 34(1): 23-28
- [14] Azeem TMA, Yosif NE, Alansary AM, et al. Dexmedetomidine vs morphine and midazolam in the prevention and treatment of delirium after adult cardiac surgery; a randomized, double-blinded clinical trial [J]. *Saudi J Anaesth*, 2018, 12(2): 190-197
- [15] Messeha MM, El-Morsy GZ. Comparison of Intranasal Dexmedetomidine Compared to Midazolam as a Premedication in Pediatrics with Congenital Heart Disease Undergoing Cardiac Catheterization [J]. *Anesth Essays Res*, 2018, 12(1): 170-175
- [16] Gaudio E, Voltan L, De Benedictis GM. Alfaxalone anaesthesia in Lemur catta following dexmedetomidine-butorphanol-midazolam sedation[J]. *Vet Anaesth Analg*, 2018, 45(3): 351-356
- [17] Stuker EW, Eskander JP, Gennuso SA. Third time's a charm: Oral midazolam vs intranasal dexmedetomidine for preoperative anxiolysis in an autistic pediatric patient [J]. *Paediatr Anaesth*, 2018, 28(4): 370-371
- [18] Lobb D, Clarke A, Lai H. Administration order of midazolam/fentanyl for moderate dental sedation[J]. *J Dent Anesth Pain Med*, 2018, 18(1): 47-56
- [19] Allen CJ, Baldor DJ, Hanna MM, et al. Early Craniectomy Improves Intracranial and Cerebral Perfusion Pressure after Severe Traumatic Brain Injury[J]. *Am Surg*, 2018, 84(3): 443-450
- [20] Lasry O, Liu EY, Powell GA, et al. Epidemiology of recurrent traumatic brain injury in the general population: A systematic review[J]. *Neurology*, 2017, 89(21): 2198-2209
- [21] Edlow BL, Chatelle C, Spencer CA, et al. Early detection of consciousness in patients with acute severe traumatic brain injury [J]. *Brain*, 2017, 140(9): 2399-2414
- [22] Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial[J]. *Crit Care Med*, 2017, 45(11): 1907-1914

(上接第 3767 页)

- [25] 段小燕,陈军,李艳,等.咬合板联合超激光及护理治疗颞下颌关节功能紊乱的临床研究[J].*激光杂志*, 2015, 36(5): 68-70
Duan Xiao-yan, Chen Jun, Li Yan, et al. Clinical study on bite plate combined super laser and nursing in the treatment of temporomandibular joint dysfunction[J]. *Laser Journal*, 2015, 36(5): 68-70
- [26] 胡伟民,邓磊,陈伟棉,等.关节松动术联合星状神经节超激光照射在颈源性眩晕中的临床研究[J].*颈腰痛杂志*, 2016, 37(2): 130-132
Hu Wei-min, Deng Lei, Chen Wei-mian, et al. Clinical study of joint mobilization combined with stellate ganglion super laser irradiation in the treatment of cervical vertigo [J]. *The Journal of Cervicodynia And Lumbodynia*, 2016, 37(2): 130-132
- [27] 古剑雄,温梦玲,梁钊明,等.超激光疼痛治疗对膝骨性关节炎患者疼痛及生活质量的影响[J].*广东医学*, 2014, 35(6): 873-875
Gu Jian-xiong, Wen Meng-ling, Liang Zhao-ming, et al. Effects of super laser pain therapy on pain and quality of life in patients with knee osteoarthritis[J]. *Guangdong Medical Journal*, 2014, 35(6): 873-875
- [28] Monticone M, Capone A, Frigau L, et al. Development of the Italian version of the High-Activity Arthroplasty Score (HAAS-I) following hip and knee total arthroplasty: cross-cultural adaptation, reliability, validity and sensitivity to change [J]. *J Orthop Surg Res*, 2018, 13(1): 81
- [29] Akil S, Newman JM, Shah NV, et al. Metal hypersensitivity in total hip and knee arthroplasty: Current concepts[J]. *J Clin Orthop Trauma*, 2018, 9(1): 3-6
- [30] Goodman SM, Byrker VP, DiCarlo E, et al. Flares in Patients with Rheumatoid Arthritis after Total Hip and Total Knee Arthroplasty: Rates, Characteristics, and Risk Factors[J]. *J Rheumatol*, 2018, 45(5): 604-611