

氨甲环酸用于全膝关节置换降低失血量的有效性及安全性

曹万军, 朱绍灵, 刘显东, 唐承杰, 郑金文, 陈星宇, 刘颖, 肖鹏(四川省骨科医院下肢科, 四川省成都市 610041)

文章亮点:

对比单侧全膝关节置换前静脉注射氨甲环酸与否对患者置换后失血的有效性及其安全性影响, 证实初次单侧全膝关节置换前静脉给予氨甲环酸能明显减少围手术期失血量及输血量, 降低输血风险及输血费用, 利于术后功能恢复, 且不增加下肢深静脉血栓的风险。

关键词:

植入物; 人工假体; 氨甲环酸; 全膝关节置换; 失血量; 深静脉血栓; 输血

主题词:

氨甲环酸; 关节成形术; 置换; 膝; 静脉血栓形成; 输血

摘要

背景: 氨甲环酸是一种人工合成的抗纤维蛋白溶解的药物, 可以经静脉有效的控制全膝关节置换后失血。

目的: 观察氨甲环酸对初次行单侧全膝关节置换患者置换后失血的有效性及其安全性。

方法: 选取 2014 至 2015 年在四川省骨科医院下肢科行单侧全膝关节置换的 100 例患者。以使用氨甲环酸与否分为试验组和对照组, 各 50 例。试验组患者在全膝关节置换前 10 min 静脉注射氨甲环酸 1 g, 而对照组不给予氨甲环酸。

结果与结论: 试验组患者置换后围手术期总失血量、置换后 24 h 引流量、输血量明显少于对照组($P < 0.05$); 试验组与对照组术中出血量、输血人数差异无显著性意义。两组患者置换前血红蛋白水平差异无显著性意义, 而置换后血红蛋白水平均下降, 且试验组患者置换后血红蛋白水平均明显高于对照组。置换后 24 h, 两组患者凝血功能差异无显著性意义。置换后 6 d, 2 组患者双下肢静脉彩色多普勒超声检查均未见深静脉血栓。提示初次单侧全膝关节置换前静脉给予氨甲环酸能明显减少围手术期失血量及输血量, 降低输血风险及输血费用, 利于术后功能恢复, 且不增加下肢深静脉血栓的风险。

曹万军, 朱绍灵, 刘显东, 唐承杰, 郑金文, 陈星宇, 刘颖, 肖鹏. 氨甲环酸用于全膝关节置换降低失血量的有效性及安全性[J]. 中国组织工程研究, 2015, 19(31):4944-4948.

doi:10.3969/j.issn.2095-4344.2015.31.005

Tranexamic acid reduces blood loss in total knee arthroplasty: effectiveness and safety

Cao Wan-jun, Zhu Shao-ling, Liu Xian-dong, Tang Cheng-jie, Zheng Jin-wen, Chen Xing-yu, Liu Ying, Xiao Peng (Department of Lower Limb, Sichuan Orthopaedic Hospital, Chengdu 610041, Sichuan Province, China)

Abstract

BACKGROUND: Tranexamic acid is a synthetic anti-fibrinolytic drug, and can effectively control blood loss after total knee arthroplasty through vein.

OBJECTIVE: To evaluate the effectiveness and safety of tranexamic acid in reducing blood loss after primary unilateral total knee arthroplasty.

METHODS: From 2014 to 2015, 100 patients from the Department of Lower Limb, Sichuan Orthopaedic Hospital underwent primary unilateral total knee arthroplasty, and randomly divided into test group which used tranexamic acid and control group which used tranexamic acid, with 50 cases in each group. 1 g tranexamic acid was infused into the vein at 10 minutes before total knee arthroplasty in the test group, but tranexamic acid was not given in the control group.

