电子、语音版

·综述·

血栓弹力图与传统凝血四项在重型颅脑损伤预后相关性中的应用新进展

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摘 要：颅脑创伤是一种常见的损伤类型，而在重型颅脑损伤后出血机制和血栓形成平衡可以改变。止血功能受损可能会加重原发性损伤，并有引发或加重出血的风险。在许多创伤性脑损伤患者受伤入院时常规凝血试验都有异常，然而这些凝血异常对重型颅脑损伤预后的影响程度以及它们是否是可改变的危险因素尚不清楚。而对于凝血功能障碍的研究，国内外应用血栓弹力图来更精确地反映凝血功能障碍和颅脑损伤程度的关系。该文将凝血功能障碍与重型颅脑损伤的研究现状做一综述。

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关键词：重型颅脑损伤；血栓弹力图；凝血功能障碍

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New advances in the application of thromboelastography and traditional four coagulation parameters in the prognosis of severe traumatic brain injury

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Abstract: Traumatic brain injury is a common type of injury, and there are often changes in the mechanism of bleeding and the balance of thrombosis after severe traumatic brain injury. Impaired hemostasis may exacerbate primary injury and have the risk of inducing or aggravating bleeding. Many patients with traumatic brain injury are found to have abnormalities in conventional coagulation tests on admission, while further studies are needed to clarify the extent to which these coagulation abnormalities affect the prognosis of severe traumatic brain injury and whether they are modifiable risk factors. For the research on coagulation disorders, thromboelastography is used in China and globally to more accurately reflect the association between coagulation disorders and the severity of traumatic brain injury. This article reviews the current status of the research on coagulation disorders and severe traumatic brain injury.

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Keywords: severe traumatic brain injury; thromboelastography; coagulation disorders

创伤性脑损伤(traumatic brain injury, TBI)仍然是创伤死亡的主要原因之一，在2020年可能会超过其他疾病，成为死亡和残疾的主要原因[1-2]。有研究表明，全世界每年有超过5 000万例TBI，而我国每年受伤人数约为1 390万，占全世界患者数的18%[3]，因此，我们需要提高对TBI的本质和最佳治疗方法的认识。凝血障碍是影响TBI患者临床病程的常见原因，近三分之二的重型TBI患者在急诊入院时常规凝血试验出现异常[4-5]。关于不同程度TBI患者的凝血功能障碍的研究依旧是近年来的热点。同时也希望为重症TBI提供一些新的诊疗思路。

1 TBI患者的凝血障碍与预后相关

TBI后凝血障碍和出血增加的临床过程通常被认为

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是反映了从高凝状态到低凝状态的快速进展,即当促凝剂组织因子(tissue factor, TF)从受损的脑中释放出来,然后凝血因子被连续消耗,导致脑出血扩大时,凝血障碍就会发生。无论有无脑损伤,引发创伤后凝血功能障碍的病理生理机制包括血小板功能障碍、内源性抗凝、内皮激活、纤维蛋白原修饰、炎症和纤溶亢进都可导致出血增加[6-14],具有潜在的危险性。在很多时候,孤立性脑损伤患者早期和迟发性凝血障碍的发生率很高,这与不良预后密切相关[15]。TBI的凝血障碍与进行性出血性损伤(progressive hemorrhage injury,PHI)和颅内出血(intracranial hemorrhage, ICH)密切相关,大约33%的TBI患者和60%的重型TBI患者会出现凝血障碍。而大约一半的重型TBI和凝血障碍患者随后在48 h内表现出最初的脑挫伤和持续的ICH的出血进展[7,16]。

1.1　凝血障碍对TBI预后的影响

凝血障碍在重型TBI中较为常见,Greuters等[15]研究就发现相对较差的预后与出现急性凝血障碍或在创伤后24 h内出现凝血障碍有关。De Oliveira Manoel等[17]研究认为孤立性重型TBI不是发生凝血障碍的危险因素。但是,发生凝血障碍的重型TBI患者死亡率极高。而Yuan等[18]通过研究432急性TBI患者来证明,凝血障碍结果可以预测患者住院死亡率。凝血试验可以增加TBI后院内死亡率标准模型的预测能力。他们通过建模的形式,建立了2个模型,在模型A中,年龄、瞳孔反应性、格拉斯评分、硬脑膜外血肿(epidural hematoma, EDH)和血糖水平是影响住院死亡率的预后因素,而在模型B中,年龄、瞳孔反应性、格拉斯评分、EDH、血糖水平、凝血实验结果中活化部分凝血活酶时间(activated partial thromboplastin time, APTT)大于36 s、国际标准化比值(international normalized ratio, INR)大于1.25对预后有显著影响。

