Treatment of Idiopathic Menorrhagia with Tranexamic Acid

Sukanya Srinil MD*,
Unnop Jaisamrarn MD, MHS*

* *Department of Obstetrics and Gynecology, Faculty of Medicine,Chulalongkorn University*

Objective: *To determine the efficacy of tranexamic acid in the treatment of idiopathic menorrhgia and to investigate the effect of medical treatment with tranexamic acid on the quality of life of the women with idiopathic menorrhagia.*
Design: *Open, non-comparative study.*
Setting: *Department of Obstetrics and Gynecology King Chulalongkorn Memorial Hospital*
Subjects: *40 women with idiopathic menorrhagia was confirmed by menstrual blood loss greater than 80 ml/ cycle (PBAC score > 100) and mid-luteal serum progesterone concentration greater than 5 pg/ml.*
Intervention: *Treatment with tranexamic acid 1 g orally, three times daily, for five days from day 1 of the menstruation for two consecutive menstrual periods.*
Main outcome measures: *Menstrual blood loss was measured using the pictorial blood loss assessment chart (PBAC). Hematological assessments were made at the beginning, after the first treatment cycle and at the end of the study. Questionnaires were given to assess subjective endpoint, quality of life. Patients were asked to report any adverse event during the study period.*
Results: *Tranexamic acid reduces the mean PBAC score by 49%, from 350.5 to 178.6. Regarding the change in the quality of life measures, the proportion of women who felt a considerable degree of impairment during the menstruation was reduced from nearly 60% to less than 5% during their third menstruation. No serious adverse events were reported.*
Conclusion: *Tranexamic acid is a safe and effective form of medical therapy in women with menorrhagia; also increases quality of life in these women.*

Keywords: *Menorrhagia, Idiopathic, Tranexamic acid, Quality of life*

J Med Assoc Thai 2005; 88 (Suppl 2): S1-6
Full text. e-Journal: *http://www.medassocthai.org/journal*

Menorrhagia, defined as a complaint of heavy menstrual bleeding over several consecutive cycles, affects approximately 10% of healthy women during their reproductive year[1]. It is objectively defined as a total menstrual blood loss greater than or equal to 80 ml per cycle. Apart from its social inconvenience, menorrhagia can cause anemia which may be difficult to combat even with continuous iron therapy may ultimately necessitate hysterectomy[2]. About half of the women who proceed to receive hysterectomy for their heavy bleeding have got their normal uteruses. In about 40% of patients with menorrhagia, local pelvic pathology such as uterine fibroids have been identified as the etiology. In other systemic diseases, such as bleeding disorders, may be their underlying problems but the rest suffer from idiopathic menorrhagia with increasing fibrinolysis, or endometrial prostaglandin imbalance[3].

It has been reported that long-term treatment of menorrhagia may be difficult and have wide variations in the drugs prescription for this condition showing a lack on consensus formedical treatment[4]. Antifibrinolytic drugs are effective in decreasing excessive menstrual bleeding by inhibiting the binding of plasminogen to fibrin filaments, which prevents clot dissolution[5].

Correspondence to : Srinil S, Department of Obstetric & Gynecology, Faculty of Medicine, Chulalongkorn University, Rama IV Rd, Bangkok 10330, Thailand. Phone: 0-2256-4241, Fax: 0-2250-1320

At present, tranexamic acid has been suggested to be a first-line drug for treatment of regular ovulatory menorrhagia, if the women prefer a non-hormonal treatment in some western countries,[6]such as in the UK and Scandinavia. The efficacy of tranexamic acid has been shown in some trials and reported in western countries. However, methodological limitation of several studies were of small sample sizes and the ethnical difference of the treatment should be considered. In addition there has been no study of the efficacy and acceptability of tranexamic acid in Thai women.

The purpose of this study was to determine the efficacy of tranexamic acid in the treatment of heavy menstrual bleeding in Thai women, objectively documented as idiopathic menorrhagia.

Quality-of-life assessment was another endpoint, i.e., to investigate whether or not medical treatment of tranexamic acid would increase the quality of life of women with heavy menstrual bleeding.

