·专家指南·

心血管外科手术围术期血液管理—抗纤溶治疗指南(2016 版)

中国心胸血管麻醉学会

心血管手术中如何减少术中出血是实施血液保护最重要的环节之一。如能明显减少术中出血,不仅可减少血制品的输入量,而且有利于患者术后康复。大量临床研究和实践已经充分证实,心血管手术死亡率及严重不良事件的发生率与输注异体血制品直接相关[1,2]。

近年来,我国心血管外科手术数量快速增长、手术的复杂程度不断增大,血液来源愈发紧张,心血管外科血制品输入的形势严峻。因此,规范抗纤溶治疗,尽可能地减少术中出血和血制品的输入具有重要的临床意义和社会意义。

血液保护

血液保护是一种以患者为中心、多模式共存、多科室协作的医疗模式,通过整合现有技术和方法,减少患者围术期出血、减少或避免输入异体血制品,从而达到合理用血和节约用血、改善患者预后的目的[3]。

风险评估 术前评估患者的出血和输血风险是血液保护的重要部分。下列三项为出血和血制品输入独立危险因素:

(1) 高龄(≥70 岁);

(2) 术前红细胞减少(包括低体重和/或术前贫血);

(3) 急诊或复杂手术(二次手术、主动脉手术,尤其是预计体外循环时间长的手术)。

术前准备 心血管手术前应努力纠正术前贫血和出凝血功能异常[4~7]。除急诊手术外,术前停用抗血栓和抗血小板药可显著减少围术期出血和输血。这些药包括 ADP 受体抑制剂、凝血酶直接抑制剂、低分子肝素、血小板膜糖蛋白抑制剂、组织型纤溶酶原激活物、链激酶等,具体停药时机取决于每种药物的半衰期[8~12]。噻吩吡啶类抗血小板药停药时间为 5~7 d[13],可逆性血小板 P2Y12 受体抑制剂停药时间可缩短至 3 d[3]。必要时考虑血栓弹力图等血小板功能检查[14]。

血制品输注标准

1. 浓缩红细胞输注标准

(1) 体外循环中 Hb<7 g/dl;

(2) 虽然体外循环中 Hb<7 g/dl,但预计经过超滤,停机时 Hb 可能>8 g/dl,则体外循环中不输入红细胞;

(3) 输入机器余血和洗涤红细胞后,Hb 仍然<8 g/dl,高龄、大血管手术 Hb<9 g/dl;

(4) 非体外循环手术,术中 Hb<8 g/dl,高龄、大血管手术 Hb<9 g/dl;

(5) Hb 虽已达到上述标准,但混合静脉血氧饱和度低于正常,排除其它因素(氧耗增加、心排血量低、组织灌注不足等)后可输入一定量的红细胞。

2. 新鲜冰冻血浆

(1) PT>1.5 倍正常值(INR>1.6),APTT>2 倍正常值,伴手术创面弥漫渗血;

(2) 大量输入库血(出血量或输血量相当于自身血容量,约 70 ml/kg);

(3) 血液回收成品血量>2 000 ml;

(4) 先天性或获得性凝血功能障碍;

(5) 血栓弹力图检查明确提示凝血因子缺乏;

(6) 紧急逆转华法林的抗凝血作用;

(7) 抗凝血酶 III 缺乏引起的肝素耐药。

3. 血小板

(1) 血小板计数<50×10^9/L;

(2) 二次手术、主动脉手术、心脏移植、体外循环时间长(>6 h)及大量输入库血;

(3) 血栓弹力图检查明确提示血小板功能低下。

抗纤溶治疗

大量研究数据和临床实践证实,赖氨酸类似物(氨甲环酸和氨基己酸)可以有效减少心血管手术围术期出血量和异体血制品输血量,并且具有很高的安全性,是目前心血管手术中抗纤溶治疗的最主要的方法[15]。由于同等剂量下,氨甲环酸抗纤溶的效价是氨甲苯酸等抗纤溶药物的 6 倍或 6 倍以上,且安全性高于其它抗纤溶药物,故临床抗纤溶治疗中以氨甲环酸最为常用。

氨甲环酸用于心血管手术围术期血液保护已有很长的历史[16~18]。氨甲环酸作为赖氨酸类似物,可以竞争性占据纤溶酶原上的赖氨酸结合位点、阻断纤溶酶原与纤维蛋白上的赖氨酸结合,减少纤维蛋白降解产物的生成,最终达到抑制纤溶活性、减少出血的作用。

