

颅内静脉窦血栓形成治疗研究进展

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【摘要】 颅内静脉窦血栓形成是特殊类型的脑卒中,确诊率逐年增加,具有较高的病残率和病死率,目前抗凝治疗、全身静脉溶栓、动脉溶栓、接触性静脉溶栓、机械取栓术和支架植入术等多种治疗方式并存。本文对颅内静脉窦血栓形成的治疗研究进展进行概述,旨在提高对颅内静脉窦血栓形成治疗方式的认知。

【关键词】 窦血栓形成,颅内; 综述

Advances in the treatment of cerebral venous sinus thrombosis

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【Abstract】 Cerebral venous sinus thrombosis (CVST) is a special type of stroke with an increasing rate of diagnosis and a higher rate of disability and mortality. Currently, anticoagulant therapy, systemic venous thrombolysis, arterial thrombolysis, contact venous catheterization thrombolysis, mechanical thrombolysis, stent implantation and other treatment methods coexist, with different therapeutic effects. This paper reviews the progress in the treatment of CVS.

【Key words】 Sinus thrombosis, intracranial; Review

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近年来,随着医疗技术的进步和神经血管影像学的发展,颅内静脉系统疾病逐渐受到关注,对颅内静脉窦血栓形成(CVST)的认知也不断深入^[1-2]。治疗方法主要包括药物治疗和血管内治疗(EVT),病残率和病死率有所下降^[3-6]。本文拟就颅内静脉窦血栓形成的治疗研究进展进行综述。

一、药物治疗

1. 抗凝治疗 抗凝治疗的目的是预防静脉血栓形成,改善机体血液高凝状态,促进侧支循环开放,防止深静脉血栓和肺栓塞等严重事件的发生。在药物选择和剂量方面,对于无严重出血倾向、严重脏器功能障碍或围手术期抗凝治疗禁忌证的患者

(颅内出血并非抗凝治疗的绝对禁忌证),早期推荐静脉滴注普通肝素或皮下注射低分子肝素。低分子肝素的应用剂量与普通肝素根据凝血功能试验进行调整的原则有所不同,须按照患者体重进行给药,即体重<50 kg者为4000 U、0.40 ml,50~70 kg者增至6250 U、0.60 ml,>70 kg者剂量则需达到10 000 U、0.80 ml;均2次/d^[7-8]。低分子肝素的疗效和安全性已经临床实践所证实^[9-10],应用原则为:颅内静脉窦血栓一经确诊即常规经皮下注射治疗2周,使活化部分凝血活酶时间(APTT)和活化凝血时间(ACT)延长,至少达到正常参考值的2倍;然后同时服用华法林,剂量根据国际标准化比值(INR)进行调整,使INR值维持在2~3,其中,已知病因且低分子肝素治疗2周临床症状明显好转的患者,华法林口服3个月即可,而对病因不明、血液呈高凝状态且低分子肝素治疗2周后临床症状无明显改善的患者,华法林治疗时间需延长至6~12个月,而复发性颅内静脉窦血栓形成患者则建议终身服药。在治疗过程中,应重视血小板计数和凝血功能的监测,

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随时调整抗凝药物的应用剂量,必要时可停用华法林或停药后采取华法林拮抗剂维生素K或肝素拮抗剂硫酸鱼精蛋白治疗^[1,3,11]。欧洲神经科学协会联盟(EFNS)关于颅内静脉窦血栓形成治疗指南建议:急性期患者静脉滴注或皮下注射抗凝药物^[12]。目前,新型抗凝药物如利伐沙班、达比加群等,给颅内静脉窦血栓形成的治疗提供了更多的选择^[13]。