RESULTS AND CONCLUSION: The amount of total blood loss, postoperative wound drainage in 24 hours, and the amount of blood transfusion were significantly less in the test group than in the control group ($P < 0.05$). No significant differences in intraoperative blood loss and the number of patients receiving blood transfusion were found between the test and control groups. No significant difference in preoperative hemoglobin levels was detected before surgery, but hemoglobin levels were decreased after surgery between the two groups. Postoperative hemoglobin levels were apparently higher in the test group than in the control group after surgery. At 24 hours after surgery, no significant difference in coagulation was detectable between the two groups. At 6 days, double lower limb vein color Doppler ultrasound examination did not reveal deep vein thrombosis in both groups. These findings verify that treatment with tranexamic acid in the vein before primary unilateral total knee arthroplasty can evidently diminish the amount of perioperative blood loss and blood transfusion, reduce the risk

曹万军, 副主任医师, 主要从事骨与关节损伤方面的研究。

中图分类号:R318

文献标识码:A

文章编号:2095-4344

(2015)31-04944-05

稿件接受: 2015-06-11

http://www.crter.org

Cao Wan-jun, Associate chief physician, Department of Lower Limb, Sichuan Orthopaedic Hospital, Chengdu 610041, Sichuan Province, China

Accepted: 2015-06-11

and cost of blood transfusion, which is good for rehabilitation and does not increase the risk of deep vein thrombosis.

Subject headings: Tranexamic Acid; Arthroplasty, Replacement, Knee; Venous Thrombosis; Blood Transfusion

Cao WJ, Zhu SL, Liu XD, Tang CJ, Zheng JW, Chen XY, Liu Y, Xiao P. Tranexamic acid reduces blood loss in total knee arthroplasty: effectiveness and safety. *Zhongguo Zuzhi Gongcheng Yanjiu*. 2015;19(31):4944-4948.

0 引言 Introduction

全膝关节置换围手术期相关血液管理已成为目前关节外科领域非常重视并广泛研究的问题。血液保护方案旨在降低输血需求,其方法多种多样,包括置换前自体血储存、围手术期使用促红细胞生成素、术中血液稀释、切口局部使用促凝血药物等。针对上述技术有效性的研究结果存在差异,而且相关的研究设计往往欠佳。此外,这些技术的花费较高且可能导致相关并发症发生。同种异体输血不仅价格昂贵,并且有传播血源性疾病的风险。输血还可能导致各种免疫调节反应,更重要的是目前已经公认其有导致关节假体周围感染的风险。而使用抗纤溶药物氨甲环酸减少全膝关节置换围手术期的出血量越来越受到重视,而使用氨甲环酸理论上会增加深静脉血栓形成的风险^[1],因此选择合适的氨甲环酸使用方案并评估其降低全膝关节置换失血量的有效性和安全性具有重要意义,现将四川省骨科医院对此相关研究报告如下。

1 对象和方法 Subjects and methods

设计: 同期非随机对比观察。

时间及地点: 试验于2014至2015年在四川省骨科医院下肢科完成。

对象: 选择2014至2015年在四川省骨科医院下肢科行单侧全膝关节置换的患者。

纳入标准: ①首次行单侧全膝关节置换且年龄位于60-90岁的骨关节炎和类风湿性关节炎患者。②置换前实验室检查及双下肢静脉彩超均正常。③无膝关节开放手术史。

排除标准: ①使用氨甲环酸禁忌者:包括血栓形成倾向的房颤患者、支架植入者。②氨甲环酸过敏者。③凝血功能异常者。④既往发生过深静脉血栓者。⑤严重心、肺、肝、肾功能不全者。

通过纳入标准及排除标准筛选出100例患者。以使用氨甲环酸与否进行分组:静脉注射氨甲环酸者为试验组($n=50$),不注射的患者为对照组($n=50$)。两组患者基本资料在年龄、性别、体质量指数、病种差异均无显著性意义($P > 0.05$)。

材料: 假体为后叉韧带替代型骨水泥固定人工膝关节,购自英国Smith & Nephew公司。

方法:

全膝关节置换: 所有手术均由同一高年资医师完成,全身麻醉下采用髌旁内侧入路,所有手术均在止血带控制下完成,并于切皮前进行止血带充气,止血带压力为

240-280 mm Hg(1 mm Hg=0.133 kPa),伤口包扎完成后释放。其余所有患者的血液管理方法两组均相同,均未予术中自体血回输。所有患者均未进行置换前自体血储存或接受促红细胞生成素治疗。两组患者均使用弹力绷带加压包扎,置换后24 h拔出引流管,置换后两组患者进行标准补液和多模式镇痛。对于血红蛋白小于75 g/L的患者予输血治疗,大于75 g/L而小于100 g/L根据患者具体情况酌情输血治疗。所有患者均按照《中国预防骨科大手术深静脉血栓形成指南》进行正规抗凝治疗^[2]。置换后2周切口拆线出院。

氨甲环酸治疗: 试验组患者在全膝关节置换前10 min将氨甲环酸1 g稀释于100 mL生理盐水后静脉注射,而对照组不给予氨甲环酸。

手术指标观察: 比较2组患者术中出血量、围手术期总失血量、置换后24 h总引流量、输血量、输血率。围手术期总失血量根据Nadler^[3]、Gross等^[4]关于失血量计算方法进行计算。

血液指标分析: 置换后6 h, 1 d, 2 d, 3 d时血红蛋白水平以及置换后24 h凝血酶原时间、活化部分凝血酶原时间、纤维蛋白原、深静脉血栓发生率及并发症情况^[5]。

主要观察指标: 2组患者的手术指标和深静脉血栓发生情况。

统计学分析: 数据采用SPSS 19.0软件包进行统计分析。计量资料数据以 $\bar{x} \pm s$ 表示。两组计量资料比较采用独立样本 t 检验;不同时期计量资料之间比较采用重复测量资料的方差分析;计数资料之间比较采用卡方检验, $P < 0.05$ 为差异有显著性意义。

2 结果 Results

2.1 患者数据分析及临床信息 患者临床信息见表1。试验流程见图1。

表1 两组全膝关节置换患者的一般资料

Table 1 General data of patients undergoing total knee arthroplasty in both groups

项目	试验组	对照组
n	50	50
年龄($\bar{x} \pm s$, 岁)	64.47 \pm 5.57	65.34 \pm 5.23
性别(男/女, n)	17/33	12/38
体质量指数($\bar{x} \pm s$, kg/m ²)	26.73 \pm 3.28	26.69 \pm 3.12
病种(骨关节炎/类风湿关节炎, n)	36/14	39/11

表注: 两组患者基本资料在年龄、性别、体质量指数、病种差异均无显著性意义($P > 0.05$)。

2.2 手术指标 试验组与对照组患者术中出血量差异无显著性意义($P > 0.05$); 试验组患者置换后围手术期总失血量、置换后 24 h 引流量、输血量明显少于对照组($P < 0.05$); 试验组与对照组输血人数分别为 6 例和 18 例, 输血率分别为 12% 和 36%, 差异无显著性意义($P < 0.05$; **表 2**)。

