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目标导向液体治疗联合右美托咪定对创伤性颅脑损伤患者血流动力学、脑氧代谢及炎症因子的影响 *

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摘要 目的：探讨目标导向液体（GDFT）治疗联合右美托咪定对创伤性颅脑损伤（TBI）患者血流动力学、脑氧代谢及炎症因子的影响。**方法：**选取 2016 年 3 月 ~2019 年 3 月期间我院收治的 TBI 患者 142 例，根据随机数字表法分为对照组 1（n=47，GDFT 治疗）、对照组 2（n=47，常规液体联合右美托咪定）和研究组（n=48，GDFT 联合右美托咪定），比较三组患者围术期指标、血流动力学、脑氧代谢及炎症因子变化情况，记录三组围术期间不良反应状况。**结果：**三组患者术后 12、24 h 心率（HR）、呼吸频率（RR）及动脉 - 颈内静脉血氧含量差（$AVDO_2$）均较术前降低，且研究组低于对照组 1、对照组 2（P<0.05）；三组患者术后 12、24 h 血氧饱和度（$SjvO_2$）较术前升高，且研究组高于对照组 1、对照组 2（P<0.05）；三组患者术后 12、24 h 白介素 -6（IL-6）、肿瘤坏死因子 -α（TNF-α）呈逐渐下降趋势（P<0.05）；研究组术后 12、24 h 的 IL-6、TNF-α 低于对照组 1、对照组 2（P<0.05）。对照组 2、对照组 1、研究组术中总液体量、胶体量、晶体量依次减少（P<0.05），住院天数依次缩短（P<0.05）。三组不良反应发生率对比未见显著差异（P>0.05）。**结论：**TBI 患者手术麻醉过程中给予 GDFT 联合右美托咪定方案，促进机体 HR、RR 趋于平稳的同时还可改善脑氧代谢及炎性因子水平，且不增加不良反应发生率。

关键词：目标导向液体治疗；右美托咪定；创伤性颅脑损伤；血流动力学；脑氧代谢；炎症因子

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Effects of Target Directed Liquid Therapy Combined with Dexmedetomidine on Hemodynamics, Cerebral Oxygen Metabolism and Inflammatory Factors in Patients with Traumatic Brain Injury*

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ABSTRACT Objective: To investigate the effects of target directed fluid therapy (GDFT) combined with dexmedetomidine on hemodynamics, cerebral oxygen metabolism and inflammatory factors in patients with traumatic brain injury (TBI). **Methods:** A total of 142 patients with TBI who were admitted to our hospital from March 2016 to March 2019 were selected, they were randomly divided into control group 1 (n=47, GDFT treatment), control group 2 (n=47, routine liquid combined with dexmedetomidine) and study group (n=48, GDFT combined with dexmedetomidine). The perioperative indexes, hemodynamics, cerebral oxygen metabolism and inflammatory factors changes were compared. The adverse reactions of the three groups during perioperative period were recorded. **Results:** The heart rate (HR), respiratory rate (RR) and blood oxygen content difference between artery and internal jugular vein ($AVDO_2$) in the three groups at 12 and 24 hours after operation were all decreased compared with the before operation, and those in the study group were lower than those in the control group 1 and control group 2 (P<0.05). The blood oxygen saturation ($SjvO_2$) of the three groups at 12 and 24 hours after operation increased, and those in the study group were higher than those in the control group 1 and control group 2 (P<0.05). The levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) of the three groups at 12 and 24 hours after operation were decreased (P<0.05). The levels of IL-6 and TNF-α in the study group at 12 and 24 hours were lower than those in the control group 1 and control group 2 (P<0.05). The total fluid volume, colloid volume and crystal volume decreased successively in control group 2, control group 1 and study group (P<0.05), and the length of stay in hospital decreased in turn (P<0.05). There was no significant difference in the incidence of adverse reactions in the three groups (P>0.05). **Conclusion:** During the surgical anesthesia of TBI patients, GDFT combined with dexmedetomidine regimen can promote the stability of human HR and RR, and improve the level of cerebral oxygen metabolism and inflammatory factors, and it do not increase the incidence of adverse reactions.