2. 静脉溶栓治疗 全身静脉溶栓治疗的基本原理是静脉滴注溶栓药物,经血液循环至颅内静脉窦内,发挥血栓溶解作用,可以选择尿激酶($500 \sim 1500$) $\times 10^3$ U/d 静脉滴注 5~7 天,测定纤维蛋白原 ≥ 1 g/L 者静脉溶栓治疗安全性良好;或 rt-PA 0.60~0.90 mg/(kg·d) 经静脉持续泵入 6 小时以上,总剂量 ≤ 50 mg^[14]。尽管有文献报道尿激酶或 rt-PA 对颅内静脉窦血栓形成具有一定溶栓效果,而且操作简便、费用相对低廉,但尚缺乏足够的循证医学证据,仅少量小样本研究获得了阳性结果。究其原因,静脉溶栓发挥治疗效果的前提是:需有足量的溶栓药物进入颅内静脉窦,与血栓充分接触,而对于颅内静脉窦完全或大部分堵塞的患者而言,静脉滴注溶栓药物无法进入颅内静脉窦内与血栓相接触,而是通过侧支循环回流,这一过程可使血药浓度显著降低,导致溶栓药物无法发挥作用^[15]。

3. 对症治疗 对症治疗的主要目的是积极治疗原发病,同时对已出现的临床症状进行合理的对症治疗。例如,感染性颅内静脉窦血栓形成尤其是已出现脑膜炎症状的患者,应根据药敏试验结果采取大剂量、足疗程、高敏性抗生素治疗;非感染性颅内静脉窦血栓形成患者,则应积极治疗原发病,例如在增加脑血容量的同时降低血液黏滞度^[16];颅内高压患者应用甘露醇或联合应用呋塞米(速尿)、白蛋白、激素等安全、快速降低颅内压药物;高热患者采用物理降温等控制体温措施;癫痫患者积极进行抗癫痫治疗^[5,6,17]。

二、外科治疗

1. 静脉窦接触性溶栓治疗 其原理是充分利用神经介入技术,将溶栓药物经导管准确输送至病变部位^[18]。与全身静脉溶栓相比,经股静脉将微导管直接置入颅内静脉窦血栓内,定位更精确、溶栓药物与血栓接触更充分,可使血栓周围药物浓度显著升高^[19];与此同时,还可将微导管置于颅内静脉窦血栓远端,经静脉泵持续输入溶栓药物,与血栓反复充分接触,尤其适用于血栓形成时间较长、体积

较大、溶栓速度缓慢的病例,可有效增加其颅内静脉窦再通率、缩短血流再通时间。溶栓药物的选择和剂量为^[20]:尿激酶($500 \sim 1500$) $\times 10^3$ U/d(2~4次/d) 静脉滴注,连续治疗 3~7 天。尿激酶静脉窦接触性溶栓主要适用于部分充分抗凝治疗后临床症状无明显改善甚至进一步恶化,且已排除其他可能引起病情进展病因的患者。与全身静脉溶栓相比,静脉窦接触性溶栓定位精准、针对性强、起效迅速,可以确保溶栓药物的局部浓度,但同时对技术和硬件设备的要求也较高,费用相对昂贵。此外,该方法为有创性操作,难以避免一定的感染或存在诱发缺血性卒中出血性转化(HT)的风险^[21]。

2. 动脉溶栓治疗 主要是通过动脉系统将溶栓药物输送至血栓部位而发挥溶栓作用^[22],通常选择经颈动脉或股动脉途径将溶栓药物顺行性通过脑毛细血管床输送至静脉系统,使其充分与血栓接触,旨在溶解皮质静脉血栓和深静脉血栓。动脉溶栓的优势在于,不仅可以溶解形成时间较短的血栓,还可以降解血液中的纤维蛋白预防继续形成血栓,稀释栓塞区域血液,从而有效促进侧支循环形成、改善局部血液循环、开放侧支静脉回流途径。溶栓药物选择和剂量:经颈动脉溶栓选择尿激酶 100×10^3 U/d, 10~30 分钟缓慢注射,连续治疗 5~7 天;经股动脉溶栓则选择尿激酶 500×10^3 U/d, 其余与颈动脉溶栓治疗方案相同。目前对动脉溶栓的疗效同样缺乏大样本循证医学证据的支持,究其原因,在颅内静脉窦完全或大部分堵塞的情况下,血流经静脉侧支循环回流,溶栓药物无法充分与血栓接触而发挥溶栓作用。Wasay 等^[21]认为,有效的循环通路是确保溶栓药物经过微循环到达颅内静脉窦血栓而发挥溶栓作用的基本前提,而动脉溶栓可以是静脉溶栓的补充。

