

doi: 10.13241/j.cnki.pmb.2018.17.025

大剂量氨甲环酸对全膝关节置换患者术后纤溶活性与炎症因子的影响 *

彭 强¹ 王 宏¹ 李宣明¹ 何 江¹ 张 健²

(1 雅安市中医医院骨科 四川 雅安 625000; 2 重庆医科大学附属第一医院 重庆 400010)

摘要 目的:探讨大剂量氨甲环酸对全膝关节置换患者术后纤溶活性与炎症因子的影响。**方法:**回顾性分析在我院行初次全膝关节置换术的 180 例患者,按照给药方式分为对照组、常规组、大剂量组,每组各 60 例。对照组患者直接给予生理盐水,常规组给予 10 mg/kg 氨甲环酸,大剂量组给予 15 mg/kg 氨甲环酸。比较三组术后总失血量、隐形失血量、术前与术后 3 天三组凝血功能(纤维蛋白原、凝血酶原时间、活化部分凝血活酶时间)、纤溶活性[纤维蛋白(原)降解产物(FDP)、D-二聚体]以及炎症因子[C-反应蛋白(CRP)、白介素-6(IL-6)]水平变化及术后 2 周血栓事件的发生情况。**结果:**大剂量组与常规组的总失血量与隐形失血量均明显低于对照组,大剂量组总失血量与隐形失血量均低于常规组($P<0.05$);三组患者纤维蛋白原、凝血酶原时间以及活化部分凝血活酶时间相比差异均无统计学意义($P>0.05$);术后 3 天,大剂量组和常规组 FDP 与 D-二聚体、CRP、IL-6 水平均显著低于对照组,且与常规组相比,大剂量组水平较低($P<0.05$);术后 2 周,三组肌间静脉血栓发生率比较均无显著差异($P>0.05$)。**结论:**在全膝关节置换术后使用氨甲环酸可进一步减少术后隐形失血量,且不会增加血栓事件的风险,且随着药物剂量的增加,其止血效果越强,同时具有更为显著的抗纤溶作用与抗炎效果。

关键词:氨甲环酸;全膝关节置换术;纤溶活性;炎症因子

中图分类号:R684.3 **文献标识码:**A **文章编号:**1673-6273(2018)17-3319-04

Effects of High Doses of Tranexamic Acid on the Fibrinolytic Activity and Inflammatory Response of Patients undergoing Total Knee Arthroplasty*

PENG Qiang¹, WANG Hong¹, LI Xuan-ming¹, HE Jiang¹, ZHANG Jian²

(1 Department of orthopedics, Ya'an Hospital of Traditional Chinese Medicine, Ya'an, Sichuan, 625000, China;

2 First Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China)

ABSTRACT Objective: To study the effect of high doses of tranexamic acid on the fibrinolytic activity and inflammatory response of patients undergoing total knee arthroplasty. **Methods:** 180 cases of patients with total knee in our hospital were retrospectively analyzed, they were divided into the control group, regular group and large dosage group with 60 cases in each group according to the drug administration. The control group was treated with normal saline, conventional group was treated with and aminoacyclic acid, 10 mg/kg, large dose group was treated with aminoacyclic acid, 15 mg/kg. The total blood loss, hidden blood loss, changes of blood coagulation function (fibrinogen, prothrombin time, activated partial blood coagulation time live enzymes), fibrinolytic activity [fibrin degradation products (FDP) (original), D - dimer] and inflammatory factor [C - reactive protein (CRP) and interleukin 6 (IL - 6)] level preoperation and postoperation and incidence of thromboembolism events at 2 weeks after testing were compared among three groups. **Results:** The total blood loss and hidden blood loss of high-dose group and regular group were significantly lower than those of the control group, they were lower in the high-dose group than those of the regular group ($P<0.05$). There was no statistically significant difference in the fibrinogen, the prothrombin time and the activated partial thrombin time between three groups ($P>0.05$). At 3 days after operation, the FDP and D-dimer, CRP, IL - 6 levels of high-dose group and regular group were significantly lower than those of the control group, they were lower in the high-dose group than those of the regular group ($P<0.05$); At two weeks after surgery, there was no significant difference in the incidence of intramuscular venous thrombosis between three groups ($P>0.05$). **Conclusion:** Using tranexamic acid after total knee arthroplast could further reduce the invisible blood loss, postoperative and do not increase the risk of thrombotic events, and with the increase of drug dose, the hemostatic effect is stronger, at the same time has more significant fibrinolytic function and anti-inflammatory effects.

