

นิพนธ์ต้นฉบับ

การศึกษาเปรียบเทียบประสิทธิภาพในการลดภาวะเลือดออกในข้อเข่าระหว่างกลุ่มที่ได้รับการฉีดเฉพาะ Tranexamic acid กับกลุ่มที่ได้รับการฉีด Tranexamic acid ร่วมกับ Epinephrine เข้าข้อเข่าภายหลังการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้า: การทดลองแบบสุ่มมีกลุ่มควบคุมชนิดปกปิดสองฝ่าย

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บทคัดย่อ

บทนำ: ภายหลังการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้า มีภาวะเลือดคั่งและอาการบวมของข้อเข่า ในช่วงแรกหลังผ่าตัดได้ การใช้ epinephrine ร่วมกับ Tranexamic acid (TXA) อาจช่วยลดอาการเลือดคั่งได้

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิภาพระหว่างการฉีด Tranexamic acid กับ Tranexamic acid ร่วมกับ Epinephrine เข้าข้อเข่าภายหลังการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้า ในการลดภาวะเลือดคั่งในข้อเข่าหลังการผ่าตัดบูรณะเส้นเอ็นไขว้หน้า

วิธีการศึกษา: การศึกษาแบบสุ่มมีกลุ่มควบคุมชนิดปกปิดสองฝ่าย ในผู้ป่วยที่เข้ารับการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้าที่โรงพยาบาลนครพิงค์ ระหว่างวันที่ 21 มิถุนายน 2564 ถึง 20 มิถุนายน 2565 แบ่งเป็น กลุ่มที่ได้รับ TXA (n = 26) และกลุ่มที่ได้รับ TXA ร่วมกับ epinephrine (n = 26) เปรียบเทียบปริมาณเลือดจากสายระบายที่ 24 และ 48 ชั่วโมงหลังผ่าตัด

ผลการศึกษา: กลุ่มที่ได้ TXA และ TXA ร่วมกับ epinephrine เพศชายร้อยละ 80.8 และ 92.3 อายุเฉลี่ย 30.23 ± 10.99 และ 28.61 ± 10.89 ปี ได้ผ่าตัดชนิด ACLR + meniscus repair มากที่สุด ร้อยละ 73.08 และ 57.69 ตามลำดับ หลังผ่าตัดปริมาณเลือดจากสายระบายที่ 24 ชั่วโมง มีค่าเฉลี่ย 90.38 ± 58.27 มิลลิลิตร และ 65 ± 38.94 มิลลิลิตร ($p = 0.123$) และที่ 48 ชั่วโมง มีค่าเฉลี่ย 148.46 ± 83.46 และ 113.85 ± 60.80 มิลลิลิตร ($p = 0.069$) ตามลำดับ ค่าเฉลี่ย VAS ที่ 24 ชั่วโมงหลังผ่าตัด 6.15 ± 1.43 และ 5.23 ± 1.61 ($p = 0.034$) มีการเพิ่มของเส้นรอบวงกึ่งกลางกระดูกสะบ้าเฉพาะที่เวลา 24 ชั่วโมง เท่ากับ 2.15 ± 0.88 และ 1.63 ± 0.82 เซนติเมตร ตามลำดับ ($p = 0.032$) และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติในตัวชี้วัดรองอื่น

สรุป: การฉีด TXA ร่วมกับ epinephrine เข้าข้อเข่าภายหลังการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้ามีแนวโน้มช่วยลดเลือดออกทางสายระบายได้ แม้การศึกษานี้ยังไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ จึงเห็นว่าควรมีการศึกษาเพิ่มเติม Thai Clinical Trial Registry number TCTR20211124002

คำสำคัญ: การผ่าตัดบูรณะเส้นเอ็นไขว้หน้า, epinephrine, tranexamic acid, การฉีดยาเข้าข้อ

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ติดต่อบทความ

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Original Article

Efficacy of intra-articular tranexamic acid alone versus tranexamic acid plus epinephrine in reducing postoperative knee hemarthrosis after arthroscopic anterior cruciate ligament reconstruction: A randomized double-blind controlled trial

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ABSTRACT

Introduction: Early postoperative hemarthrosis and knee swelling may occur following arthroscopic anterior cruciate ligament (ACL) reconstruction. The use of epinephrine in combination with tranexamic acid (TXA) may help reduce postoperative hemarthrosis.