Material and Method

From May 2004 to November 2004, women attending the Gynecological Clinic at King Chulalongkorn Memorial Hospital, aged 18-45 with complaint of heavy regular : 21-35 days cycles mens and no history of systemic disease such as platelet disorder or coagulopathies related to menorrhagia, previous history of thromboembolic disease, renal or hepatic impairment and acquired disturbances of color vision, pregnancy and no concomitant use of oral contraceptives or NSAID (including aspirin) were recruited into this study. All women had to receive pelvic examination and transvaginal ultrasonography and they would be excluded if they had any pelvic pathology. All of them gave informed consent in written document. The study has been approved by the Ethics Committee, Faculty of Medicine, Chulalongkorn University.

Menstrual blood loss (MBL) was measured each cycle using the pictorial blood loss assessment chart (PBAC)[7] : a method that correlates well with the alkaline haematin test[8]. The women were asked to use certain sanitary pads which have been shown to have similar absorbent capacities. During their menstruation, they were requested to record the quantity of the sanitary pads used each day, the degree of soiling of each pad, the number and size of clot passed. Scores were assigned to the different degrees of sanitary product soiling and clot size (Table 1). A PBAC score of greater than 100 indicated a menstrual blood loss greater than 80 ml and was considered diagnosis for menorrhagia.

Table 1. PBAC Scoring

Pads :	Lightly soiled	1
	Moderately soiled	5
	Saturated	20
Clots :	Small (size of a nickel or smaller)	1
	Large (larger than nickel)	5

Reference: Higham JM, et al. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990; 97: 734-9

Intravenous blood of all patients were taken at 5-9 days before their menses for a test of mid luteal phase serum progesterone in baseline cycle.

MBL in excess 80 ml/cycle (PBAC>100) and mid luteal phase serum progesterone level greater than 5 pg/ml, was objectively documented ovulatory menorrhagia or idiopathic menorrhagia[9]. The patients received treatment with tranexamic acid 1 g orally three times daily throughout day one to five of each menstrual period for two consecutive menstrual cycles.

The medication was supplied in individual pack for each subject and their compliance was checked by counting the remaining tablets after each course of treatment. No additional medication was allowed and women did not receive iron supplementation during the study.

The venous concentration of hemoglobin was measured upon their entry, after first treatment cycle and at the of the study.

Measurements of MBL during baseline cycle was compared to two consecutive treatment cycles and one post-treatment cycle. The subjects were requested to record the details of their menstrual cycle: date of start, duration of menstruation, possible intermenstrual bleeding, subjective assessment of menstrual flow and any side effects. As a part of the baseline investigations, all subjects were asked to rate their MBL as “heavy”, “normal”, or “slight”. During re-visit and final visit, the subjects were also asked whether they judged their menstrual blood loss to increased or decreased by the treatment received.

The data registered during the baseline visit, the re-visit and the final visit focused primarily on the effect of the treatment and safety of the therapy. The quality of life and their subjective experiences state of health in their social activities, i.e., at work, tiredness, productivity, appetite and overall well-being were assessed by using the four-graded questions (1:not impaired; 4: very impaired). The questionnaire was developed on the basis of results presented by

Edlund et al[10].

Statistical analysis

The results are expressed as mean ± SD Wilcoxon Signed Ranks Test (non parametric version of the paired t test) was used to test the statistical significance of the difference in pretrial and post-trial average PBAC scores.

The difference in the pretrial and post-trial hemoglobin concentrations and rating score in quality of life were analyzed using a paired t test. Statistics were generated using SPSS for Windows, Release 10.0.5, SPSS Inc.

Results

Forty patients recruited into the study had objective evidence of menorrhagia. The average age was 34.6 years (range = 24.0-45.0 yr). The average body mass index (BMI) was 22.9 (range = 18.5-27.6).

The mean PBAC scores during the baseline period was 350.5± 113.9 (range, 137.0 to 657.0) decreasing to 261.0 ± 133.11 (range, 94.0 to 602.0), 178.6 ±106.3 (range, 25.0 to 523.0) in the first and second cycle of treatment, respectively. The beneficial effect of tranexamic acid was evident from the first treatment cycle, and the reduction in mean PBAC score during treatment with tranexamic acid was significant ($p<0.0001$, Wilcoxon Ranks Test). This represented a 49% decrease in the mean of menstrual blood flow after two cycles of treatment.