Key words: Tranexamic acid; Total knee arthroplasty; Fibrinolytic activity; Inflammatory cytokines

Chinese Library Classification(CLC): R684.3 **Document code:** A

Article ID: 1673-6273(2018)17-3319-04

前言

骨性关节炎为临床常见疾病,其病变部位包括软骨和骨

* 基金项目:四川省卫生计生委科研项目(120308)

作者简介:彭强(1979-),男,大学本科,主治医师,研究方向:髌(膝)关节置换方面,电话:18328550235, E-mail:luoxia8509@163.com

(收稿日期:2018-04-15 接受日期:2018-05-10)

质,严重影响患者的膝关节功能,给患者日常生活带来不便。全膝关节置换术是目前临床治疗骨科疾病的首选方案,其疗效已得到临床证实,但其围手术期出血量大,不仅增加了手术风险,同时输血会增加免疫反应与疾病传播的风险,虽然临床通过术前纠正贫血、术中优化了手术操作,使术中及术后的显性失血量明显减少,降低了输血率,但发现隐形失血量仍偏高^[1]。相关研究显示手术创伤与止血带效应所引发的纤溶抗进是导致隐形失血的重要原因^[2]。因此,在全膝关节置换术中使用抗纤溶药物具有重要临床意义。

氨甲环酸是临床常见的抗纤溶药物,多项研究均证实可减少全膝关节置换术后的失血量^[3]。且有文献显示氨甲环酸可降低全膝关节置换患者术后炎症反应^[4]。但目前对于大剂量氨甲环酸对全膝关节置换患者术后的纤溶活性及炎症因子的影响研究较为罕见。对此,本研究通过回顾性分析在我院初次行单侧全膝关节置换术患者的临床资料,探讨了大剂量氨甲环酸对全膝关节置换患者术后纤溶活性与炎症因子的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择2015年10月至2017年10月我院收治的180例行初次单侧全膝关节置换术的患者为研究对象,根据用药方法的不同分为三组。对照组60例,包括男27例,女33例;年龄43-74岁,平均年龄(52.43±6.73)岁;病程8~14年,平均病程(10.32±2.24)年;ASA分级:I级36例,II级24例。常规剂量组60例,包括男31例,女29例;年龄45-76岁,平均年龄(54.32±5.83)岁;病程9~15年,平均病程(11.32±3.04)年;ASA分级:I级33例,II级27例。大剂量组60例,包括男26例,女24例;年龄44-75岁,平均年龄(51.84±6.04)岁;病程7~14年,平均病程(11.84±2.84)年;ASA分级:I级35例,II级25例。三组患者一般资料比较无显著差异($P>0.05$),具有可比性。

1.2 纳入标准

(1)符合《骨关节炎诊断及治疗指南》中临床诊断标准^[5],同时经过X线等检查确诊为单侧膝关节骨性关节炎,且均行初次单侧全膝关节置换术;(2)手术前血小板与凝血功能均正常;(3)无静脉血栓以及血管外科手术病史;(4)无凝血功能障碍,可耐受抗凝治疗。

1.3 排除标准

(1)临床资料不全、依从性差、对本研究使用药物过敏者;(2)伴有肝肾功能障碍;(3)合并糖尿病、神经系统功能障碍性疾病;

病;(4)入院治疗前1周使用过抗血小板药物或抗凝剂治疗;(5)血栓形成高危患者。

1.4 治疗方法

手术假体均采用后交叉韧带替代型骨水泥固定人工膝关节假体,采用髌旁内侧入路,髌骨不进行置换,仅给予进行骨面修正,在进行股骨髌截骨前给予止血带,其压力为患者收缩压加100 mmHg。安装膝关节假体,骨水泥完全固化后松止血带,之后常规组给予10 mg/kg。