Objective: To evaluate the efficacy of intra-articular tranexamic acid alone versus tranexamic acid plus epinephrine in reducing postoperative knee hemarthrosis after arthroscopic anterior cruciate ligament reconstruction in reducing postoperative hemarthrosis.

Methods: A double-blind randomized controlled trial was conducted in patients undergoing arthroscopic anterior cruciate ligament (ACL) reconstruction at Nakornping Hospital between June 21, 2021, and June 20, 2022. Patients were allocated into two groups: the intra-articular TXA group (n = 26) and the intra-articular TXA plus epinephrine group (n = 26). The primary outcome was drain output volume at 24 hours postoperatively. Secondary outcomes included drain output volume at 48 hours, pain intensity assessed using the Visual Analog Scale (VAS), change in hemoglobin level, mid-patellar circumference, knee range of motion, Lysholm score, International Knee Documentation Committee (IKDC) score, hemarthrosis grading, and calf circumference.

Results: The proportions of male patients in the TXA group and the TXA plus epinephrine group were 80.8% and 92.3%, respectively. The mean ages were 30.23 ± 10.99 and 28.61 ± 10.89 years. The most common surgical procedure was ACL reconstruction with meniscus repair (73.08% and 57.69%, respectively). At 24 hours postoperatively, the mean drain output volumes were 90.38 ± 58.27 mL in the TXA group and 65 ± 38.94 mL in the TXA plus epinephrine group ($p = 0.123$). At 48 hours, the mean drain output volumes were 148.46 ± 83.46 mL and 113.85 ± 60.80 mL, respectively ($p = 0.069$). The mean VAS scores at 24 hours postoperatively were 6.15 ± 1.43 and 5.23 ± 1.61 ($p = 0.034$). The increase in mid-patellar circumference at 24 hours was 2.15 ± 0.88 cm and 1.63 ± 0.82 cm, respectively ($p = 0.032$). No statistically significant differences were observed in other secondary outcomes.

Conclusion: Intra-articular TXA combined with epinephrine following arthroscopic ACL reconstruction tended to reduce postoperative drain output volume; however, the difference was not statistically significant. Further studies are warranted to confirm these findings. Thai Clinical Trial Registry number TCTR20211124002.

Keywords: anterior cruciate ligament reconstruction, epinephrine, tranexamic acid, intra-articular injection

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Introduction

Anterior cruciate ligament (ACL) injury occurs at a rate of 68.6 per 100,000 persons annually, with a higher incidence in males.^[1] Arthroscopically assisted ACL reconstruction (ACLR) is the standard surgical treatment. However, postoperative hemarthrosis remains a recognized complication, occurring in approximately 3–10% of cases.^[2] Hemarthrosis may delay rehabilitation, increase pain, and occasionally require joint aspiration, thereby increasing the risk of infection and healthcare costs.^[2–5]

Tranexamic acid (TXA), an antifibrinolytic agent, inhibits plasmin formation and reduces fibrinolysis. TXA administration has been shown to decrease postoperative bleeding and transfusion requirements without increasing thromboembolic risk in orthopedic surgery.^[6] Epinephrine enhances local hemostasis through vasoconstriction and platelet aggregation.^[7,8]

Both intravenous and intra-articular routes of TXA are effective in reducing hemarthrosis after ACLR, although intravenous administration may provide greater reduction in postoperative bleeding.^[9–12] Despite its use, residual postoperative hemarthrosis and swelling may still occur. In total knee arthroplasty, intra-articular epinephrine—alone or combined with TXA—has been associated with reduced postoperative blood loss without increased complications.^[13–16] However, evidence regarding its adjunctive use in ACL reconstruction remains limited.