Key words: Targeted liquid therapy; Dexmedetomidine; Traumatic brain injury; Hemodynamics; Cerebral oxygen metabolism; Inflammatory factors

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前言

近年来创伤性颅脑损伤(traumatic brain injury,TBI)的发生率不断升高,因 TBI 致死、致残的患者逐年递增。TBI 患者术前颅高压引起的脱水、呕吐,术中出血、麻醉药物的使用引起的血管扩张,均可导致血管内容量减少,进而影响机体脏器组织的灌注,危及患者性命[1-3]。目标导向液体治疗(Target directed fluid therapy,GDFT)是指在血流动力学指标的有效监测和信息反馈指导下,采取的一种个体化液体治疗策略[4,5]。此外,TBI 的病理生理机制十分复杂,主要分为原发性脑损伤和继发性脑损伤,TBI 发病后,机体处于强烈的血流波动下,炎症因子大量分泌,均会影响患者预后。既往研究表明[6],右美托咪定具有良好的镇静、镇痛、抗应激作用。目前,对于接受 GDFT 的 TBI 患者,有关其复合右美托咪定的报道尚不十分多见,鉴于此,本研究通过探讨 GDFT 联合右美托咪定对 TBI 患者血流动力学、脑氧代谢及炎症因子的影响,以期为临床 TBI 患者麻醉方案的选择提供参考。

1 资料与方法

1.1 一般资料

选取 2016 年 3 月 ~2019 年 3 月期间我院收治的 TBI 患者 142 例,此次研究已获取我院伦理学委员会批准进行。纳入标准:(1)经 MRI 确诊为均为轻中度颅脑损伤,并在受伤 24 h 内入院;(2)具备手术指征者;(3)美国麻醉协会分级Ⅰ~Ⅱ级;(4)入院时格拉斯哥昏迷评分[7]9~15 分;(5)患者及其家属知情本研究且签署同意书。排除标准:(1)合并原发性心、肝、肾等器官病变;(2)双瞳散大,已进入脑疝晚期或脑死亡;(3)既往存在精神疾病、脑功能认知障碍者;(4)存在恶性肿瘤者;(5)妊娠或哺乳期妇女;(6)术中给予血管活性药者。根据随机数字表法分为对照组 1(n=47,GDFT 治疗)、对照组 2(n=47,右美托咪定治疗)和研究组(n=48,GDFT 联合右美托咪定治疗),其中对照组 1 男 26 例,女 21 例,年龄 18~63 岁,平均(38.62± 4.93)岁;受伤至入院时间 1~23 h,平均(12.60± 2.45)h;致伤原因:交通伤 19 例,高处坠落伤 14 例,砸伤 15 例。对照组 2 男 25 例,女 22 例,年龄 20~59 岁,平均(39.16± 5.03)岁;受伤至入院时间 1~20 h,平均(13.08± 2.61)h;致伤原因:交通伤 22 例,高处坠落伤 13 例,砸伤 12 例。研究组男 27 例,女 21 例,年龄 22~65 岁,平均(40.68± 7.81)岁;受伤至入院时间 2~19 h,平均(13.25± 3.06)h;致伤原因:交通伤 23 例,高处坠落伤 14 例,砸伤 11 例。三组患者一般资料对比未见统计学差异(P>0.05)。

