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Does Tranexamic Acid Effectively and Safely Reduce Menstrual Blood Loss (MBL) in Women with Menorrhagia or IUD Induced MBL?

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Does Tranexamic Acid effectively and safely reduce menstrual blood loss (MBL) in women with Menorrhagia or IUD induced MBL?

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ABSTRACT

OBJECTIVE: To determine if Tranexamic Acid effectively and safely reduce menstrual blood loss (MBL) in women with Menorrhagia or IUD induced MBL?


DATA SOURCES: Randomized Controlled Trials comparing Tranexamic Acid (TA) to placebo were found using MEDLINE, OVID, and COCHRANE databases.

OUTCOME MEASURED: Each of the three trials measured levels of reducing menstrual blood loss in women with menorrhagia or IUD induced MBL by using 4 instruments for assessing QOL: Health-Related QOL instrument, Short Form-36, Center for Epidemiologic Studies Depression Scale, Modified Ruta Menorrhagia Severity Scale. MBL and prevention of Menorrhagia measured by pictorial blood loss assessment chart (PBAC), Hemoglobin count and the number of sanitary protection soiled with blood (Pads or Tampons). Subjective systematic relief (safety 7 efficacy)-Visual Analog Scale (VAS), student T test, 2 way ANOVA.

RESULTS: All three randomized controlled trials included in this review found that TA more effectively and safely reduced MBL than the placebo groups. In all three trials, the most common adverse effect experienced in the treatment groups in both Kripilani and Kouides was headache.

CONCLUSIONS: The results of RCT’s reviewed demonstrate that TA dose taking daily is effective in reducing MBL in women with Menorrhagia or IUD induced MBL. Further research with TA is needed to determine the optimal dosage for maximizing efficacy and minimizing adverse effects.

KEY WORDS: Tranexamic Acid, Transamin, Menorrhagia, Quality of life, Menstrual Blood Loss, IUD Induced MBL.
INTRODUCTION

Menorrhagia is defined as women experiencing heavy or prolonged menstrual with blood lost of 5-6 tablespoons (about 80 milliliters +) of blood during their menstrual period usually from 7-21 days. A normal female usually loses 2 to 3 tablespoons (35 to 40 milliliters) of blood over three to seven days. Losing a lot of blood during the menstrual period can cause medical problems like anemia and can also be caused by many medical conditions. It is a common clinical problem, reported by 5-10% of women of reproductive age. Women with menorrhagia traditionally undergo frequent intensive investigation, yet 50% of these cases, the cause are never identified. The optimal management of women with menorrhagia has not been determined. Currently, there are many effective treatments but with adverse reactions or side effects. Approximately 35% of women with dysfunctional uterine bleeding (DUB) will undergo hysterectomy, which is the definitive cure for menorrhagia but, associated operative and long term morbidity and rarely mortality for essentially a benign condition, especially in younger women where hysterectomy is inappropriate, those nearing menopause, this is not considered insignificant. Thus, drug therapy should be the first line of treatment before turning to surgery. Currently, Chinese women most popularly use of contraception in China is intrauterine device (IUD); however with so many adverse effects, especially bleeding, it is essential to prevent IUD induced menstrual blood loss (MBL).

Approximately 7 million women are affected. 1/20 women aged 25-44 years will visit her general practitioner each year requesting treatment for heavy periods. 71% of women do not discuss their menorrhagia symptoms with their physician and do not receive treatment. Heavy periods can be debilitating, can lead to social embarrassment and medical problems, symptoms such as fatigue, exhaustion, shortness of breath, and anemia. Each year the United Kingdom
spends over $7 million on drug treatments, pharmaceutical costs and procedures costs $1 to over $7 million. In America, costs are unknown, however procedures, pharmaceuticals can start at $10,000 a year. Depending on the type of treatment or cause, women with menorrhagia office visits can range from 2- 6 times a year. What is known/unknown about the condition is that the most common causes include anovulation and abnormal growths in the uterus (polyps or fibroids), having condition that increases bleeding. Some symptoms and affects of menorrhagia is the constant need to change pads/tampons >3 hrs or use > 21 pads/ tampons during a period, need of both pads and tampons at the same time, change pads or tampons during the night, pass blood clots larger than 1 inch, and also Iron Deficiency Anemia (IDA). Treatment depends on cause of bleeding, preferences of the woman, and the desire for children. The usual methods are used to treat the condition are Pharmaceuticals including Hormonal birth control, hormonal IUD, Implant, Depo-Provera, Antifibrinolytics, NSAIDS, Progestrin, GnRH agonists. If pharmaceuticals do not control symptoms, surgery is an option. Surgeries include Endometrial ablation and hysterectomies.