3. 支架植入术 通过在颅内静脉窦内植入支架,即刻恢复血流,快速实现血管再通的方法^[23-24]。该治疗方法的适应证为病程较长的慢性颅内静脉窦狭窄,尤其适用于单纯规范化药物抗凝治疗 6 个月以上临床症状仍无明显改善,且颅内静脉窦溶栓效果欠佳且存在局限性狭窄,其中最关键的是需明确颅内压升高的直接原因是否为局限性颅内静脉窦狭窄。通常颅内静脉窦远近端压力梯度 > 15 mm Hg(1 mm Hg = 0.133 kPa) 提示存在局限性狭窄,可考虑施行支架植入术^[25-26]。

4. 机械取栓术 系指采用机械性方法直接切割

或破碎血栓,再利用取栓装置快速完成静脉重建的手术方法。其主要适应证为,病程较长的主干颅内静脉窦血栓、已机化或严重钙化的血栓、有溶栓药物禁忌证或溶栓效果欠佳、颅内出血^[27]。对于此类患者,单纯溶栓治疗不仅无法使阻塞的颅内静脉窦再通,还有可能增加出血风险。机械取栓的方法包括圈套器和导丝切割、经导管血栓清除、球囊扩张和Solitaire支架取栓等^[28-30]。在临床上,通常采用机械取栓术与溶栓药物联合应用,通过切割血栓或直接取栓,增加溶栓药物与血栓的接触面积,从而增加溶栓效率和血管再通率。随着科学技术尤其是新型材料的不断研发,目前出现了越来越多的微导管和微支架,各种全新术式也应运而生,Tsang等^[31]的研究显示,重症颅内静脉窦血栓形成患者经静脉入路行抽吸取栓术+颅内静脉窦内局部溶栓,具有良好的疗效。因此,术者需充分评估患者的实际情况,根据现有的临床经验和技能,以及医疗条件选择最适宜的术式。

5. 开颅手术 既往的开颅手术主要指血栓切除术,但是由于手术创伤大、疗效有限,临床极少应用。目前的开颅手术则指通过手术降低颅内高压,以及对于因巨大血肿出现进行性或严重神经功能障碍而行手术以清除血栓,主要针对脑疝等危及患者生命的紧急情况,目的是挽救患者生命^[30]。欧洲神经科学协会联盟(EFNS)的颅内静脉窦血栓形成治疗指南建议,对于因急性脑水肿或脑出血致脑疝的颅内静脉窦血栓形成患者,应即刻行开颅血肿清除术+去骨瓣减压术,挽救患者生命,改善预后^[5]。去骨瓣减压术对重症颅内静脉窦血栓形成的疗效显著,这主要与颅内高压的发生机制有关,与动脉性梗死不同,静脉性梗死首先是静脉回流不畅,引起脑水肿和脑肿胀,继发脑血流量减少和颅内高压,但神经元功能仍保留,若此时及时通过去骨瓣减压术可有效地降低颅内压、解除静脉压迫、增加脑血流量、迅速恢复神经元功能,从而明显改善患者预后^[32-34]。

综上所述,颅内静脉窦血栓形成采用单一治疗方法难以在短时间内消除阻塞,术者应充分评估并根据患者具体情况选择个体化治疗方案。选择最佳治疗方法或联合治疗方法,才能够真正提高治疗效果、缩短治疗时间、减少并发症、挽救患者生命、改善预后。