1.2 方法

1.2.1 麻醉方法 三组患者入室前 0.5 h 肌注 0.5 mg 阿托品和 100 mg 苯巴比妥,入室后,面罩吸氧,常规监测患者血压、心电图、脑电双频指数等,开放外周静脉通道,局麻下于左侧桡动脉置管,于麻醉诱导开始前 10 min,对照组 2、研究组持续泵注右美托咪定(江苏恒瑞医药股份有限公司,国药准字 H20090248,规格:2 mL:200 μg(按右美托咪定计))1 μg/kg,随后以 0.5 μg/kg·h 的速率输注至手术结束。对照组 1 则输注等量生理盐水。三组患者麻醉诱导:地塞米松(马鞍山丰原制药有限公司,国药准字 H20051748,规格:5 mg(按地塞米松磷酸钠计))10 mg,咪达唑仑(江苏九旭药业有限公司,国药准字 H20153019,规格:3 mL:15 mg)0.05 mg/kg,丙泊酚(广东嘉博制药有限公司,国药准字 H20133360,规格:50 mL:500 mg)2 mg/kg,舒芬太尼(宜昌人福药业有限责任公司,国药准字 H20054256,规格:按 $C_{22}H_{30}N_2O_2S$ 计 5 mL:250 μg)0.4 μg/kg,罗库溴铵(福安药业集团庆余堂制药有限公司,国药准字 H20183106,规格:5 mL:50 mg)0.6 mg/kg,麻醉诱导成功后行气管插管,连接麻醉机行机械通气。麻醉维持选用丙泊酚 3~6 mg/kg·h,瑞芬太尼 0.1~0.3 μg/kg·min,术中间断给予顺式苯磺酸阿曲库铵(江苏恒瑞医药股份有限公司,国药准字 H20183042,5 mL:10 mg (按 $C_{53}H_{72}N_2O_{12}$ 计))0.06 mg/kg 维持肌松。关硬脑膜时停用丙泊酚,其余用药根据患者具体情况调整。

1.2.2 液体治疗方案 对照组 2 予以常规液体方案治疗,对照组 1、研究组均于切皮前 0.5 h 内匀速输注醋酸钠林格液 10 mL/kg。术中以醋酸钠林格液及琥珀酰明胶作为输入液体,晶胶比例为(1~2):1,输注速率为 5 mL/ (kg·h)。 根据每搏量变异度(Variation of stroke volume,SVV) <12%为指导予以扩容治疗;若 SVV>12%,则在 5~15 min 内输注羟乙基淀粉氯化钠注射液 250 mL。

1.3 观察指标

(1)比较三组患者住院天数、术中总液体量、胶体及晶体液量。(2)记录三组患者术前、术后 12 h、术后 24 h 的心率(heart rate,HR)、呼吸频率(respiratory rate,RR)。(3)于术前、术后 12 h、术后 24 h 采集患者颈静脉球部血和桡动脉血各 2 mL 行血气分析,采用丹麦雷度公司生产的血气分析仪检测其脑氧代谢指标变化,包括血氧饱和度(Blood oxygen saturation,$SjvO_2$)、动脉 - 颈内静脉血氧含量差(Blood oxygen content difference between artery and internal jugular vein,$AVDO_2$)。(4)于术前、术后 12 h、术后 24 h 采集患者肘静脉血 4 mL,经 3000 r/min 离心 12 min,离心半径 18 cm,分离上清液,置于 -40℃冰箱中待测。采用购自福建三强公司生产的试剂盒,按照试剂盒操作步骤采用酶联免疫吸附试验检测白介素 -6(Interleukin -6,IL-6)、肿瘤坏死因子 -α(Tumor necrosis factor-α,TNF-α)水平。(5)记录三组围术期间不良反应状况。

1.4 统计学方法

采用 SPSS20.0 进行数据分析。计量资料以均值± 标准差的形式表示,两组间比较行 t 检验,多组间比较行 F 检验。计数资料以率的形式表示,比较行卡方检验。检验标准设置为 α=0.05。

2 结果

2.1 血流动力学指标比较

三组术后 12 h、术后 24 h 的 HR、RR 均较术前降低,且研究组低于对照组 1、对照组 2(P<0.05);三组患者术后 12 h 与术后 24 h HR、RR 比较无差异(P>0.05);详见表 1。

2.2 三组患者脑氧代谢指标比较

三组患者术后 12 h、术后 24 h $SjvO_2$ 较术前升高,$AVDO_2$ 较术前降低(P<0.05);三组患者术后 12 h 与术后 24 h $SjvO_2$、$AVDO_2$ 比较无差异(P>0.05);研究组术后 12 h、术后 24 h $SjvO_2$ 高于对照组 1、对照组 2,$AVDO_2$ 低于对照组 1、对照组 2(P<0.05);详见表 2。

表 1 三组患者血流动力学指标比较($\bar{x}\pm s$)

Table 1 Comparison of hemodynamic indexes in three groups($\bar{x}\pm s$)