1.2　血小板功能障碍对TBI预后的影响

血小板—内皮相互作用和血小板功能障碍对微血管系统的损害和血脑屏障的破坏进一步触发了血小板与受干扰的内皮细胞或暴露的内皮下基质之间的相互作用,导致血小板黏附,直接或通过血小板配体,例如:vWF;血小板计数减低和血小板功能障碍似乎是导致凝血障碍的主要因素,这些情况增加了重症TBI后出血并发症的风险。例如,血小板计数低于175×10^9/L被证明增加了脑出血进展的风险,而低于100×10^9/L的血小板计数与增加9倍的风险有关[17]。关于实验性脑外伤小鼠血管内微血栓形成后周围血流量减少的报道支持这一假设[19]。血小板凝血障碍可能是TBI患者预后和总体预后的有力预测指标,Kaya等[20]认为孤立性钝性脑损伤后随即发生血小板功能障碍,他们通过研究,随着脑外伤严重程度的增加而更加明显,血小板功能障碍可能预示着住院死亡率的增加,尽管其机制尚不清楚。需要进一步深入研究。我们还要进一步的研究来确定这是疾病严重程度的标志还是治疗的靶点,例如输注血小板。Hess等[21]研究发现,在9种损伤严重程度中,血小板计数和住院死亡率之间存在线性关系。同样,Brown等[22]研究也是如此,结果显示,随着入院时血小板计数的增加,24 h内死亡的概率会降低。在Hamada等[23]研究中尽管血小板计数主要在正常范围内,但它与创伤严重程度和凝血障碍有关,并可预测出血强度和预后。在严重出血的患者中,早期输注6 h内的血小板与降低死亡率有关。需要进一步的研究来确定哪些剂量的血小板输注将改善严重创伤后的预后。

1.3　纤溶系统对TBI预后的影响

虽然已经提出了通过组织因子过度激活凝血以促进TBI后的纤溶亢进,但已经提出了另一种替代机制,例如从挫伤脑组织中局部释放内源性组织型纤溶酶原激活剂(tissue-type plasminogen activator, t-PA)和尿激酶型纤溶酶原激活剂(urokinase-type plasminogen activator, UPA)或耗尽α-2-纤溶酶抑制剂而增加纤溶酶[4]。纤溶酶是纤溶反应的主要效应物,是循环中的裂解产物。据报道,t-PA和UPA浓度在实验损伤的小鼠大脑中都会短暂升高,但时间分布不同。最近,纤溶关闭的作用被认为是另一种机制,使脑外伤患者可能容易处于高凝状态。Farrell等[24]研究纤维蛋白原与凝血障碍之间的相关性。认为纤维蛋白原水平与凝血动力学呈负相关,表现为INR缩短。Karri等[25]研究发现TPA与D—二聚体和PHI呈正相关,证明TBI后早期纤溶与出血进展相关,Fair等[26-27]证明进行性颅内出血可能激活了纤溶系统。指出凝血实验中的D—二聚体水平可能在临床环境中作为进行性颅内出血的预测指标。

2　血栓弹力图的应用与优势

血栓弹力图和其他凝血指标的测定可以反映体内凝血指标变化的情况,血栓弹力图中K是达到标准凝块硬度的时间(距基线20 mm),反映凝血动力学;K受纤维蛋白原激活、纤维蛋白积聚和交联的影响。MA是示踪的最宽部分,反映了凝血的强度;MA受血小板和纤维蛋白原的影响。LY30是达到最大幅度后30 min的凝块纤溶量不同的值可以代表不同的凝血系统因子变化。他们提供全血中凝块形成、强度和溶解的完整图像(包括血小板、纤维蛋白原和凝血因子的作用),为凝血疾病的研究和出血的目标控制增加价值[28-29]。Holcomb[30]做的一项研究中证明在控制年龄、损伤机制、创伤评分、碱基过剩和血红蛋白等的基础上,得出α角对大量红细胞输注的预测优于PT/aPTT或INR,α角预测血浆输注优于纤维蛋白原,在预测血小板输注方面,MA优于血小板计数测定,LY30可以更好地显示机体本身的纤溶。