Tranexamic Acid (TA) is a non-hormonal drug that enhances blood clotting is used more in Europe than in the US and is proving to be very effective. Increased dissolution of clots is one of the causes of DUB. TA is an antifibrinolytic reversibly locks lysine binding sites on plasminogen and thus fibrin degradation and can be promoted as treatment for DUB. There are few side effects reported with TA. It was first approved by the FDA in 1986 as Cyklokapron and has been used to prevent bleeding in patients with hemophilia after tooth extraction. There is hope that Tranexamic Acid can effectively treat and improve symptoms of women experiencing menorrhagia, either IUD induced or idiopathic.
OBJECTIVE

The objective of this systematic review is to determine if “Tranexamic Acid effectively and safely reduces menstrual blood loss in women with Menorrhagia or IUD induced MBL”. Recent studies have shown other drugs such as desmopression have been effective in reducing menstrual blood loss and menorrhagia, however Tranexamic Acid has not previously been tested and thus the efficacy of the drug in treating women with menorrhagia/MBL is not known.

METHODS

All three studies for this review met the following criteria used for selection of studies. The population(s) and/or problems: menorrhagia confirmed through Pictorial Blood Assessment Chart (PBAC) >100, completion of QOL survey, d/c OCP, (-) Pap smear in 12 mo, (-) pelvic exam, 20-40 y/o Chinese women. The interventions used in the studies, pts were given Tranexamic Acid at different times and different dosages, use after IUD. The comparisons used were intranasal Desmopressin, Medroxyprogesterone acetate, Placebo pill. The main outcomes are measured: Quality of Life (QOL), reduced MBL, reduced abnormal lab hemostasis, safety and efficacy, decreased side effects, well tolerated, safe option for those who want to conceive, prevention in Chinese women, reduced dose w/ similar effects. The types of studies included: 1 Crossover RCT, 1 RCT, 1 Double Blind RCT. The articles were selected based on the importance of outcomes to the patient (Patient Oriented Evidence that Matters, or POEMS). Studies that were included were those that were randomized, controlled and were based on a patient oriented outcome. The key words used in searches were Menorrhagia, Tranexamic Acid, Transamin. All three articles were written in English, all published in peer reviewed journals and chosen and selected using OVID and Medline using Cochrane. Inclusions/Exclusions criteria were that females with menorrhagia, articles had to be randomized in fashion. Articles must be
published between 1996-present without prior meta-analysis or systematic reviews. Under these criteria, three randomized control trials were identified, and are included in this review.

Summary of statistics reported or used: P-value, RRR, NNT, ARR, Anova, X2 test. Table 1 includes the demographics of the three included studies, which were reported.

**Table 1 - Demographics & Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kouides, 2009 (1)</td>
<td>Cross over RCT</td>
<td>116</td>
<td>Mean age 18-50</td>
<td>(-) Pelvic exam, PAP smear w/in last 12 mo, regular periods q39d, d/c OCP or Rx affecting coagulation, confirmed Menorrhagia: PBAC &gt; 100, abnormalities in hemostasis.</td>
<td>Ineligible: Administer screening questionnaire, (-) PBAC &gt; 100, Lab testing (-)</td>
<td>80</td>
<td>PO Tranexamic Acid for 2 periods</td>
</tr>
<tr>
<td>Kriplani, 2006 (2)</td>
<td>RCT</td>
<td>100</td>
<td>Mean 36.67 +/- 7.54 years (19-49)</td>
<td>Heavy menstrual bleeding, OB medical hx was taken, PBAC &gt; 100, (-) gyn pathology</td>
<td>Hx of Fibroids, suspected adenomyosis, endometriosis, atypia thyroid disease, on hormone therapy, unwilling to accept medical management</td>
<td>6</td>
<td>PO Tranexamic Acid 2g/day or 500mg QID</td>
</tr>
<tr>
<td>Lin, 2007 (3)</td>
<td>Double Blind RCT</td>
<td>175</td>
<td>20-40</td>
<td>Chinese Women w/ regular menstrual cycles &amp; willing to insert IUD's</td>
<td>Women with medical histories of organic, concomitant disease influencing menstruation, C/I to Transamin, intake of any Rx in month, OCP x 3 mo</td>
<td>18</td>
<td>PO doses of Transamin (1 and 0.5g BID)</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

The primary outcomes measured in all three studies had to be POEMs such as improving the quality of life those women experiencing menorrhagia, decrease of menstrual blood loss and the safety, efficacy and decrease of side effects such as headaches. The outcomes measured based on improving quality of life were assessed based on 4 instruments: Health-Related QOL instrument, a 14-item tool assessing the number of physically and mentally unhealthy days in the past 30 days; Short-Form-36, a 36 item, generic health status survey covering eight health concepts that include sub scores of a physical and mental components; Center of Epidemiologic Studies Depression Scale, and Modified Ruta Menorrhagia Severity Scale, a 13-item scale measuring the physical, psychological and social effects of menorrhagia on a woman’s health status. Change in MBL were estimated by the PBAC recorded at baseline and during a total of four menstrual cycles throughout the treatment phase of the studies, as well as the amount of soiled tampons/pads recorded included in the PBAC. The safety, efficacy and decreased side effects were measured by Student t-test, 2 way Anova, Independent t test. This was based on the women’s satisfaction with their treatment by subjective increase of symptomatic relief assessed by visual analogue scale.