The mean PBAC score during the medication-free, post-treatment menstrual cycle, was 188.0±118.3 (range, 13.0 to 460.0); it also was significantly reduced by 46.1% from the baseline ($p<0.0001$, Wilcoxon Signed Ranks Test). Mean pre- and post-treatment PBAC scores are shown in Fig. 1.

Treatment with tranexamic acid did not alter the duration of the menstrual flow and there were no reported episodes of intermenstrual bleeding. A significant reduction in number of sanitary pads used was found in patients treated with tranexamic acid ($p<0.002$, mean sanitary pads used from 27 to 17 pads/cycle). The mean hemoglobin concentration during the pre-treatment cycle (12.0±1.2 mg/dl) did not differ significantly from the mean hemoglobin concentration during post-treatment cycle (11.9±1.2 mg/dl).

Menstrual flow was reported to be heavy by all patients in the pre-treatment cycle and in the post-treatment cycle; eighteen patients (90%) thought their menstrual loss was less. None of them complained of any side effects during their treatment.There was no patient discontinued their therapy.

The results of the rating of the effect of treatment on quality of life and subjectively experienced state of health are presented in Fig. 2 and 3.

Treatment with tranexamic acid changed the investigated quality-of-life parameters. The Proportion of women who felt a considerable degree of impairment during their menstruation (rating 4) was reduced from nearly 80% at the baseline to less than 5% during the post-treatment cycle. These reductions are statistically highly significant ($p<0.001$). There was a corresponding marked increase in the proportion of women who felt unaffected or little affected (rating1, 2) by their menstruation (Fig. 3).

Discussion

Tranexamic acid is a synthetic derivative of the amino acid lysine. It produces an antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. It has been widely used in multiple setting of body system for blood loss,

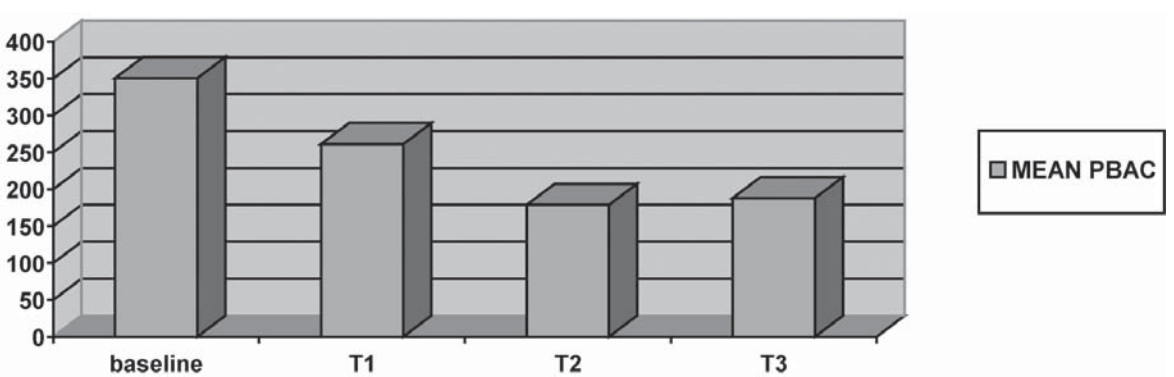

Fig. 1 Mean PBAC scores during each cycle (T1,2,3: Treatment cycles 1,2 and 3)

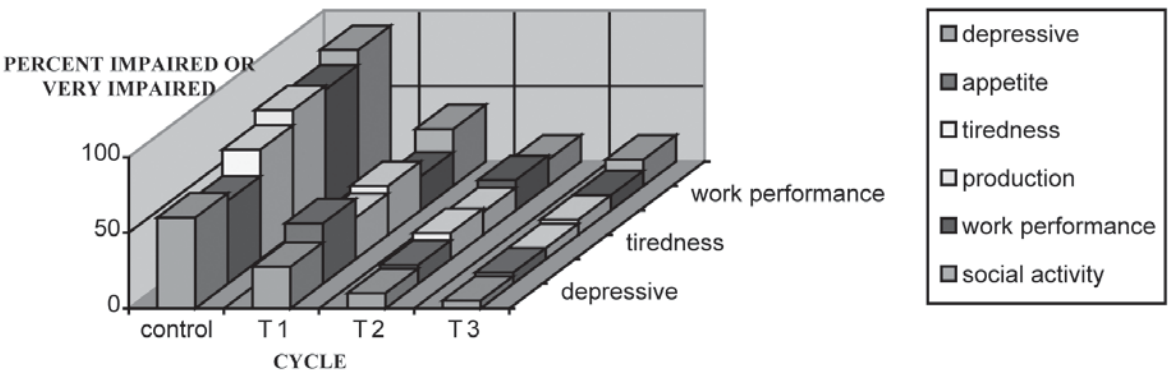

Fig. 2 Effect of tranexamic acid treatment on the percentage of women rating themselves impaired and very impaired in various quality of life aspects during menstruation