Groups	HR(beats/min)			RR(beats/min)		
	Before operation	12 h after operation	24 h after operation	Before operation	12 h after operation	24 h after operation
Control group 1(n=47)	98.54± 2.64	90.57± 2.35*#	90.12± 2.89*#	33.35± 4.56	29.05± 3.31*#	28.94± 4.86*#
Control group 2(n=47)	97.49± 2.93	91.10± 2.27*#	90.93± 2.43*#	33.41± 5.62	29.87± 3.87*#	29.08± 3.03*#
Study group(n=48)	96.16± 2.39	83.54± 2.31*	82.27± 2.25*	33.28± 4.20	25.91± 4.35*	25.33± 4.27*
F	0.341	19.652	23.571	0.057	26.825	35.614
P	0.735	0.000	0.000	0.955	0.000	0.000

Note: compared with before operation, *P<0.05; compared with the study group, #P<0.05.

表 2 三组患者脑氧代谢指标比较($\bar{x}\pm s$)

Table 2 Comparison of brain oxygen metabolism indexes in three groups($\bar{x}\pm s$)

Groups	$SjvO_2$(%)			$AVDO_2$(mL/dl)		
	Before operation	12 h after operation	24 h after operation	Before operation	12 h after operation	24 h after operation
Control group 1(n=47)	50.68± 6.32	54.08± 6.86*#	54.16± 6.74*#	7.44± 0.57	6.38± 0.44*#	6.29± 0.51*#
Control group 2(n=47)	50.35± 7.48	54.97± 6.31*#	54.99± 5.59*#	7.52± 0.63	6.31± 0.53*#	6.24± 0.49*#
Study group(n=48)	50.14± 7.24	59.93± 5.27*	60.71± 6.32*	7.41± 0.75	4.88± 0.79*	4.75± 0.64*
F	0.385	13.657	16.592	0.218	19.582	14.831
P	0.701	0.000	0.000	0.828	0.000	0.000

Note: compared with before operation, *P<0.05; compared with the study group, #P<0.05.

2.3 三组患者炎症因子指标比较

三组患者术后 12 h、术后 24 h IL-6、TNF-α 呈逐渐下降趋势(P<0.05);研究组术后 12 h、术后 24 h IL-6、TNF-α 低于对照组 1、对照组 2(P<0.05);详见表 2。

表 3 三组患者炎症因子指标比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory factors in three groups($\bar{x}\pm s$)

Groups	IL-6(ng/L)			TNF-α(ng/L)		
	Before operation	12 h after operation	24 h after operation	Before operation	12 h after operation	24 h after operation
Control group 1(n=47)	117.93± 18.23	75.59± 7.06*#	47.78± 5.12*&#	174.98± 15.82	128.38± 13.43*#	85.43± 14.12*&#
Control group 2(n=47)	118.83± 17.09	75.18± 8.23*#	46.73± 6.21*&#	175.82± 14.87	127.89± 13.69*#	84.08± 12.58*&#
Study group(n=48)	117.31± 15.28	51.89± 6.36*	32.41± 4.29*&	176.14± 17.22	98.17± 16.18*	51.18± 6.32*&
F	0.179	9.682	16.891	0.340	23.571	26.834
P	0.859	0.000	0.000	0.735	0.000	0.000

Note: compared with before operation, *P<0.05; compared with 12 hours after operation, &P<0.05; compared with the study group, #P<0.05.

2.4 三组患者围术期指标比较

对照组 2、对照组 1、研究组术中总液体量、胶体量、晶体量依次减少(P<0.05),住院天数依次缩短(P<0.05),详见表 4。

表 4 三组患者围术期指标比较($\bar{x}\pm s$)

Table 4 Comparison of perioperative indexes in three groups($\bar{x}\pm s$)

Groups	Length of stay(d)	Total intraoperative fluid volume(mL)	Colloid quantity(mL)	Crystal quantity(mL)
Control group 1(n=47)	18.28± 1.33	3211.32± 73.92	923.38± 26.09	1642.83± 55.73
Control group 2(n=47)	23.29± 1.89*	3573.94± 82.22*	1004.29± 25.02*	2041.37± 62.34*
Study group(n=48)	15.59± 1.25*&	3057.66± 76.35*&	866.79± 6.31*&	1388.53± 76.26*&
F	29.684	56.298	46.739	55.648
P	0.000	0.000	0.000	0.000

Note: compared with control group 1,*P<0.05; compared with control group 2, &P<0.05.