2.1　血栓弹力图提供更早干预时机

血栓弹力图比起传统凝血四项来说,拥有更加及时

和更准确的结果,两者相辅相成,可以提供了更多的机会来纠正血液的凝血障碍,并最终改善患者的预后[31-32]。血栓弹力图有指导临床医师尽早干预的预测力。Gratz等[33]的一项研究旨在评估基于ROTEM的算法在TBI患者中的实施成功率,发现高达88%至91%的协议遵从率。然而,这项研究没有包括任何临床结果。而Rimaitis等[34]在一项前瞻性的研究中,入选了患者134例(对照组65例,病例组69例)。对照组26例(40%)为凝血功能障碍(对照组—亚组),病例组34例(49.3%)为凝血功能障碍(病例—亚组)。25例病例对照组患者存在Rotem异常,其中24例接受了治疗。总的基于Rotem的协议黏附率为85.3%。病例—亚组患者术后Rotem参数明显改善,凝血功能障碍患者减少。PHI(对照组与病例组)和神经外科再干预(对照-CP亚组与病例-CP亚组)的发生概率可以被Rotem指导(P<0.05)。

2.2　血栓弹力图直接测出血小板功能障碍

血小板功能障碍同样可以被血栓弹力图直接获得,给予临床干预治疗的准确时机。在TBI患者中,TEG-PM®AA的抑制高于健康对照组。TBI与非TBI患者相比,TEG-PM®AA抑制作用也更强[35]。而单纯性TBI患者的TEG-PM®ADP抑制也高于对照组。重症TBI患者的血小板功能障碍也明显高于轻至中度TBI患者。几项研究表明,TBI患者在发病时更容易出现高凝状态,这可能是由于血小板聚集增加所致。TEG结果表明TBI患者的血小板聚集与ICU住院时间延长、总住院时间延长和死亡率增加相关[35-36]。

2.3　血栓弹力图引导下的输血治疗

Webb认为纤维蛋白的消耗可能和进行性出血有关系。他研究141名重型TBI患者,其中64例患者在发病后24 h内发生PHI。使用较新的检测手段血栓弹力图,评估血栓弹力图在TBI中的作用,其中因为K时间(P=0.035)和α角(P=0.015)有差异,得出在重型TBI患者中,K时间延长和α角变窄与进行性出血损伤有关,但是这个研究结果只是针对原发性TBI,而非继发性TBI[37]。Sugiyama等[38-39]研究中发现在早期使用血液冷沉淀物可减少合并重型TBI的多发伤患者的凝血功能障碍。是否TBI后出现纤维蛋白原的病理性活性低下,有必要进一步研究来确定,可以使用血栓弹力图来评估冷沉淀物在这一患者群体中的应用。在使用TEG引导的治疗中可以使医生能够快速提供有针对性的治疗,准确纠正凝血障碍,同时更好的地利用保存血液产品。尽管如此,关于应用TEG是否与改善患者结局和降低死亡率相关,仍存在不同和相互矛盾的结果[40-42]。其中几项研究表明,与TBI后输血治疗中(PT、aPTT、纤维蛋白原和D-二聚体)相比,使用TEG的复苏策略可提高存活率[43]。院前使用医用血浆(PAMPER)试验中的一项分析支持了这一结论,发现在TEG的指导下使用院前血浆的TBI患者亚组患者的存活率增加[44-45]。使用有针对性的管理方法可以减少脑部炎症、脑内出血和脑缺血,从而潜在地有助于改善TBI后的预后[41]。

综上,TBI后发生凝血功能障碍的机制复杂,并且没有统一的诊断标准,但其出现往往导致进展性颅内出血的发生,由此导致不可逆的继发性脑损伤,严重影响患者的预后[46]。尤其在重型TBI的临床治疗中,止血和出血进展的改变是实质性的和持续的挑战。关于重型TBI中止血紊乱的模式和定向止血复苏策略的作用的数据缺乏,这可能不同于一般创伤所需的止血复苏策略。有必要进行研究,阐明重型TBI后止血异常的各种表型和机制,包括它们的临床表现,以及如何用诊断设备快速识别它们。以及对于血栓弹力图的应用需要大量的临床研究来奠定基础。尤其是关于血小板功能障碍和内皮功能异常研究较少。

参　考　文　献

[1] HYDER AA, WUNDERLICH CA, PUVANACHANDRA P, et al. The impact of traumatic brain injuries: a global perspective [J]. NeuroRehabilitation, 2007, 22(5): 341-353.

[2] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the global burden of disease study 2015[J]. Lancet, 2016, 388(10053): 1545-1602.

[3] JIANG JY, GAO GY, FENG JF, et al. Traumatic brain injury in China[J]. Lancet Neurol, 2019, 18(3): 286-295.

[4] MAEGELE M, SCHÖCHL H, MENOVSKY T, et al. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management[J]. Lancet Neurol, 2017, 16(8): 630-647.