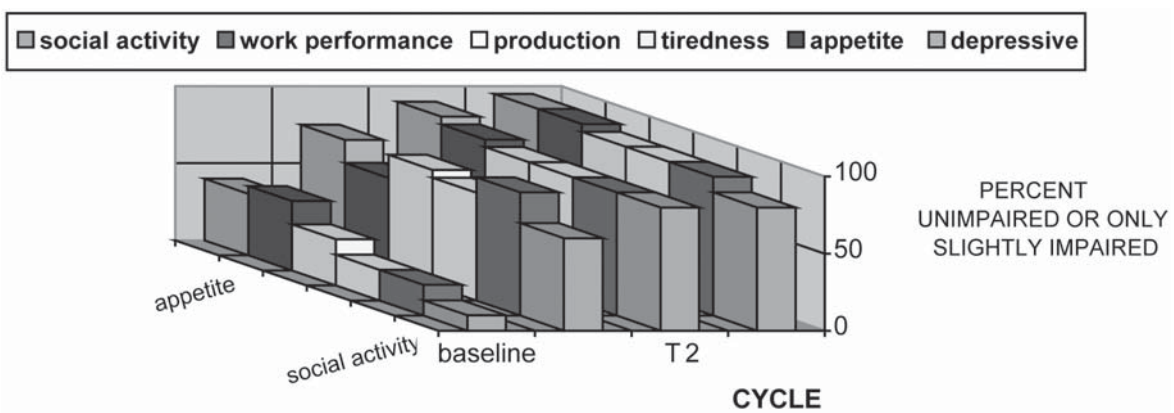

Fig. 3 Effect of treatment on the percentage of women rating themselves unimpaired in or only slightly impaired in various quality of life aspects during menstruation

including cardiac surgery, gastrointestinal bleeding and many conditions of obstetrics and gynecology. These drug has been used successfully to control blood loss and resulting in a decrease of the requirement for blood transfusion[11].

The use of tranexamic acid for menorrhagia is limited in Thailand even though it has been shown to be one of the most effective treatments. The resent of present trial agree with other meta-Analysis[12] of seven studies that showed a 47 percent reduction in menstrual blood loss with tranexamic acid compared to pre-treatment levels. From the available evidences, antifibrinolytics appear to be more effective than placebo, NSAIDs, luteal phase oral progestagens, and ethamsylate[13]. Tranexamic acid and NSAIDs reduce menstrual blood loss by about one-half and one-third, respectively[14].

Our study confirms the efficacy of tranexamic acid in the treatment of idiopathic menorrhagia. Tranexamic acid reduced the average menstrual blood loss per cycle from mean baseline PBAC score 350.5 to 178.6 at second treatment cycles ($p<0.0001$). The reduction in the mean PBAC score by 46.1% of medication-free menstrual cycle (third cycle after treated) has also been shown statistically significant ($p<0.0001$) compared with the baseline cycle. However, the mechanism of this effect in medication-free menstrual cycle cannot be clearly understood. The baseline values recorded in this study show the significant impact of the heavy menstrual bleeding on the quality of life of women with this ailment. This leads to an overall feeling of impairment owing to the menstrual bleeding in almost 60% of the women with heavy menstrual bleeding. The results of the present study clearly demonstrate that effective medication treatment of heavy menstrual bleeding brings about a significant

improvement in the quality of life of the majority of the women. This favourable effect of tranexamic acid on the quality of life is a consequence of the reduction in menstrual blood flow by the treatment. The great majority of the women in the present study also perceived their menstrual blood loss to be reduced by the treatment.

The dose of tranexamic acid used in this study is presently used in clinical practice and has previously been shown to be optimal for the effective treatment of idiopathic menorrhagia[15]. Higher doses of tranexamic acid have been shown to reduce menstrual blood loss even more, but they are unfortunately associated with an increased frequency of side effects, such as nausea and gastric irritation.