Therefore, this study aimed to determine whether the addition of intra-articular epinephrine to TXA reduces postoperative hemarthrosis following ACL reconstruction.

Study Design and Setting

A double-blind randomized controlled trial was conducted at Nakornping Hospital, Chiang Mai, Thailand, in patients with arthroscopically assisted ACL reconstruction between June 21, 2021, and June 20, 2022. This research was approved by Nakornping Hospital Ethics Committee for Research Involving Human Subjects, approved date June 21, 2021, and the study registration number was TCTR20211124002 in the Thai Clinical Trial Registry. Before being enrolled in the study, all patients provided written informed consent.

Patient sample and data collection

Patients who underwent primary single-bundle ACL reconstruction using a hamstring autograft with or without meniscal surgeries at Nakornping Hospital from June 21, 2021, to June 20, 2022, were included in the study. Inclusion criteria were aged ≥ 18 years and provision of informed consent. Exclusion criteria included the use of other grafts (e.g., allograft, bone–patellar tendon–bone autograft), revision ACL reconstruction, concomitant knee cartilage or collateral ligament surgeries, history of knee surgery on the affected knee, concomitant fracture, significant preoperative pain (visual analog scale [VAS] score > 5),

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coagulation or bleeding disorders, preoperative anticoagulation treatment, and history of tranexamic acid or epinephrine allergy.

Demographic data including age, sex, BMI, site of injury, time from injury, type of surgery, VAS score, range of motion, patellar circumference, and Lysholm score were collected.

After obtaining informed consent, all enrolled patients were randomly allocated into two groups: the intra-articular tranexamic acid injection group (IA TXA group) and the intra-articular tranexamic acid plus epinephrine injection group (IA TXA + Epi group). Randomization was performed using a web-based randomization program (Sealed Envelope Ltd., London, UK).^[17] with a pre-specified seed (239895118402080) and variable block sizes of 4, 6, and 8 to ensure balanced allocation.

Protocols for surgery

All patients underwent primary single-bundle arthroscopic anterior cruciate ligament reconstruction using a hamstring autograft under spinal anesthesia. Prophylactic intravenous cefazolin (1 g) was administered preoperatively. Standard arthroscopic techniques were used, and concomitant meniscal procedures were performed when indicated. Graft fixation was achieved using an all-inside technique with cortical suspensory fixation.

A Radivac drain was placed intra-articularly before wound closure. The

study medication was prepared by operating room nurses to maintain blinding. The surgeon and the patients were blinded to group allocation throughout the study. The control group (IA TXA) received intra-articular tranexamic acid (15 mg/kg diluted to 50 mL normal saline), whereas the intervention group (IA TXA + Epi) received tranexamic acid (15 mg/kg) plus 0.25 mg epinephrine (1:200,000), diluted to 50 mL (Figure 2). The solution was injected via the drain line, which was clamped for 2 hours. Postoperative outcomes were recorded using standardized assessment protocols.

Outcome Measurement

The primary outcome was drain output volume (mL) measured at 24 hours postoperatively. The secondary outcomes included drain output volume at 48 hours postoperatively; change in hemoglobin level, defined as the difference between preoperative hemoglobin and the value measured at 24 hours postoperatively; knee range of motion (ROM), measured in degrees using a goniometer; mid-patellar circumference (cm), measured at the midpoint of the patella using a measuring tape; pain intensity assessed using a 10-point Visual Analog Scale (VAS); Lysholm knee score; International Knee Documentation Committee (IKDC) subjective knee score; hemarthrosis grading at 72 hours postoperatively according to the Coupens and Yates classification; calf

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circumference (cm), measured at the point of maximal calf diameter.

Statistical Analysis

The sample size was estimated based on the formula for continuous data derived from the research of Rui^[12] in TKA patients, where it was found that the use of IA epinephrine with tranexamic acid can significantly reduce total blood loss compared to patients receiving only IA tranexamic acid, by approximately 20%. Therefore, it was anticipated that the mean in the intervention group would decrease by about 20% compared to the control group.