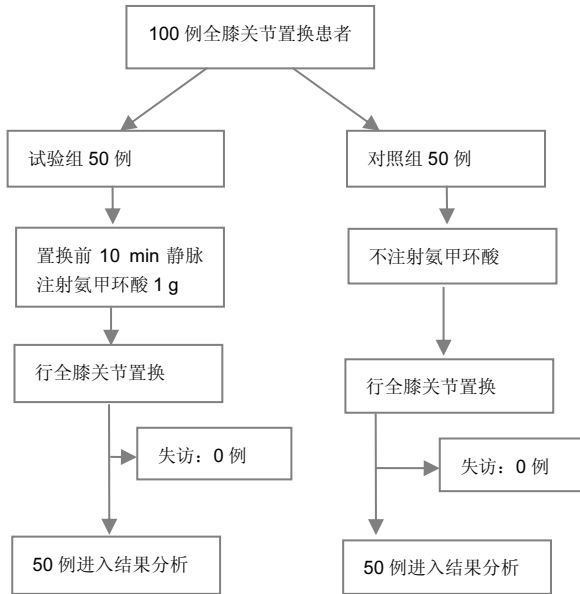


图 1 氨甲环酸对全膝关节置换影响的试验流程

Figure 1 Flowchart of effects of tranexamic acid on total knee arthroplasty

表 2 氨甲环酸对全膝关节置换患者输血的影响 ($n=50$)
Table 2 Effects of tranexamic acid on blood transfusion in patients undergoing total knee arthroplasty

项目	试验组	对照组	P
术中出血量($\bar{x}\pm s$, mL)	41.47±9.35	42.15±7.82	0.842
围手术期总失血量($\bar{x}\pm s$, mL)	925.63±437.57	1 736.33±632.19	< 0.05
术后 24 h 总引流量($\bar{x}\pm s$, mL)	137.23±61.37	352.00±89.71	< 0.05
输血量($\bar{x}\pm s$, mL)	125.32±156.28	375.43±260.16	< 0.05
输血率(%)	12	36	< 0.05

2.3 血红蛋白水平 两组患者患者置换前血红蛋白水平差异无显著性意义, 而置换后血红蛋白水平均下降(与置换前相比, $P < 0.05$), 且试验组患者置换后血红蛋白水平明显高于对照组($P < 0.05$; **表 3**)。

表 3 氨甲环酸对全膝关节置换患者血红蛋白水平变化的影响 ($\bar{x}\pm s$, $n=50$, g/L)

Table 3 Effects of tranexamic acid on changes in hemoglobin levels in patients undergoing total knee arthroplasty

时间	试验组	对照组	F	P
术前	131.31±13.45	133.47±14.38	0.21	0.812 9
术后 6 h	117.35±14.36	100.18±10.64	16.10	0.000 0
术后 1 d	108.43±14.57	94.26±8.56	11.37	0.000 0
术后 2 d	110.48±13.24	89.51±8.53	24.04	0.000 0
术后 3 d	105.82±10.29	80.42±8.87	63.67	0.000 0
F	17.59	113.30		
P	0.000 0	0.000 0		

2.4 凝血功能 置换后 24 h, 两组患者凝血功能差异无显著性意义($P > 0.05$; **表 4**)。

表 4 氨甲环酸对全膝关节置换患者凝血功能的影响 ($\bar{x}\pm s$, $n=50$)
Table 4 Effects of tranexamic acid on coagulation in patients undergoing total knee arthroplasty

项目	试验组	对照组
凝血酶原时间(s)	11.01±0.42	10.92±0.47
活化部分凝血酶原时间(s)	33.51±3.64	33.10±3.27
纤维蛋白原水平(g/L)	3.85±0.47	3.82±0.54

2.5 并发症 两组患者置换后 6 d 行双下肢静脉彩超检查 两组患者均未见深静脉血栓形成, 置换后 2 周切口拆线, 切口 I/甲愈合, 均未出现并发症。

3 讨论 Discussion

全膝关节置换的失血量通常较大, 而置换后失血相关并发症也更为严重。通常认为膝关节周围软组织内出血会加重疼痛、关节僵硬并使术后恢复时间延长。此外, 关节腔内积血会导致膝关节肿胀、伤口延迟愈合并增加感染的风险。而目前与之相关的血液方案包括术前自体血储存、围手术期使用促红细胞生成素^[6]、术中血液稀释、切口局部使用促凝血药物等, 花费较高且可能导致相关并发症发生。同种异体输血不仅价格昂贵, 并且有传播血源性疾病的风险^[7-8]。输血还可能导致各种免疫调节反应, 更重要的是目前已经公认其有导致关节假体周围感染的风险^[9]。