Tranexamic acid appears to be well tolerated with side effects generally limited to mild gastrointestinal complaints, including nausea and vomiting or diarrhea. None of our patients developed any side effects or thrombotic complications. Rybo (1991)[16] reported that during the period 1969 to 1987, the rate of thromboembolism in women being treated for menorrhagia with tranexamic acid was not higher than the reported spontaneous rate in the fertile women.

There is no doubt that hysterectomy is a highly effective way of treating menorrhagia, but operative morbidity and long-term morbidity cannot be considered to be insignificant. Can hysterectomy be justified if an alternative and simpler treatment form become available? Tranexamic acid given during menstruation is a safe and highly effective treatment for excessive bleeding. Patients with idiopathic menorrhagia should be offered a medical treatment with tranexamic acid before surgery.

In research studies, the gold standard for objectively measuring menstrual blood loss remains the alkaline haematin test. This test involves the collection of all sanitary materials and soaking them in sodium hydroxide or detergent for 48 hours. Menstrual blood is determined by comparing the optical density of this extraction solution to a sample of the women's venous blood. We decided to use the PBAC because it is simpler, less time-consuming and has no requirement of sanitary product collection. This method records the number of pads and tampons used, and grades the degree of staining. PBAC scores and menstrual blood loss (ml) were highly correlated (r=0.847), making this pictorial chart an effective alternative to the costly chemical assay. A PBAC score of greater than or equal to 100, when used as a diagnostic test for menorrhagia, was found to have a sensitivity of 86 percent and a specificity of 89 percent comparing to the alkaline haematin method[7].

Methodological limitations in the present study include the small sample size and the absence of blinding, so a certain placebo effect cannot be excluded. Randomized controlled trials with larger numbers are needed to compare the antifibrinolytics to other medical therapies, such as the combined oral contraceptive pill, the levonorgestrel releasing intrauterine system, oral progestagens taken, and mefenamic acid.

References

1. Hallberg L, H^gdahl A-M, Nillsson L, Rybo G. Menstrual blood loss: a population study. Acta Obstet Gynaecol Scand 1966;45:320-51.
2. Cohen BJB, Gibor Y. Anemia and menstrual blood loss. Obstet Gynecol Surv 1980;35:597-618.
3. Clarke A, Black N, Rowe P, Mott S, Howle K. Indications for and outcome of total abdominal hysterectomy for benign disease:a prospective cohort study. Br J Obstet Gynaecol 1995;102:611-20.
4. Coulter A, Kelland J, Peto V, Rees MC. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. Int J Tech Assess Health Care 1995;11:456-71.
5. Vermylen J, Verhaegen-Declercq ML, Verstraete M, Fierens F. A double blind study on the effect of tranexamic acid in essential menorrhgia, Thromb Diath Haemorrh 1968;20:583-7.
6. Sally Hope. 10-minute consultation menorrhagia. BMJ 2000;321:935.
7. Higham JM, 0'Brien PMS, Shaw RW. Asessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990;97:734-9.
8. Hallberg L, Nillsson L. Determination of menstrual blood loss. Scand J Clin Lab Invest 1964;16:244-8.
9. Mishell DR Jr, Stenchever MA, Droegemueller W, Herbst AL. Abnormal uterine bleeding: ovulatory and anovulatory dysfunctional uterine bleeding, management of acute and chronic excessive bleeding. In: Mishell DR, Stenchever MA, Droegemueller W, Herbst AL,editors. Comprehensive gynae-cology, 3rd ed. St. Louis: Mosby-year book, 1997:1025-42.
10. Edlund M, Magnusson C, Von Schoultz B. Quality of life- a Swedish survey of 2200 women. Key Papr Conference (published by the Royal Society of Medicine Press Limited) 1994;1:36-7.
11. Wellington K, Wagstaff JA. Tranexamic acid: a review of its use in the management of menorrhagia. Drug 2003;63:1417-33.