利益冲突 无

参 考 文 献

- [1] Karsy M, Harmer JR, Guan J, Brock AA, Ravindra VM, Chung LS, Tkach A, Majersik JJ, Park MS, Schmidt RH, Jian . Outcomes in adults with cerebral venous sinus thrombosis: a retrospective cohort study[J]. J Clin Neurosci, 2018, 53:34-40.
- [2] Ferro JM, Canhão P, Stam J, Bousser MJ, Barinagarrementeria F, ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)[J]. Stroke, 2004, 35: 664-670.
- [3] Lurkin A, Derex L, Fambrini A, Bertolotti L, Epinat M, Mismetti P, Dargaud Y. Direct Oral Anticoagulants for the Treatment of Cerebral Venous Thrombosis[J]. Cerebrovasc Dis, 2019, 48:32-37.
- [4] Dmytriv AA, Song JSA, Yu E, Poon CS. Cerebral venous thrombosis: state of the art diagnosis and management [J]. Neuroradiology, 2018, 60:669-685.
- [5] Einhäupl K, Stam J, Bousser MG, Bruijn SFTMD, Ferro JM, Martinelli I, Masuhr F, European Federation of Neurological Societies. EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients[J]. Eur J Neurol, 2010, 17:1229-1235.
- [6] Behrouzi R, Punter M. Diagnosis and management of cerebral venous thrombosis[J]. Clin Med (Lond), 2018, 18:75-79.
- [7] Coutinho JM, Ferro JM, Canhão P, Barinagarrementeria F, Bousser MG, Stam J, ISCVT Investigators. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis[J]. Stroke, 2010, 41:2575-2580.
- [8] Xu WL, Gao LS, Li T, Shao AW, Zhang JM. Efficacy and risks of anticoagulation for cerebral venous thrombosis[J]. Medicine (Baltimore), 2018, 97:e10506.
- [9] Zuurbier SM, Coutinho JM. Cerebral Venous Thrombosis [J]. Adv Exp Med Biol, 2017, 906:183-193.
- [10] Rawahi BAL, Almegren M, Carrier M. The efficacy and safety of anticoagulation in cerebral vein thrombosis: a systematic review and meta-analysis[J]. Thromb Res, 2018, 169:135-139.
- [11] Medel R, Monteith SJ, Crowley RW, Dumont AS. A review of therapeutic strategies for the management of cerebral venous sinus thrombosis[J]. Neurosurg Focus, 2009, 27:E6.
- [12] Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentali F, Minno M, Maino A, Martinelli I, Masuhr F, Aguiar D de Sousa, Stam J, European Stroke Organization. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis-endorsed by the European Academy of Neurology[J]. Eur J Neurol, 2017, 24:1203-1213.
- [13] Rusin G, Wypasek E, Papuga-Szela E, Zuk J, Undas A. Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience [J]. Neurol Neurochir Pol, 2019, 53:384-387.
- [14] Viegas LD, Stolz E, Canhão P, Ferro JM. Systemic thrombolysis for cerebral venous and dural sinus thrombosis: a systematic review[J]. Cerebrovasc Dis, 2014, 37:43-50.
- [15] Masuhr F, Einhäupl K. Treatment of cerebral venous and sinus thrombosis[J]. Front Neurol Neurosci, 2008, 23:132-143.
- [16] Sader N, De Lotbinière - Bassett M, Tso MK, Hamilton M. Management of Venous Sinus Thrombosis[J]. Neurosurg Clin N Am, 2018, 29:585-594.
- [17] Habibabadi JM, Saadatnia M, Tabrizi N. Seizure in cerebral venous and sinus thrombosis[J]. Epilepsia Open, 2018, 3:316-322.
- [18] Roethlisberger M, Gut L, Zumofen DW, Fisch U, Boss O,