氨甲环酸(上海信谊金朱药业有限公司,5 mL:0.25 g,20150926)稀释于250 mL生理盐水中静脉点滴,滴速控制为40~60滴/min,在第1次给药3 h后,以相同剂量再次给药;大剂量组剂量为15 mg/kg,方法同上;对照组仅给予250 mL盐水静脉滴注,第1次给药3 h后重复滴注1次。三组均使用血液回收装置,将术后6 h内引流的血液回输患者,并在术后24 h拔除血液回收装置。术后10 h,给予三组患者皮下注射低分子肝素钙(Sanofi Winthrop IndustrieT,4100AXaIU;0.6ml,20150912)4100U,1天1次,共治疗2周。术后2周,进行双下肢血管超声检查,明确是否形成血栓。

1.5 观察指标

(1)围手术期总失血量与隐形失血量,总失血量根据红细胞压积通过Gross方程与Nadler方程计算;隐形失血量为总失血量减去术后引流量的差值;(2)术前及术后3天凝血功能,采用全自动凝血仪检查纤维蛋白原水平、凝血酶原时间以及活化部分凝血活酶时间;(3)术前及术后3天纤溶指标及炎症因子变化,纤溶指标包括血清FDP、D-二聚体水平,炎症因子包括CRP与IL-6,其水平测定均用酶联免疫吸附ELISA法,试剂盒购于武汉默沙克生物科技有限公司,操作严格按照说明书进行;(4)术后2周血栓事件形成的发生率。

1.6 统计学方法

所有数据采用SPSS20.0统计软件进行分析,计量资料用均数±标准差($\bar{x} \pm s$)表示,数据符合正态分布,组间对比用独立样本t检验,计数资料采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 各组失血与血栓发生情况的比较

大剂量组与常规组的总失血量与隐形失血量均明显低于对照组,且大剂量组上述指标均低于常规组,组间差异均具有统计学意义($P<0.05$);术后2周,三组肌间静脉血栓发生率比较差异无统计学意义($P>0.05$),详见表1。

表1 各组患者失血与血栓发生情况比较

Table 1 Comparison of blood loss and incidence of thrombosis between different groups

Groups	n	Total blood loss(mm)	Invisible blood loss(mm)	Intramuscular vein thrombosis(n)
High dose group	60	503.13±124.84 ^{ab}	413.84±87.21 ^{ab}	5(10.00)
Regular group	60	553.54±135.43 ^a	471.94±98.94 ^a	6(13.33)
Control group	60	621.12±184.82	593.81±123.47	5(10.00)

Note: Compared with control group, ^a $P<0.05$; Compared with regular group, ^b $P<0.05$.

2.2 各组手术前后凝血指标的比较

手术前后,三组患者纤维蛋白原、凝血酶原时间以及活化

部分凝血活酶时间相比差异均无统计学意义($P>0.05$),详见表2。

表 2 各组凝血指标的比较($\bar{x} \pm s$)Table 2 Comparison of the blood coagulation indexes between different groups($\bar{x} \pm s$)

Groups	n	Fibrinogen(g/L)		Prothrombin time(s)		Activated partial thrombin time(s)	
		Preoperation	Postoperation	Preoperation	Postoperation	Preoperation	Postoperation
High dose group	60	3.17 $\pm$ 0.42	2.37 $\pm$ 0.72	11.75 $\pm$ 1.53	12.37 $\pm$ 1.92	27.12 $\pm$ 4.04	27.93 $\pm$ 6.04
Regular group	60	3.24 $\pm$ 0.32	3.44 $\pm$ 0.83	12.05 $\pm$ 1.21	12.43 $\pm$ 1.84	26.69 $\pm$ 3.43	28.19 $\pm$ 5.84
Control group	60	3.15 $\pm$ 0.46	3.21 $\pm$ 0.58	11.89 $\pm$ 1.64	12.32 $\pm$ 2.03	27.03 $\pm$ 4.12	26.84 $\pm$ 6.12

2.3 各组手术前后纤溶活性的比较

术前, 三组 FDP 以及 D- 二聚体水平比较差异均无统计学意义($P>0.05$); 术后, 三组上述指标均较术前显著升高, 而大剂

量组和常规组 FDP 与 D- 二聚体水平均显著低于对照组, 且大剂量组 FDP 与 D- 二聚体水平与常规组相比均明显降低, 差异均具有统计学意义($P<0.05$), 详见表 3。