由于全膝关节置换后的出血主要是由于纤溶亢进所致^[10-11], 因此越来越多的关节外科医师开始关注抗纤溶药物在全膝关节置换中的应用。氨甲环酸作为一种合成的抗纤溶药物, 其不良反应相对较少, 最早 1995 年 Royston^[12] 在胸外科手术中使用, 目前已广泛应用于心脏外科、肝脏移植及妇科等手术中^[1, 13-15], 并且获得了满意的止血效果。Hiippala 等^[16] 对 75 例接受全膝关节置换的患者进行随机对照研究, 发现使用氨甲环酸者围手术期的失血量和平均输血量均明显减少。近年来已有相关文献报道氨甲环酸应用于脊柱外科及关节外科, 其止血效果满意。最近的 Meta 分析报道氨甲环酸可以有效降低全膝关节置换后的失血量^[16]。

与此同时, 对于氨甲环酸的使用方案也并未形成统一的意见, 使用方法包括静脉滴注、肌内注射、关节腔内局部使用和口服。静脉使用氨甲环酸后血浆浓度达到峰值的时间为 5-15 min, 明显短于肌注和口服, 因此静脉使用被认为是最有效的方法。Maniar 等^[17] 发现手术前后不同时间点使用氨甲环酸者的出血量均比未使用者下降, 而术前使用的效果要优于松止血带时使用的效果, 并由此推断出在纤溶亢进的开始阶段使用的效果优于纤溶达顶峰时使用的效果。本试验中氨甲环酸的使用方法仅在切皮前静脉滴注 1 g 剂量的氨甲环酸。与 MacGillavray 等^[18] 的结果不同, 本

试验中患者对异体输血的需求较低, 对照组患者置换后对异体输血的需求是试验组的3倍, 结果体现了应用氨甲环酸的益处。

由于氨甲环酸具有抗纤维蛋白溶解效应, 因此在理论上存在发生深静脉血栓事件的风险^[1, 14, 16, 18-39], 而关节置换患者本身就存在较高的静脉血栓栓塞事件风险, 因此在这些患者使用氨甲环酸仍存在一定的顾虑。本试验于置换后6 d常规进行多普勒超声检查监测下肢深静脉血栓形成情况, 发现2组患者均未出现静脉血栓栓塞体征或症状。这进一步证实了meta分析关于氨甲环酸并不会增加全关节置换病例深静脉血栓事件发生率的结论^[40-42]。

本试验的主要不足之处在于回顾性研究具有一定局限性, 一些未检测到的混杂变量可能会影响到研究结果的准确性。然而, 本试验是对在—较短时期内(12个月)接受单侧全膝关节置换的连续病例进行的评估, 全部手术均由同一名医师采用标准临床路径完成, 且研究期间无任何可能影响术后失血量的医疗护理方案的更改。此外, 未发现2组患者置换前特征有差异。本试验的优势在于研究设计上具有很高的均质性(单一术者、完全相同的假体和手术技术)、无混杂变量(无术前自体血储存、未采用其他血液保护方法且未放置引流)以及病例样本量较大。

综上所述, 本试验发现在单侧全膝关节置换切皮前注射单次剂量氨甲环酸(1 g)可以显著降低围手术期失血量及输血率, 避免为输血而额外付费, 同时避免了输血相关并发症的风险, 该使用方案有效并且安全。下一步将通过对比氨甲环酸不同的使用方法, 寻找到最佳的用药方案。