[5] HOYT DB. A clinical review of bleeding dilemmas in trauma[J]. Semin Hematol, 2004, 41(1 Suppl 1): 40-43.

[6] CHANG R, CARDENAS JC, WADE CE, et al. Advances in the understanding of trauma-induced coagulopathy[J]. Blood, 2016, 128(8): 1043-1049.

[7] YUAN Q, SUN YR, WU X, et al. Coagulopathy in traumatic brain injury and its correlation with progressive hemorrhagic injury: a systematic review and meta-analysis[J]. J Neurotrauma, 2016, 33(14): 1279-1291.

[8] MAEGELE M. The coagulopathy of trauma[J]. Eur J Trauma Emerg Surg, 2014, 40(2): 113-126.

[9] MAEGELE M, SCHÖCHL H, COHEN MJ. An update on the coagulopathy of trauma[J]. Shock, 2014, 41(Suppl 1): 21-25.

[10] CASTELLINO FJ, CHAPMAN MP, DONAHUE DL, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats[J]. J Trauma Acute Care Surg, 2014,

76(5): 1169-1176.

[11] MASSARO AM, DOERFLER S, NAWALINSKI K, et al. Thromboelastography defines late hypercoagulability after TBI: a pilot study[J]. Neurocrit Care, 2015, 22(1): 45-51.

[12] DI BATTISTA AP, RIZOLI SB, LEJNIEKS B, et al. Sympathoadrenal activation is associated with acute traumatic coagulopathy and endotheliopathy in isolated brain injury[J]. Shock, 2016, 46(3 Suppl 1): 96-103.

[13] CARDENAS JC, WADE CE, HOLCOMB JB. Mechanisms of trauma-induced coagulopathy[J]. Curr Opin Hematol, 2014, 21(5): 404-409.

[14] ATEFI G, AISIKU O, SHAPIRO N, et al. Complement activation in trauma patients alters platelet function[J]. Shock, 2016, 46(3 Suppl 1): 83-88.

[15] GREUTERS S, VAN DEN BERG A, FRANSCHMAN G, et al. Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury[J]. Crit Care, 2011, 15(1): R2.

[16] ZHANG DF, GONG S, JIN H, et al. Coagulation parameters and risk of progressive hemorrhagic injury after traumatic brain injury: a systematic review and meta-analysis[J]. Biomed Res Int, 2015, 2015: 261825.

[17] DE OLIVEIRA MANOEL AL, NETO AC, VEIGAS PV, et al. Traumatic brain injury associated coagulopathy[J]. Neurocrit Care, 2015, 22(1): 34-44.

[18] YUAN Q, YU J, WU X, et al. Prognostic value of coagulation tests for in-hospital mortality in patients with traumatic brain injury[J]. Scand J Trauma Resusc Emerg Med, 2018, 26(1): 3.

[19] ABDELMALIK PA, BOORMAN DW, TRACY J, et al. Acute traumatic coagulopathy accompanying isolated traumatic brain injury is associated with worse long-term functional and cognitive outcomes[J]. Neurocrit Care, 2016, 24(3): 361-370.

[20] KAY AB, MORRIS DS, COLLINGRIDGE DS, et al. Platelet dysfunction on thromboelastogram is associated with severity of blunt traumatic brain injury[J]. Am J Surg, 2019, 218(6): 1134-1137.

[21] HESS JR, LINDELL AL, STANSBURY LG, et al. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center[J]. Transfusion, 2009, 49(1): 34-39.

[22] BROWN LM, CALL MS, MARGARET KNUDSON M, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients[J]. J Trauma, 2011, 71(2 Suppl 3): S337-S342.

[23] HAMADA SR, GARRIGUE D, NOUGUE H, et al. Impact of platelet transfusion on outcomes in trauma patients[J]. Crit Care, 2022, 26(1): 49.

[24] FARRELL DH, RICK EA, DEWEY EN, et al. γ′ fibrinogen levels are associated with blood clot strength in traumatic brain injury patients[J]. Am J Surg, 2020, 220(2): 459-463.

[25] KARRI J, CARDENAS JC, MATIJEVIC N, et al. Early fibrinolysis associated with hemorrhagic progression following traumatic brain injury[J]. Shock, 2017, 48(6): 644-650.

[26] FAIR KA, FARRELL DH, MCCULLY BH, et al. Fibrinolytic activation in patients with progressive intracranial hemorrhage after traumatic brain injury[J]. J Neurotrauma, 2021, 38(8): 960-966.