表 3 各组纤溶指标的比较($\bar{x} \pm s$, mg/L)Table 3 Comparison of the fibrinolytic indexes between different groups($\bar{x} \pm s$, mg/L)

Groups	n	FDP		D - dimer	
		Preoperation	Postoperation	Preoperation	Postoperation
High dose group	60	2.89 $\pm$ 1.02	12.24 $\pm$ 2.05 ^{abc}	0.53 $\pm$ 0.12	4.02 $\pm$ 1.03 ^{abc}
Regular group	60	2.74 $\pm$ 0.74	13.41 $\pm$ 2.74 ^{ac}	0.49 $\pm$ 0.14	4.74 $\pm$ 0.82 ^{ac}
Control group	60	3.01 $\pm$ 1.03	15.83 $\pm$ 3.06 ^c	0.51 $\pm$ 0.18	5.18 $\pm$ 1.06

Note: Compared with control group, ^a $P<0.05$; Compared with regular group, ^b $P<0.05$; Compared with before treatment, ^c $P<0.05$.

2.4 各组手术前后炎症因子水平的比较

术前, 三组患者血清 CRP 与 IL-6 水平比较均无显著差异($P>0.05$); 术后, 三组血清 CRP、IL-6 水平均较术前显著升高, 大

剂量组与常规组血清 CRP、IL-6 水平均显著低于对照组, 且与常规组比较, 大剂量组血清 CRP、IL-6 水平较低, 差异均具有统计学意义($P<0.05$), 详见表 4。

表 4 各组血清炎症因子水平的比较($\bar{x} \pm s$)Table 4 Comparison of the serum inflammatory indicators between different groups($\bar{x} \pm s$)

Groups	n	CRP(mg/L)		IL-6(ng/L)	
		Preoperation	Postoperation	Preoperation	Postoperation
High dose group	60	3.96 $\pm$ 0.91	42.81 $\pm$ 9.05 ^{abc}	4.64 $\pm$ 0.97	20.84 $\pm$ 6.91 ^{abc}
Regular group	60	3.83 $\pm$ 0.83	45.63 $\pm$ 8.54 ^{ac}	4.78 $\pm$ 1.03	24.84 $\pm$ 5.83 ^{ac}
Control group	60	4.06 $\pm$ 1.04	50.32 $\pm$ 9.83	4.52 $\pm$ 0.92	30.43 $\pm$ 8.43

Note: Compared with control group, ^a $P<0.05$; Compared with regular group, ^b $P<0.05$; Compared with before treatment, ^c $P<0.05$.

3 讨论

对于保守治疗无效的骨性关节炎患者而言, 全膝关节置换术为其主要治疗方式, 可通过切除已经受损的关节表面, 使用人工表面关节部件给予替换, 从而有效消除病损关节损伤, 增加关节的稳定性。此术式不仅可以缓解患者疼痛, 还能改善患者的膝关节功能, 提高其生活质量^[6-8]。但多项临床研究显示全膝关节置换术的创伤较大, 术中需要截取大量骨质, 松解膝关节周围软组织, 因此术中出血、术后血栓等并发症较多, 影响了术后功能康复, 同时还可能影响伤口的愈合, 从而增加感染的风险^[9]。为了减少术中失血, 抗纤溶药物的使用较为广泛, 其中以氨甲环酸最为常见。

氨甲环酸为一种合成的赖氨酸衍生物, 与纤维酶原的赖氨酸结合位点具有高度的亲和性, 使其位点达到一个饱和状态, 导致纤溶酶原失去与纤维蛋白相互结合的能力, 从而抑制了纤维蛋白的降解, 达到止血的作用^[10,11]。由于此过程并不会增加纤维蛋白的合成, 因此理论上不会增加血栓发生的风险。本研究

结果显示术后给予患者使用氨甲环酸后, 其隐形失血量显著降低, 且随着药物剂量的增加, 其失血量越低, 但肌间静脉血栓的发生率无明显变化, 并且所有患者均未发生深静脉血栓的临床症状。此外, 本研究通过对比患者手术前后纤维蛋白原、凝血酶原时间以及活化部分凝血活酶时间, 结果显示患者手术前后此三项指标均无显著变化, 可见氨甲环酸虽然具有较强的止血功能, 但不会影响患者的凝血功能^[12]。