Since the sample size was calculated to be 51 individuals per group and the estimated dropout rate from the project is approximately 20%, the sample size was increased to 62 individuals per group. Thus, the total sample size in this project is 124.

For data analyses, intention-to-treat strategies were applied. Continuous variables were compared using independent t-tests. For non-normally distributed data, median, interquartile range, maximum, and minimum values were used, and the rank sum test was performed. Fisher's exact probability test was used to analyze categorical variables.

All analyses were performed using Stata Statistical Software, version 16.^[18] A two-sided p-value < 0.05 was considered statistically significant.

Results

The baseline characteristics of the study participants were comparable between the two groups, as shown in Table 1. The primary outcomes were presented in Figure 1 and Table 2. The drain output volumes between the two groups were compared using the independent t-test.

Table 1 Patient demographics and baseline characteristics

Characteristics	IA TXA group (n=26)	IA TXA + Epi group (n=26)	p-value
Male, n (%)	21 (80.8%)	24 (92.3%)	0.419
Age, years, mean ± SD	30.23 ± 10.99	28.61 ± 10.89	0.965
Surgical procedure, n (%)			0.401
ACLR only, n (%)	5 (19.23%)	10 (38.46%)	
ACLR + Partial meniscectomy, n (%)	2 (7.69%)	1 (3.85%)	
ACLR + meniscus repair, n (%)	19 (73.08%)	15 (57.69%)	
VAS score, mean ± SD	0.88 ± 1.48	1.11 ± 1.18	0.536
Knee flexion ROM (degrees), mean ± SD	123.46 ± 6.29	123.27 ± 7.61	0.921
Knee extension ROM (degrees)	0	0	NA
Patellar circumference (cm), mean ± SD	37.85 ± 2.43	38.42 ± 3.42	0.486
Lysholm knee score, mean ± SD	75.46 ± 14.04	71.73 ± 14.99	0.359
IKDC score, mean ± SD	50.11 ± 11.60	48.69 ± 7.71	0.605

ACLR, anterior cruciate ligament reconstruction; VAS, visual analog scale; ROM, range of motion; IKDC, International Knee Documentation Committee.

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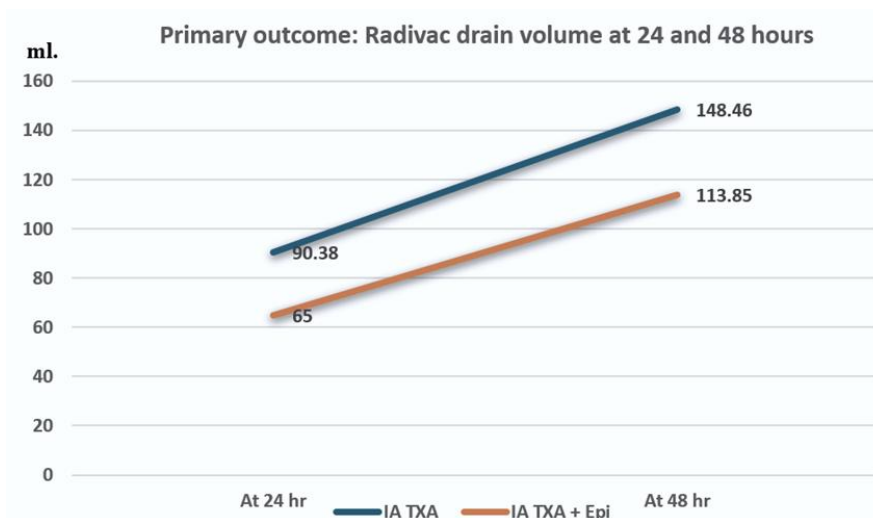


Fig.1 Drain output volume (mL) at 24 and 48 hours postoperatively

Table 2 Primary outcome

	IA TXA group (n=26)	IA TXA + Epi group (n=26)	p-value
Drain output volume at 24 hr. (mL)	90.38 ± 58.27	65 ± 38.94	0.123
Drain output volume at 48 hr. (mL)	148.46 ± 83.46	113.85 ± 60.80	0.069

In the control group, the mean drain output volume was 90.38 ± 58.27 mL at 24 hours postoperatively and 148.46 ± 83.46 mL at 48 hours. In the intervention group, the mean drain output volume was 65 ± 38.94 mL at 24 hours and 113.85 ± 60.80 mL at 48 hours. Although the drain output volume was lower in the intervention group compared with the control group, the differences were not statistically significant ($p = 0.123$ at 24 hours and $p = 0.069$ at 48 hours).