作者贡献: 曹万军进行试验设计, 实施为曹万军、朱绍灵、刘显东等, 试验评估为曹万军, 资料收集为朱绍灵, 成文、审校均为第一作者曹万军, 并对文章负责。

利益冲突: 文章内容不涉及相关的利益冲突。

伦理要求: 试验获得四川省骨科医院伦理委员会批准。

学术术语: 全膝关节置换后深静脉血栓高发率的原因? 深静脉血栓形成是指血液在深静脉腔内不正常凝结, 阻塞静脉管腔, 导致静脉回流障碍, 造成不同程度的慢性深静脉回流功能不全, 全身主干静脉均可发生。手术中出血较多, 深静脉受牵拉, 静脉壁受损为术后血栓的形成提供了条件; 关节腔、肌肉渗血及局部水肿压迫静脉血液回流受阻。全膝关节置换后深静脉血栓病因及发病机制有着多方面的因素, 深静脉血管壁损伤, 血流缓慢和高凝状态是静脉血栓形成的3个因素。患者的全身状况差, 合并其他疾病, 关节置换的创伤大, 手术麻醉方法, 手术时间延长, 肢体固定以及长期卧床都是下肢深静脉血栓形成的高危因素。下肢深静脉血栓和肺栓塞是导致关节置换后患者高致残率和高死亡率的主要原因。提示临床医生对关节置换患者应于术前对深静脉血栓形成的危险因素进行系统评估。

作者声明: 文章为原创作品, 无抄袭剽窃, 无泄密及署名和专利争议, 内容及数据真实, 文责自负。

4 参考文献 References

- [1] Crantford JC, Wood BC, Claiborne JR, et al. Evaluating the safety and efficacy of tranexamic acid administration in pediatric cranial vault reconstruction. *J Craniofac Surg.* 2015;26(1):104-107.
- [2] 中华医学会骨科分会. 预防骨科大手术深静脉血栓形成指南(草案)[J]. *中国矫形外科杂志*, 2009, 17(2): 118-119.
- [3] Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery.* 1962;51(2):224-232.
- [4] Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology.* 1983;58(3):277-280.
- [5] Sarzaeem MM, Razi M, Kazemian G, et al. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. *J Arthroplasty.* 2014;29(8):1521-1524.
- [6] Ishii Y, Noguchi H, Sato J, et al. Effect of a single injection of tranexamic acid on blood loss after primary hybrid TKA. *Knee.* 2015;22(3):197-200.
- [7] Hourlier H, Reina N, Fennema P. Single dose intravenous tranexamic acid as effective as continuous infusion in primary total knee arthroplasty: a randomised clinical trial. *Arch Orthop Trauma Surg.* 2015;135(4):465-471.
- [8] Samujh C, Falls TD, Wessel R, et al. Decreased blood transfusion following revision total knee arthroplasty using tranexamic acid. *J Arthroplasty.* 2014;29(9 Suppl):182-185.
- [9] Patel JN, Spanyer JM, Smith LS, et al. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. *J Arthroplasty.* 2014;29(8):1528-1531.
- [10] Lotke PA, Faralli VJ, Orenstein EM, et al. Blood loss after total knee replacement. Effects of tourniquet release and continuous passive motion. *J Bone Joint Surg Am.* 1991;73(7): 1037-1040.
- [11] Ishida K, Tsumura N, Kitagawa A, et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. *Int Orthop.* 2011;35(11):1639-1645.
- [12] Royston D. Blood-sparing drugs: aprotinin, tranexamic acid, and epsilon-aminocaproic acid. *Int Anesthesiol Clin.* 1995;33(1):155-179.
- [13] Hiiipala ST, Strid LJ, Wennerstrand MI, et al. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesth Analg.* 1997;84(4): 839-844.
- [14] Faraoni D, Rozen L, Willems A, et al. Experimental model of hyperfibrinolysis designed for rotational thromboelastometry in children with congenital heart disease. *Blood Coagul Fibrinolysis.* 2015;26(3):290-297.
- [15] Aoki A, Suezawa T, Yamamoto S, et al. Effect of antifibrinolytic therapy with tranexamic acid on abdominal aortic aneurysm shrinkage after endovascular repair. *J Vasc Surg.* 2014;59(5):1203-1208.
- [16] Gandhi R, Evans HM, Mahomed SR, et al. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. *BMC Res Notes.* 2013;6: 184.
- [17] Maniar RN, Kumar G, Singhi T, et al. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. *Clin Orthop Relat Res.* 2012;470(9):2605-2612.