研究表明手术创伤应激与术后疼痛是导致纤溶亢进的主要诱因^[13]。其中, FDP 与 D- 二聚体是敏感性较高的纤溶指标, 二者水平的增加提示继发性纤溶亢进^[14,15]。文献显示初次全膝关节置换术后 6h 纤溶亢进达到峰值^[16]。本研究结果显示患者术后 FDP 与 D- 二聚体水平均较术前显著升高, 而使用氨甲环酸的患者其水平均较低, 且剂量增加患者血清 FDP 与 D- 二聚体水平随之降低, 提示随着氨甲环酸的剂量增加, 其抗纤溶活性的作用越强。机体炎症因子水平的高低可从一定程度上提示机体创伤应激的强弱, 而近年来越来越多的研究显示^[17-19]氨甲环酸存在潜在的抗炎作用。有学者经研究发现在围手术期使用氨

甲环酸可有效降低术后炎症因子水平^[15]。本研究结果也显示患者在使用大剂量氨甲环酸后血清 CRP 与 IL-6 水平明显低于使用常规剂量的患者。由此可见,氨甲环酸可有效减轻全膝关节置换术患者的炎症反应水平。

综上所述,在全膝关节置换术后使用氨甲环酸可进一步减少术后隐性失血量,且不会增加血栓事件的风险,且随着药物剂量的增加,其止血效果越强,同时具有更为显著的抗纤溶作用与抗炎效果。

参考文献(References)