At 24 hours postoperatively, the intervention group demonstrated

significantly lower Visual Analog Scale (VAS) scores ($p = 0.034$) and mid-patellar circumference ($p = 0.032$) compared with the control group.

However, no significant differences were observed between the two groups at other time points. Additionally, no significant differences were found in hemoglobin level change, range of motion, Lysholm knee score, International Knee Documentation Committee (IKDC) score, hemarthrosis grading, or calf circumference, as shown in Table 3.

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Table 3 Secondary outcomes

Outcomes	IA TXA group (n=26) mean $\pm$ SD	IA TXA+Epi group (n=26) mean $\pm$ SD	p-value
Change in hemoglobin level (g/dL)			
24 hr. post operatively	1.07 $\pm$ 0.67	0.85 $\pm$ 0.45	0.241
Change in mid-patellar circumference (cm)			
24 hr. post operatively	2.15 $\pm$ 0.88	1.63 $\pm$ 0.82	0.032
48 hr. post operatively	1.69 $\pm$ 0.93	1.38 $\pm$ 0.75	0.285
72 hr. post operatively	1.05 $\pm$ 0.88	0.79 $\pm$ 0.97	0.236
Lysholm knee score			
2 wk. post operatively	45.35 $\pm$ 19.61	39.88 $\pm$ 18.63	0.313
6 wk. post operatively	55.52 $\pm$ 14.91	55.32 $\pm$ 11.67	0.958
12 wk. post operatively	71.87 $\pm$ 13.32	72.04 $\pm$ 10.62	0.961
International Knee Documentation Committee (IKDC) score			
2 wk. post operatively	28.61 $\pm$ 7.55	27.36 $\pm$ 8.92	0.589
6 wk. post operatively	40.40 $\pm$ 6.77	38.28 $\pm$ 9.93	0.382
12 wk. post operatively	50.96 $\pm$ 9.34	51.28 $\pm$ 11.63	0.916
Visual analog scale (VAS, 0-10)			
24 hr. post operatively	6.15 $\pm$ 1.43	5.23 $\pm$ 1.61	0.034
48 hr. post operatively	3.92 $\pm$ 1.29	3.50 $\pm$ 1.61	0.300
72 hr. post operatively	2.11 $\pm$ 0.91	1.96 $\pm$ 1.15	0.594
Hemarthrosis grading (Coupens and Yates) 72 hr. post operatively			
0	1 (3.85%)	4 (15.38%)	0.305
1	22 (84.62%)	21 (80.77%)	
2	3 (11.54%)	1 (3.85%)	
Change in calf circumference (cm)			
72 hr. post operatively	0.27 $\pm$ 0.45	0.27 $\pm$ 0.45	1.00

Discussion

The results of this study evaluated the effect of adjunctive intra-articular epinephrine combined with tranexamic acid on postoperative outcomes following arthroscopic ACL reconstruction. In our investigation, we observed trends in drain output volume and various clinical parameters between the control group, which received intra-articular (IA) tranexamic acid alone, and the intervention group, which received IA tranexamic acid along with low-dose epinephrine.

Our findings regarding drain output volume at 24- and 48-hour postoperatively revealed a trend towards reduced drainage in the intervention group compared to the control group. Despite the lower drain output volume observed in the intervention group, this difference did not reach statistical significance. While this result may suggest a potential benefit of epinephrine in reducing postoperative fluid accumulation, further studies with larger sample sizes are warranted to confirm these findings conclusively.