12. Cooke I, Lethaby A, F arquhar C. Antifibrinolytic for heavy menstrual bleeding (Cochrane Review). In: The Cochrane Library,Issue 3,2000. Oxford: Update Software.
13. Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. Br J Obstet Gynaecol 1995;102:401-6.
14. Bonnar J, Sheppard BL. Treatment of menorhagia during menstruation: randomized controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. BMJ 1996;313 :579-82.
15. Lee YJ, Hahn PM, Dijk JPV, Reid RL. Treatment of menorrhagia with tranexamic acid. J Soc Obstet Gynecol Can 2000;22:794-8.
16. Rybo G. Tranexmic acid herapy: effective treatment in heavy menstrual bleeding. Clinical update on safety. Therapeutic Advances 1991; 4 : 1-8.

การศึกษาผลของการรักษาภาวะเลือดระดูออกมากกว่าปกติโดยไม่ทราบสาเหตุด้วยยากรด-ทรานเนซามิค

สุกัญญา ศรีนิล, อรรณพ ใจสำราญ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยากรดทรานเนซามิค และผลของการรักษาด้วยยานี้ต่อคุณภาพชีวิตของผู้ป่วยภาวะเลือดระดูออกมากกว่าปกติ โดยไม่ทราบสาเหตุ*

รูปแบบการวิจัย: *การวิจัยเชิงทดลองทางคลินิก*

สถานที่: *ภาควิชาสูติศาสตร์-นรีเวชวิทยาคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

ผู้ป่วยที่ได้ทำการศึกษา: *ผู้ป่วยที่มีภาวะเลือดระดูออกมากกว่าปกติ โดยไม่ทราบสาเหตุ ได้รับการตรวจยืนยันโดยการประเมินปริมาณเลือดระดูจากแบบบันทึกปริมาณเลือดระดู มีคะแนนมากกว่า 100 ผลตรวจร่างกายและตรวจภายในปกติ และระดับฮอร์โมนโปรเจสเตอโรนในเลือดช่วงวันที่ 5 ถึงวันที่ 9 ก่อนมี เลือดระดู มีค่ามากกว่า 5 นาโนกรัมต่อมิลลิลิตร ผู้ป่วยไม่มีข้อห้ามในการใช้ยา*

วัสดุและวิธีการ: *ผู้ป่วยที่มีภาวะเลือดระดูออกมากกว่าปกติ โดยไม่ทราบสาเหตุ จำนวน 40 คน ได้รับการรักษาด้วยการรับประทานยากรดทรานเนซามิค ขนาด 1 กรัม วันละ 3 ครั้ง เริ่มรับประทานตั้งแต่วันแรกถึงวันที่ 5 ของรอบระดูนานติดต่อกัน 2 รอบระดู ผู้ป่วยทุกคนได้รับการตรวจความเข้มข้นเลือดก่อนเข้ารับการศึกษาระหว่างรับการศึกษา และเมื่อสิ้นสุดการศึกษาเก็บข้อมูลเกี่ยวกับลักษณะทั่วไปของผู้ป่วย ให้ผู้ป่วยบันทึกแบบประเมินปริมาณเลือดระดูที่ออก ตอบแบบสอบถามที่ทำขึ้นเพื่อประเมินผลการรักษา ผลข้างเคียงจากยา และคุณภาพชีวิตหลังได้รับการรักษาด้วยตนเอง*

ผลการศึกษา: *ยากรดทรานเนซามิค ลดปริมาณเลือดระดูได้ร้อยละ 49 โดยศึกษาจากค่าเฉลี่ยของคะแนนแบบบันทึกการประเมินเลือดระดูที่ออกในรอบก่อนให้การรักษา 350.5 ลดลงเหลือ 178.6 ภายหลังให้การรักษา ผลของการรักษาต่อคุณภาพชีวิตผู้ป่วยที่มีภาวะเลือดระดูออกมากกว่าปกติ พบว่าจำนวนผู้ป่วยที่รู้สึกว่าคุณภาพชีวิตบกพร่องมากในช่วงมีเลือดระดูลดลงจากร้อยละ 60 เหลือเพียงร้อยละ 5 ในรอบระดูก่อนให้การรักษา และหลังได้รับการรักษาตามลำดับ ไม่พบผลข้างเคียงที่รุนแรงจากยา*

สรุป: *จากผลการศึกษาพบว่ายากรดทรานเนซามิค ปลอดภัยและมีประสิทธิภาพในการรักษาภาวะเลือดระดูออกมากกว่าปกติ ร่วมกับเพิ่มคุณภาพชีวิตในผู้ป่วยเหล่านี้*