- [1] Vaishya R, Vijay V, Agarwal AK. Total Knee Arthroplasty Using Patient-specific Blocks after Prior Femoral Fracture without Hardware Removal[J]. Indian J Orthop, 2018, 52(2): 154-160
- [2] Humbyrd CJ. The Ethics of Bundled Payments in Total Joint Replacement: "Cherry Picking" and "Lemon Dropping" [J]. J Clin Ethics, 2018, 28(1): 62-68
- [3] Prakash J, Seon JK, Song EK, et al. Is Combined Administration of Tranexamic Acid Better than Both Intravenous and Topical Regimes for Total Loss, Hidden Loss and Post-operative Swelling? A Randomized Control Trial[J]. Indian J Orthop, 2018, 52(2): 117-123
- [4] Adravanti P, Di Salvo E, Calafiore G, et al. A prospective, randomized, comparative study of intravenous alone and combined intravenous and intraarticular administration of tranexamic acid in primary total knee replacement[J]. Arthroplast Today, 2017, 4(1): 85-88
- [5] 中华医学会风湿病学分会.骨关节炎诊断及治疗指南[J].中华风湿病学杂志, 2010, 14(6): 416-419
Rheumatology branch of Chinese Medical Association. Guideline for diagnosis and treatment of osteoarthritis [J]. Chinese Journal of Rheumatology, 2010, 14 (6): 416-419
- [6] Špička J, Lošťák J, Gallo J, et al. Influence of Enhanced Recovery Regime on Early Outcomes of Total Knee Arthroplasty [J]. Acta Chir Orthop Traumatol Cech, 2017, 84(5): 361-367
- [7] Li Y, Lu M, Tian H, et al. Effect of different tourniquet releasing strategy on blood loss in total knee arthroplasty [J]. Zhonghua Yi Xue Za Zhi, 2017, 97(41): 3219-3224
- [8] Schnettler T, Papillon N, Rees H. Use of a Tourniquet in Total Knee Arthroplasty Causes a Paradoxical Increase in Total Blood Loss [J]. J Bone Joint Surg Am, 2017, 99(16): 1331-1336
- [9] Gao HL, Xiao LB, Zhai WT, et al. Comparison of analgesic effects between multimodal and patient-controlled intravenous analgesia in patients with rheumatoid arthritis in the perioperative period of total knee arthroplasty[J]. Zhongguo Gu Shang, 2017, 30(4): 356-359
- [10] Dong YL, Qian YN, Zhong XQ, et al. Effects of tranexamic acid combined with temporary drain clamping on postoperative blood loss in total knee arthroplasty [J]. Zhongguo Gu Shang, 2017, 30 (4): 329-333
- [11] Kim C, Park SS, Dhotar HS, et al. Topical tranexamic acid reduces transfusion rates in simultaneous bilateral total knee arthroplasty: a retrospective case series[J]. Can J Surg, 2017, 60(5): 311-315
- [12] Yu Z, Yao L, Yang Q. Tranexamic acid plus diluted-epinephrine versus tranexamic acid alone for blood loss in total joint arthroplasty: A meta-analysis[J]. Medicine (Baltimore), 2017, 96(24): e7095
- [13] McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis[J]. Drugs, 2012, 72(5): 585-617
- [14] Kamiyatsuri K, Tominaga N, Kobayashi S. Preoperative elevated FDP may predict severe intraoperative hypotension after dural opening during decompressive craniectomy of traumatic brain injury [J]. JA Clin Rep, 2018, 4(1): 8
- [15] Merron B, Lavery R, Speers H, et al. Age adjusted D-dimer in the Belfast Health and Social Care Trust: A retrospective study[J]. Ulster Med J, 2018, 87(1): 27-29
- [16] Adravanti P, Di Salvo E, Calafiore G, et al. A prospective, randomized, comparative study of intravenous alone and combined intravenous and intraarticular administration of tranexamic acid in primary total knee replacement[J]. Arthroplast Today, 2017, 4(1): 85-88
- [17] Yu Z, Yao L, Yang Q. Tranexamic acid plus diluted-epinephrine versus tranexamic acid alone for blood loss in total joint arthroplasty: A meta-analysis[J]. Medicine (Baltimore), 2017, 96(24): e7095
- [18] Mi B, Liu G, Lv H, et al. Is combined use of intravenous and intra-articular tranexamic acid superior to intravenous or intraarticular tranexamic acid alone in total knee arthroplasty? A meta-analysis of randomized controlled trials[J]. J Orthop Surg Res, 2017, 12(1): 61
- [19] Mi B, Liu G, Zhou W, et al. Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials[J]. Arch Orthop Trauma Surg, 2017, 137 (7): 997-1009
- [20] Demos HA, Lin ZX, Barfield WR, et al. Process Improvement Project Using Tranexamic Acid Is Cost-Effective in Reducing Blood Loss and Transfusions After Total Hip and Total Knee Arthroplasty [J]. J Arthroplasty, 2017, 32(8): 2375-2380
- [21] Clark N, Morris S, Sargent N, et al. Anaphylactic reaction to tranexamic acid in an adolescent undergoing posterior spinal fusion[J]. Paediatr Anaesth, 2018, 28(2): 184-185

(上接第 3359 页)

- [27] Yam M, Chawla A, Kwek E. Rewriting the tip apex distance for the proximal femoral nail anti-rotation[J]. Injury, 2017, 48(8): 1843-1847
- [28] Turgut A, Kalenderer Ö, Karapınar L, et al. Which factor is most important for occurrence of cutout complications in patients treated with proximal femoral nail antirotation? Retrospective analysis of 298 patients[J]. Arch Orthop Trauma Surg, 2016, 136(5): 623-630
- [29] 徐凤瑞,何明武,姚忠军,等.PFNA 内固定与人工股骨头置换术治疗高龄骨质疏松性股骨粗隆间骨折的比较[J].中国骨与关节损伤杂志, 2016, 31(2): 130-133
- Xu Feng-rui, He Ming-wu, Yao Zhong-jun, et al. Comparison of PFNA and artificial femoral head replacement in treatment of senile osteoporotic femoral intertrochanteric fractures [J]. Chinese Journal of Bone and Joint Injury, 2016, 31(2): 130-133
- [30] 侯勇,李经坤,司萌,等.PFNA 治疗老年股骨粗隆间骨折临床疗效分析[J].创伤外科杂志, 2017, 19(3): 164-168
Hou Yong, Li Jing-kun, Si Meng, et al. Evaluation of the clinical curative effects of PFNA and Gamma nail in the treatment of intertrochanteric fractures [J]. Journal of Traumatic Surgery, 2017, 19 (3): 164-168