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Interestingly, our study uncovered significant differences in certain clinical parameters at the 24 hours postoperatively. The intervention group exhibited a notable decrease in both Visual Analog Scale (VAS) scores and patellar circumference compared to the control group. This suggests that patients who received the combined therapy experienced less pain and swelling early in the postoperative period. These findings underscore the potential synergistic effects of epinephrine and tranexamic acid in enhancing early recovery outcomes following ACLR surgery. Intra-articular interventions have also been explored for pain control following ACL reconstruction.^[19]

Furthermore, previous studies have reported that the combination of epinephrine and tranexamic acid may

reduce perioperative blood loss in orthopedic surgery. In total knee arthroplasty, Gao et al. demonstrated that topical tranexamic acid combined with diluted epinephrine significantly reduced postoperative hidden blood loss compared with tranexamic acid alone.^[14] Similarly, Zeng et al. reported that low-dose epinephrine combined with tranexamic acid reduced early postoperative blood loss and inflammatory response in primary TKA patients.^[15] A systematic review by Wu et al. also demonstrated that this combination therapy may reduce blood loss without increasing complications.^[16] A comparison of previous studies evaluating the combined use of tranexamic acid and epinephrine in orthopedic surgery is summarized in Table 4.

Table 4 Comparison of previous studies on combined tranexamic acid and epinephrine use in orthopedic surgeries

Study	Study design	Population	Intervention	Control	Outcome	Main findings
Gao et al. ^[14]	RCT	TKA	TXA + Epi	TXA alone	Blood loss	Reduced hidden blood loss
Zeng et al. ^[15]	RCT	TKA	TXA + Epi	TXA alone	Blood loss	Reduced early blood loss
Wu et al. ^[16]	Systematic review	Orthopedic procedure	TXA + Epi	TXA alone	Blood loss	Reduced blood loss
Present study	Randomized double-blind controlled trial	ACL reconstruction	IA TXA + Epi	IA TXA	Drain output volume	Lower drain output volume (NS)

Abbreviations: TXA, tranexamic acid; IA, intra-articular; Epi, epinephrine; TKA, total knee arthroplasty; ACL, anterior cruciate ligament; NS, not statistically significant.

However, evidence regarding the use of epinephrine as an adjunct to tranexamic acid in ACL reconstruction remains limited, and the present study

contributes additional evidence in this clinical setting. Importantly, no significant differences were observed between the two groups

at other time points or in various secondary outcome measures, including hemoglobin levels, range of motion, Lysholm score, International Knee Documentation Committee (IKDC) score, hemarthrosis grading, and calf circumference. These results suggest that while combined therapy may offer benefits in terms of early pain relief and swelling reduction, its impact on overall functional outcomes and long-term recovery remains uncertain.

Several factors may have contributed to the lack of statistically significant differences observed in our study. These include the relatively small sample size, variations in patient demographics and surgical techniques, and the short-term follow-up period. Additionally, the heterogeneity of ACLR patients and the multifactorial nature of postoperative recovery may have influenced our results.

Further research with larger sample sizes and longer follow-up durations is needed to fully elucidate the potential clinical implications of this combination

of therapy. These findings contribute to the growing body of literature on perioperative management strategies in ACLR surgery and may inform clinical decision-making regarding optimal treatment approaches for improving patient outcomes.

Conclusion

Our study provides preliminary evidence suggesting that the adjunctive use of epinephrine with tranexamic acid in ACLR surgery did not reduce postoperative drain output volume compared with intra-articular tranexamic acid alone on postoperative day 1. Other benefits in terms of early pain management and swelling reduction may need to be validated in the future.

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การศึกษาเปรียบเทียบประสิทธิภาพในการลดภาวะเลือดออกในข้อเข่าระหว่างกลุ่มที่ได้รับการฉีดเฉพาะ Tranexamic acid กับกลุ่มที่ได้รับการฉีด Tranexamic acid ร่วมกับ Epinephrine เข้าข้อเข่าภายหลังการผ่าตัดส่องกล้องบูรณะเส้นเอ็นไขว้หน้า: การทดลองแบบสุ่มมีกลุ่มควบคุมชนิดปกปิดสองฝ่าย

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