- [18] MacGillivray RG, Tarabichi SB, Hawari MF, et al. Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. *J Arthroplasty*. 2011;26(1):24-28.
- [19] Orpen NM, Little C, Walker G, et al. Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. *Knee*. 2006;13(2):106-110.
- [20] Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. *Br J Anaesth*. 2003;90(5):596-599.
- [21] Zhang F, Gao Z, Yu J. Clinical comparative studies on effect of tranexamic acid on blood loss associated with total knee arthroplasty. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2007;21(12):1302-1304.
- [22] Sepah YJ, Umer M, Ahmad T, et al. Use of tranexamic acid is a cost effective method in preventing blood loss during and after total knee replacement. *J Orthop Surg Res*. 2011;6:22.
- [23] Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *J Bone Joint Surg Br*. 1996;78(3):434-440.
- [24] Kelley TC, Tucker KK, Adams MJ, et al. Use of tranexamic acid results in decreased blood loss and decreased transfusions in patients undergoing staged bilateral total knee arthroplasty. *Transfusion*. 2014;54(1):26-30.
- [25] Lee SH, Cho KY, Khurana S, et al. Less blood loss under concomitant administration of tranexamic acid and indirect factor Xa inhibitor following total knee arthroplasty: a prospective randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(11):2611-2617.
- [26] Oremus K, Sostaric S, Trkulja V, et al. Influence of tranexamic acid on postoperative autologous blood retransfusion in primary total hip and knee arthroplasty: a randomized controlled trial. *Transfusion*. 2014;54(1):31-41.
- [27] Caglar GS, Tasci Y, Kayikcioglu F, et al. Intravenous tranexamic acid use in myomectomy: a prospective randomized double-blind placebo controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2008;137(2):227-231.
- [28] Dietrich W, Spannagl M, Boehm J, et al. Tranexamic acid and aprotinin in primary cardiac operations: an analysis of 220 cardiac surgical patients treated with tranexamic acid or aprotinin. *Anesth Analg*. 2008;107(5):1469-1478.
- [29] Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010;92(15):2503-2513.
- [30] Santos AT, Kalil RA, Bauemann C, et al. A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting. *Braz J Med Biol Res*. 2006;39(1):63-69.
- [31] Lin PC, Hsu CH, Huang CC, et al. The blood-saving effect of tranexamic acid in minimally invasive total knee replacement: is an additional pre-operative injection effective? *J Bone Joint Surg Br*. 2012;94(7):932-936.
- [32] Camarasa MA, Ollé G, Serra-Prat M, et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial. *Br J Anaesth*. 2006;96(5):576-582.
- [33] Charoencholanich K, Siritwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. *Clin Orthop Relat Res*. 2011;469(10):2874-2880.
- [34] Alvarez JC, Santiveri FX, Ramos I, et al. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. *Transfusion*. 2008;48(3):519-525.
- [35] Ho KM, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care*. 2003;31(5):529-537.
- [36] Konig G, Hamlin BR, Waters JH. Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty. *J Arthroplasty*. 2013;28(9):1473-1476.
- [37] Tan J, Chen H, Liu Q, et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. *J Surg Res*. 2013;184(2):880-887.
- [38] Gomez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, et al. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. *J Bone Joint Surg Am*. 2014;96(23):1937-1944.
- [39] Zhou XD, Tao LJ, Li J, et al. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch Orthop Trauma Surg*. 2013;133(7):1017-1027.
- [40] Gillette BP, DeSimone LJ, Trousdale RT, et al. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res*. 2013;471(1):150-154.
- [41] Wu Q, Zhang HA, Liu SL, et al. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2015;25(3):525-541.
- [42] Zhao-Yu C, Yan G, Wei C, et al. Reduced blood loss after intra-articular tranexamic acid injection during total knee arthroplasty: a meta-analysis of the literature. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(12):3181-3190.