大量研究均已证实氨甲环酸能有效减少心脏外科手术围术期的失血量并降低输血率,且不增加术后深静脉血栓栓塞症的发生风险和死亡率[3,16,19,20]。

有关氨甲环酸有效性和剂量的研究 Henry 等[15]和 Ngaage 等[21]报道,氨甲环酸可减少输血的相对风险 32%~47%,减少输血 298~300 ml,而且与安慰剂比较,氨甲环酸可减少由于出血导致的二次开胸止血[16,21]。

在氨甲环酸的给药剂量方面,早年人们多采用 Horrow 等[22]提出的经典方案,即负荷量 10 mg/kg + 维持量 1 mg·kg^{-1}·h^{-1}。2008 年 5 月 14 日发表的 BART 研

究[18]采用了较高的给药剂量，即负荷量 30 mg/kg＋预充量 2 mg/kg＋维持量 16 mg·kg^{-1}·h^{-1}。目前国外临床中心大多采用与 BART 研究中相似的氨甲环酸剂量。最近有研究者比较了两种氨甲环酸剂量方案的差异，发现高剂量可以进一步减少心血管手术的输血量、失血量和二次开胸止血率[23]。亚组分析提示，氨甲环酸对于术前服用双抗血小板药的高危患者具有更加显著的止血效果。有证据证实，氨甲环酸可部分改善花生四烯酸诱导的(阿司匹林)和 ADP 诱导的(氯吡格雷)血小板聚集功能缺陷[24～26]。同时，氨甲环酸可以减轻纤溶酶诱导的血小板抑制[27]。

对于小儿心血管手术，氨甲环酸的效果与成人相似。在一项包括超过2 000例小儿心血管手术的荟萃分析中，氨甲环酸可减少出血 11 ml/kg，减少红细胞输注 4 ml/kg，氨甲环酸与抑肽酶的作用相当[28]。与之相似，一项回顾性研究[29]包括 231 例儿童心血管手术患者，发现在术中和术后 48 h 内氨甲环酸可显著减少出血量、输血量，降低输血率。以上两项研究都没有发现在紫绀组和非紫绀组间有任何差异。虽然最近有 2 篇儿童中氨甲环酸药代动力学的报道[30,31]，但是氨甲环酸在儿童心脏外科手术中理想的剂量仍然未知[32]。在离体试验中，抑制纤溶亢进所需要氨甲环酸的剂量在新生儿中比在成人中低很多(6.5 μg/ml 和 17 μg/ml)[31]，这对临床用药剂量有一定的提示作用。

氨甲环酸的不良反应

1. 血栓性事件和对重要脏器功能的影响

目前已经有充分的证据显示，氨甲环酸并不增加心血管手术围术期血栓性事件(包括心肌梗死、脑卒中、深静脉血栓和肺栓塞等)的发生率[18,21,33～35]。氨甲环酸对肾脏、肝脏等重要脏器功能未见明显影响[18,36～38]。

2. 围术期癫痫

研究指出，使用大剂量的氨甲环酸可以增加术后癫痫的发生率[39,40]，但是并无长期后遗症，也不会导致脑结构性改变。氨甲环酸导致癫痫发作的可能机制与甘氨酸或 GABA 受体抑制有关[41～43]。

最近，人们已经将氨甲环酸列为心血管手术围术期癫痫的危险因素[44]。使用高剂量的氨甲环酸可以增加癫痫的发生率[44,45]。在对超过11 000病例的多因素分析中，Sharma 等[46]发现氨甲环酸可能是术后癫痫的独立危险因素。但目前氨甲环酸可增加术后癫痫的发生率国内尚未见报道。

3. 其他不良反应

氨甲环酸其他的不良反应包括胃肠道反应、皮肤过敏、视觉变化等[47]，但在手术中难以见到。

氨甲环酸的临床应用

1. 在成人心血管手术中的应用

氨甲环酸的给药方式和剂量在不同文献报道和不同临床中心之间的差异很大[22,23,48,49]。综合相关文献、临床研究和临床经验，推荐负荷量加维持量的给药方式。负荷量在麻醉诱导后、外科切皮前不少于 20 min 泵注，随后维持量在手术过程中持续泵注。以个体化医疗的原则，根据患者的出血风险评估，采用如下剂量：