- Maldaner N, Croci DM, Taub E, Corti N, Burkhardt JK, Guzman R, Bozinov O, Mariani L. Cerebral venous thrombosis requiring invasive treatment for elevated intracranial pressure in women with combined hormonal contraceptive intake: risk factors, anatomical distribution, and clinical presentation [J]. *Neurosurg Focus*, 2018, 45:E12.
- [19] Andrade GC, Lesczynsky A, Climaco VM, Pereira ER, Marcelino PO, Franco A, Almeida DF. Cerebral venous sinuses thrombosis in both transverse sinus and torcula: Multistep endovascular treatment and stenting [J]. *Interv Neuroradiol*, 2017, 23:84-89.
- [20] Mokin M, Lopes DK, Binning MJ, Veznedaroglu E, Liebman KM, Arthur AS, Doss VT, Levy EI, Siddiqui AH. Endovascular treatment of cerebral venous thrombosis: Contemporary multicenter experience [J]. *Interv Neuroradiol*, 2015, 21:520-526.
- [21] Wasay M, Bakshi R, Kojan S, Bobustuc G, Dubey N, Unwin DH. Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis [J]. *Stroke*, 2001, 32:2310-2317.
- [22] Ziu E, Haley O, Ibrahim M, Langan S, Simon S. A Series of Cerebral Venous Sinus Thromboses Treated with Intra-Arterial tPA infused over Ten Hours with a 0.027-inch Catheter and Literature Review [J]. *Cureus*, 2016, 8:e654.
- [23] Li K, Ren M, Meng R, Ding Y, Rajah GB, Wang F, Ji XM. Efficacy of stenting in patients with cerebral venous sinus thrombosis - related cerebral venous sinus stenosis [J]. *J Neurointerv Surg*, 2019, 11:307-312.
- [24] Chen CW, Wang QJ, Li XF, Lu ZM, He J, Fang QR, Ke XC, Duan CZ, Li TL. Stent retriever thrombectomy combined with local thrombolytic therapy for cerebral venous sinus thrombosis: A case report [J]. *Exp Ther Med*, 2017, 14:3961-3970.
- [25] Drofa A, Kouznetsov E, Tomek S, Wiisanen M, Manchak M, Lindley T, Mitchell S, Hui F, Breker D. Successful Endovascular Management of Massive Pansinus Thrombosis: Case Report and Review of Literature [J]. *Pediatr Neurosurg*, 2016, 51:318-324.
- [26] Qiu ZM, Sang HF, Dai QL, Xu GL. Endovascular treatments for cerebral venous sinus thrombosis [J]. *J Thromb Thrombolysis*, 2015, 40:353-362.
- [27] Ilyas A, Chen CJ, Raper DM, Ding D, Buell T, Mastorakos P, Liu KC. Endovascular mechanical thrombectomy for cerebral venous sinus thrombosis: a systematic review [J]. *J Neurointerv Surg*, 2017, 9:1086-1092.
- [28] Styczen H, Tsogkas I, Liman J, Maus V, Psychogios MN. Endovascular Mechanical Thrombectomy for Cerebral Venous Sinus Thrombosis: A Single - Center Experience [J]. *World Neurosurg*, 2019, 127:e1097-e1103.
- [29] Siddiqui FM, Weber MW, Dandapat S, Scaife S, Buhnerkempe M, Ortega - Gutierrez S, Aksan N, Elias A, Coutinho JM. Endovascular Thrombolysis or Thrombectomy for Cerebral Venous Thrombosis: Study of Nationwide Inpatient Sample 2004-2014 [J]. *J Stroke Cerebrovasc Dis*, 2019, 28:1440-1447.
- [30] Lee SK, Mokin M, Hetts SW, Fifi JT, Boussier MC, Fraser JF, Society of NeuroInterventional Surgery. Current endovascular strategies for cerebral venous thrombosis: report of the SNIS Standards and Guidelines Committee [J]. *J Neurointerv Surg*, 2018, 10:803-810.
- [31] Tsang ACO, Hwang AC, Chiu RHY, Chan DYC, Tsang FCP, Ho WS, Lee R, Leung GKK, Lui WM. Combined aspiration thrombectomy and continuous intrasinus thrombolysis for cerebral venous sinus thrombosis: technical note and case series [J]. *Neuroradiology*, 2018, 60:1093-1096.
- [32] Lechanoine F, Janot K, Herbretau D, Maldonado IL, Velut S. Surgical Thrombectomy Combined with Bilateral Decompressive Craniectomy in a Life-Threatening Case of Coma from Cerebral Venous Sinus Thrombosis: Case Report and Literature Review [J]. *World Neurosurg*, 2018, 120:485-449.
- [33] Avnani R, Gopalakrishnan MS, Devi BI, Bhat DI, Shukla DP, Shanbhag NC. Role of Decompressive Craniectomy in the Management of Cerebral Venous Sinus Thrombosis [J]. *Front Neurol*, 2019, 10:511.
- [34] Westwick HJ, Obaid S, Bordeleau-Roy F, Truffer E, Weil AG. Surgical Superior Sagittal Sinus Thrombectomy in Refractory Thrombosis: A Technical Note [J]. *Pediatr Neurosurg*, 2019, 54: 212-217.

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