2.5 三组患者不良反应发生率比较

围术期间，对照组 1 出现 2 例谵妄、3 例心动过缓、2 例低血压，不良反应发生率为 14.89%(7/47)；对照组 2 出现 4 例谵妄、2 例心动过缓、3 例低血压，不良反应发生率为 19.15%(9/47)；研究组出现 4 例谵妄、2 例心动过缓、3 例低血压，不良反应发生率为 18.75%(9/48)；三组不良反应发生率对比未见显著差异(x^2=0.362，P=0.836)。

3 讨论

TBI 是指各种外伤作用下导致的颅脑多重损伤，危重情况下可出现脑死亡[8-10]。液体输注治疗是抢救 TBI 患者的主要手段之一，然而由于 TBI 患者伴有较高的颅内压和脑水肿，液体输入过多则可加重脑水肿，而液体输入量过少引起脑缺血、缺氧，使 TBI 患者的病死率增加[11-13]。GDFT 是一个个体化治疗方案，该方案可有效评估患者容量状态[14]。由于 TBI 患者遭受围术期的多种刺激，引起血流波动，同时颅脑损伤导致脑氧和合代谢障碍亦可引起患者继发性脑损伤[15-17]。既往研究报道[18]，在存活的 TBI 患者中，轻度损伤患者种约有 10%的患者可遗留有终身残疾，而中度和重度损伤患者终身残疾遗留率分别达 66%和 100%，严重影响患者预后。因此，如何防治继发性脑损伤，亦成为 TBI 患者治疗的主要目标之一。右美托咪定是一种高选择性的 α2 肾上腺素受体，可促进脑血管收缩、降低脑血流量，发挥脑保护等多重功效[19-21]，在多种手术中被广泛应用，因此其联合 GDFT 输注治疗可能提升 TBI 患者的治疗效果。

本次研究结果显示，三组患者术后不同时间点血流动力学、脑氧代谢、炎性因子水平均得到有效改善，且 GDFT 联合右美托咪定治疗者改善效果更佳，分析其原因，GDFT 是在血流动力学指标的监测和信息反馈指导下，采取个体化液体治疗策略，在预防围术期潜在的血容量不足或过量的情况下，还可有效维持患者血容量，从而最大限度地增加患者心输出量，保证组织器官的供氧[22,23]。联合右美托咪定后，右美托咪定可抑制机体应激反应，主要作用机制表现为激动孤束核的突出后膜上的 α2 受体，抑制去甲肾上腺素的释放，从而达到稳定血流循环的作用[24]。同时右美托咪定可改善脑氧代谢的主要机制可能在于其可降低脑细胞外血浆儿茶酚胺的浓度，从而减少大脑血流量，降低脑细胞耗氧，保持脑氧供需平衡[25]。TBI 发病时由于术前的损伤，术中的各种刺激、牵拉、缺血再灌注损伤均可诱导机体产生局部或全身的炎性反应[26]。IL-6 是典型的促炎因子，主要由胶质细胞合成并分泌，脑损伤时可使小胶质细胞大量激活并分泌 IL-6[27]；TNF-α 可诱导胶质细胞及相关神经细胞合成更多的促炎因子[28]。而右美托咪定可减轻机体的炎性反应，可能与其能抑制外周和中枢神经系统活性，减轻机体应激，减少兴奋性神经递质谷氨酸盐的释放，从而抑制炎性因子的分泌有关[29,30]。此外，与对照组 1、对照组 2 相比，研究组术中总液体量、胶体量、晶体量、住院天数等围术期指标均改善显著，从客观方面亦证实了联合治疗可有效维持机体内环境稳定，从而可以减少术中液体输注，TBI 患者得以快速恢复，减少了住院时间。另三组不良反应发生率对比未见显著差异，可见 GDFT 联合右美托咪定方案安全性较好。

综上所述，TBI 患者手术麻醉过程中给予 GDFT 联合右美托咪定方案，有助于促进 HR、RR 趋于稳定，可改善机体脑氧代谢及炎性因子水平，且不增加不良反应发生率。

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