(1)大剂量：出血高风险，负荷量 30 mg/kg，维持量 20 mg·kg^{-1}·h^{-1}；

(2)中剂量：出血中风险，负荷量 20 mg/kg，维持量 15 mg·kg^{-1}·h^{-1}；

(3)小剂量：出血低风险，负荷量 10 mg/kg，维持量 10 mg·kg^{-1}·h^{-1}。

在全部外科手术过程中，氨甲环酸的总量应该控制如下：

(1) 非体外循环手术，氨甲环酸总量 20～30 mg/kg；

(2) 一般体外循环手术，氨甲环酸总量 80～100 mg/kg；

(3) 二次手术、大血管手术和心脏移植手术，氨甲环酸总量 100～150 mg/kg。

2. 在小儿心血管手术中的应用

虽然在离体试验中，新生儿抑制纤溶亢进所需要氨甲环酸的剂量仅为成年人的 1/3～1/2[29]，但是仍然缺乏小儿心血管手术中氨甲环酸理想剂量的循证医学证据[50]。在临床实践中，需要根据患儿出血风险、拟施手术类型、临床中心的实践经验等合理制定氨甲环酸的使用剂量。

药品选择

遵照我国相关的法律、法规和临床诊疗规范，心血管外科手术围术期的抗纤溶治疗药品应选用说明书中具有明确心脏手术适应症的氨甲环酸制剂，并参照说明书中推荐剂量使用。

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参 考 文 献

[1] Karkouti K, Wijeysundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion, 2004, 44(10): 1453-1462.

[2] Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion,

2006,46(3):327-338.

[3] Society of Thoracic Surgeous Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg, 2011, 91(3):944-982.

[4] Monk TG. Preoperative recombinant human erythropoietin in anemic surgical patients. Crit Care, 2004, 8 Suppl 2: S45-S48.

[5] Madi-Jebara SN, Sleilaty GS, Achouh PE, et al. Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth, 2004, 18(1):59-63.

[6] Price S, Pepper JR, Jaggar SI. Recombinant human erythropoietin use in a critically ill Jehovah's Witness after cardiac surgery. Anesth Analg, 2005,101(2):325-327.

[7] Weltert L, D'Alessandro S, Nardella S, et al. Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: a randomized blind controlled study. J Thorac Cardiovasc Surg, 2010, 139(3):621-627.

[8] Berger JS, Frye CB, Harshaw Q, et al. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. J Am Coll Cardiol, 2008, 52(21):1693-1701.

[9] Mahla E, Metzler H, Tantry US, et al. Controversies in oral antiplatelet therapy in patients undergoing aortocoronary bypass surgery. Ann Thorac Surg, 2010,90(3):1040-1051.

[10] Vaccarino GN, Thierer J, Albertal M, et al. Impact of preoperative clopidogrel in off pump coronary artery bypass surgery: a propensity score analysis. J Thorac Cardiovasc Surg, 2009,137(2):309-313.

[11] Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery. The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol, 2009, 53(21):1965-1972.

[12] Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet, 2009, 373(9665):723-731.

[13] Society of Thoracic Surgeous Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg, 2007,83(5 Suppl):S27-S86.

[14] Rahe-Meyer N, Solomon C, Winterhalter M, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg, 2009, 138(3):694-702.

[15] Henry D, Carless P, Fergusson D, et al. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. CMAJ, 2009,180(2):183-193.

[16] Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev, 2011(3): CD001886.

[17] Ortmann E, Besser MW, Klein AA. Antifibrinolytic agents in current anaesthetic practice. Br J Anaesth, 2013,111(4): 549-563.

[18] Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Eng J Med, 2008,358(22):2319-2331.

[19] Mazer CD. Blood conservation in cardiac surgery: guidelines and controversies. Transfus Apher Sci, 2014, 50(1):20-25.

[20] Ng W, Jerath A, Wasowicz M. Tranexamic acid: a clinical review. Anaesthesiol Intensive Ther, 2015,47(4):339-350.

[21] Ngaage DL, Bland JM. Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies. Eur J Cardiothorac Surg, 2010,37(6):1375-1383.

[22] Horrow JC, Van Riper DF, Strong MD, et al. The dose-response relationship of tranexamic acid. Anesthesiology, 1995, 82(2):383-392.

[23] Sigaut S, Tremey B, Ouattara A, et al. Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology, 2014, 120 (3):590-600.

[24] Weber CF, Görlinger K, Byhahn C, et al. Tranexamic acid partially improves platelet function in patients treated with dual antiplatelet therapy. Eur J Anaesthesiol, 2011, 28(1): 57-62.