[27] ZHANG J, HE M, SONG YL, et al. Prognostic role of D-dimer level upon admission in patients with traumatic brain injury[J]. Medicine (Baltimore), 2018, 97(31): e11774.

[28] LIRAS IN, CAPLAN HW, STENSBALLE J, et al. Prevalence and impact of admission acute traumatic coagulopathy on treatment intensity, resource use, and mortality: an evaluation of 956 severely injured children and adolescents[J]. J Am Coll Surg, 2017, 224(4): 625-632.

[29] LEEPER CM, NEAL MD, MCKENNA C, et al. Abnormalities in fibrinolysis at the time of admission are associated with deep vein thrombosis, mortality, and disability in a pediatric trauma population[J]. J Trauma Acute Care Surg, 2017, 82(1): 27-34.

[30] HOLCOMB JB, MINEI KM, SCERBO ML, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients[J]. Ann Surg, 2012, 256(3): 476-486.

[31] SPAHN DR, BOUILLON B, CERNY V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition[J]. Crit Care, 2019, 23(1): 98.

[32] MOORE HB, MOORE EE, NEAL MD. Trauma induced coagulopathy[M]. 2nd ed. Cham: Springer, 2021.

[33] GRATZ J, GÜTING H, THORN S, et al. Protocolised thromboelastometric-guided haemostatic management in patients with traumatic brain injury: a pilot study[J]. Anaesthesia, 2019, 74(7): 883-890.

[34] RIMAITIS M, BILSKIENĖ D, TAMOŠUITIS T, et al. Implementation of thromboelastometry for coagulation management in isolated traumatic brain injury patients undergoing craniotomy[J]. Med Sci Monit, 2020, 26: e922879.

[35] GUILLOTTE AR, HERBERT JP, MADSEN R, et al. Effects of platelet dysfunction and platelet transfusion on outcomes in traumatic brain injury patients[J]. Brain Inj, 2018, 32(13-14): 1849-1857.

[36] BARTELS AN, JOHNSON C, LEWIS J, et al. Platelet adenosine diphosphate inhibition in trauma patients by thromboelastography correlates with paradoxical increase in platelet dense granule content by flow cytometry[J]. Surgery, 2016, 160(4): 954-959.

[37] WEBB AJ, BROWN CS, NAYLOR RM, et al. Thromboelastography is a marker for clinically significant progressive hemorrhagic injury in severe traumatic brain injury[J]. Neurocrit Care, 2021, 35(3): 738-746.

[38] SHIBAHASHI K, NISHIMURA S, SUGIYAMA K, et al. Initial results of empirical cryoprecipitate transfusion in the treatment of isolated severe traumatic brain injury: use of in-house-produced cryoprecipitate[J]. Neurol Med Chir (Tokyo), 2019, 59

(10): 371-378.

[39] SUGIYAMA K, FUJITA H, NISHIMURA S. Effects of in-house cryoprecipitate on transfusion usage and mortality in patients with multiple trauma with severe traumatic brain injury: a retrospective cohort study[J]. Blood Transfus, 2020, 18(1): 6-12.

[40] DRAGAN B, ADAMIK B, BURZYNSKA M, et al. Platelet receptor activity for predicting survival in patients with intracranial bleeding[J]. J Clin Med, 2021, 10(10): 2205.

[41] FLETCHER-SANDERSJÖÖ A, THELIN EP, MAEGELE M, et al. Time course of hemostatic disruptions after traumatic brain injury: a systematic review of the literature[J]. Neurocrit Care, 2021, 34(2): 635-656.

[42] OLOGUN GO, PAMULA A, ALEGBEJO-OLARINOYE M, et al. Rethinking the use of routine platelet transfusions for head injured patients on antiplatelet therapy[J]. Cureus, 2019, 11(11): e6136.

[43] FOLKERSON LE, SLOAN D, DAVIS E, et al. Coagulopathy as a predictor of mortality after penetrating traumatic brain injury [J]. Am J Emerg Med, 2018, 36(1): 38-42.

[44] GRUEN DS, GUYETTE FX, BROWN JB, et al. Association of prehospital plasma with survival in patients with traumatic brain injury: a secondary analysis of the PAMPer cluster randomized clinical trial[J]. JAMA Netw Open, 2020, 3(10): e2016869.

[45] SPERRY JL, GUYETTE FX, BROWN JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock[J]. N Engl J Med, 2018, 379(4): 315-326.

[46] 陈益磊, 刘劲芳. 颅脑创伤后凝血功能障碍的研究进展[J]. 国际神经病学神经外科学杂志, 2020, 47(2): 208-212.

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