[25] Shi J, Wang G, Lv H, et al. Tranexamic acid in on-pump coronary artery bypass grafting without clopidogrel and aspirin cessation: randomized trial and 1-year follow-up. Ann Thorac Surg, 2013, 95(3):795-802.

[26] Shi J, Ji H, Ren F, et al. Protective effects of tranexamic acid on clopidogrel before coronary artery bypass grafting: a multicenter randomized trial. JAMA Surg, 2013, 148(6): 538-547.

[27] de Haan J, van Oeveren W. Platelets and soluble fibrin promote plasminogen activation causing downregulation of platelet glycoprotein Ib/IX complexes: protection by aprotinin. Thromb Res, 1998, 92(4):171-179.

[28] Shimizu K, Toda Y, Iwasaki T, et al. Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial. J Anesth, 2011,25(6):823-830.

[29] Giordano R, Palma G, Poli V, et al. Tranexamic acid therapy in pediatric cardiac surgery: a single-center study. Ann Thorac Surg, 2012,94(4):1302-1306.

[30] Goobie SM, Meier PM, Sethna NF, et al. Population phar-

macokinetics of tranexamic acid in paediatric patients undergoing craniosynostosis surgery. Clin Pharmacokinet, 2013, 52(4):267-276.

[31] Yee BE, Wissler RN, Zanghi CN, et al. The effective concentration of tranexamic acid for inhibition of fibrinolysis in neonatal plasma in vitro. Anesth Analg, 2013, 117(4): 767-772.

[32] Faraoni D, Goobie SM. The efficacy of antifibrinolytic drugs in children undergoing noncardiac surgery: a systematic review of the literature. Anesth Analg, 2014, 118(3): 628-636.

[33] Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ, 2012, 344: e3054.

[34] Perel P, Ker K, Morales Uribe CH, et al. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database Syst Rev, 2013(1): CD010245.

[35] Adler Ma SC, Brindle W, Burton G, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: s systematic review and meta-analysis. J Cardiothorac Vasc Anesth, 2011,25(1):26-35.

[36] Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. N Eng J Med, 2006,354(4): 353-365.

[37] Mangano DT, Miao Y, Vuylsteke A, et al. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. JAMA, 2007,297(5):471-479.

[38] Schneeweiss S, Seeger JD, Landon J, et al. Aprotinin during coronary-artery bypass grafting and risk of death. N Eng J Med, 2008,358(8):771-783.

[39] Martin K, Wiesner G, Breuer T, et al. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. Anesth Analg, 2008, 107(6):1783-1790.

[40] Murkin JM, Falter F, Granton J, et al. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg, 2010, 110(2): 350-353.

[41] Lecker I, Wang DS, Romaschin AD, et al. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. J Clin Invest, 2012,122(12):4654-4666.

[42] Martin K, Breuer T, Gertler R, et al. Tranexamic acid versus ε-aminocaproic acid: efficacy and safety in paediatric cardiac surgery. Eur J Cardiothorac Surg, 2011, 39(6): 892-897.

[43] Lecker I, Orser BA, Mazer CD. "Seizing" the opportunity to understand antifibrinolytic drugs. Can J Anesth, 2012, 59(1):1-5.

[44] Kaabachi O, Eddhif M, Rais K, et al. Inadvertent intrathecal injection of tranexamic acid. Saudi J Anaesth, 2011, 5(1):90-92.

[45] Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. Can J Anesth, 2012,59(1):6-13.

[46] Sharma V, Katznelson R, Jerath A, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia, 2014,69(2):124-130.

[47] McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs, 2012,72(5):585-617.

[48] Armillin G, Vinciguerra A, Bonato R, et al. Tranexamic acid in primary CABG surgery: high vs low dose. Minerva Anestesiol, 2004,70(3):97-107.

[49] Jiménez JJ, Iribarren JL, Brouard M, et al. Safety and effectiveness of two treatment regimes with tranexamic acid to minimize inflammatory response in elective cardiopulmonary bypass patients: a randomized double-blind, dose-dependent, phase IV clinical trial. J Cardiothorac Surg, 2011, 6: 138.

[50] Faraoni D, Goobie SM. New insights about the use of tranexamic acid in children undergoing cardiac surgery: from pharmacokinetics to pharmacodynamics. Anesth Analg, 2013,117(4):760-762.

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