RESULTS

The results pertaining to primary outcome were not all presented as dichotomous data. Though, all three randomized controlled trials were performed with intention to treat with the study participants having menorrhagia and symptoms of menorrhagia. All three studies reported Tranexamic Acid as more effective than their placebo or control groups. Table 2 shows results from each study. Kripilani trial was presented in dichotomous data. Table 3. Kouides and Lin were not. In the Kripinlni study, out of 100 women recruited, six women did not follow the
schedule and were excluded from the analysis. 49 patients in the TA acid group and 45 in the medroxyprogesterone group as the control. In this study, the mean blood loss with TA based on the PBAC score at 3 months of treatment was 58.2%, 61.0%, and 60.3% at 1st, 2nd, 3rd months of treatment, respectively. Reduction with MPA was 54.6%, 51.5% and 57.7% at the three-follow ups of treatment. A total of 38.8% patients and 33.3% patients of MPA had a PBAC score of <100 at their follow up.

The Kouides study had a total of 235 participants that met the criterion for menorrhagia (PBAC score > 100) with a score of 100-300 range. 116 participants agreed to participate in the treatment trial. Treatment was evaluated using a crossover analysis; on average the estimated decrease in PBAC from baseline was -64.1 (95% CI= -88.0, -40.3) for IN-DDAVP (Desmopression) and -105.7 (95% CI=-130.5, -81.0) for TA. The magnitude of the decrease of PBAC score was larger for TA than for IN-DDAVP control group. PBAC scores at baseline at end of second treatment period were -21.4% for IN-DDAVP and -51.7% for TA and -19.6% for IN-DDVAP and TA -42.6% for those initially randomized to TA. Effect of TA on QOL generally improved based on the four QOL assessment measures. Of the four different QOL measures the Ruta menorrhagia severity scale showed the most statistically significant improvements.

A total of 252 eligible women were invited into the Lin study, 57 refused, allowing 195 subjects to participate. An overall assessment integrating repeated MBL after IUD insertion measures in the treatment cycles estimated indicated that 19.9 and 23.8 ml lower than that in the placebo group (p<0.05). Based on the PBAC assessment, Transamin treated women had a significantly lower occurrence of menorrhagia compared with the placebo group. Placebo showed 27.69%, 58.46%, 60.0%, 58.62% Run-in, first cycle, second cycle, third cycle
respectively. TXA 2 g treatment showed 36.67%, 55.00%, 40.35%, 26.79% with CI of .25-.86 and with 1 g treatment 24.00%, 58%, 50%, 45.83% and CI of .41-1.54.

**Table 2—Response on duration of bleeding and MBL on PBAC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time frame</th>
<th>Control group</th>
<th>TA</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kouides, 2009 (1)</td>
<td>6 mo: 3 mo of treatment, 3 mo F/U</td>
<td>Mean of 55%</td>
<td>Mean of 60%</td>
<td>&lt;0.005</td>
<td>19.6-63.</td>
</tr>
<tr>
<td>Kriplani, 2006 (2)</td>
<td>4 cycles</td>
<td>Mean of 20.5%</td>
<td>Mean of 47.15%</td>
<td>&lt;0.005</td>
<td>N/A</td>
</tr>
<tr>
<td>Lin, 2007 (3)</td>
<td>3 cycles</td>
<td>Mean of 38%</td>
<td>Mean of 51%</td>
<td>&lt;0.05</td>
<td>0.25-1.54</td>
</tr>
</tbody>
</table>

As can be seen in Table 2, the percentage reductions from baseline of PBAC were well reduced as compared to control groups with the use of Tranexamic Acid when treating females with menorrhagia. All three studies showed results over a time period of more than 3 cycles or months resulting in accurate comparisons. In the three trials, all P values were <0.005 showing statistically significant results.

Two out of the three study trials were presented in “continuous data” form therefore could not have been converted into “dichotomous” data to analyze the results. The Kriplani study however, was in dichotomous form. Through this study, the Control Event Rate (CER) was determined as well as the The Experimental Event Rate (EER) to calculate the Relative Risk Reduction Rate (RRR) and Absolute Risk Reduction Rate (ARR). The Numbers Needed to Treat (NNT) of patients using Tranexamic Acid to improve their QOL and MBL can be determined from the Absolute risk reduction from subtracting EER from CER, and using the inverse result of 1/ARR. The calculated analysis of Outcomes and NNT in order to decrease the mean severity
score of patients treated with Tranexamic Acid vs. Medroxyprogesterone Acetate (MPA) for Menorrhagia can be seen in Table 3.

**Table 3 – Outcomes and NNT in order to decrease the mean severity score of patients treated with Tranexamic Acid vs. Medroxyprogesterone Acetate (MPA) for Menorrhagia**

<table>
<thead>
<tr>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>.29</td>
<td>.06</td>
<td>.6-.29 = 0.79</td>
<td>.06-.29 = 0.79</td>
<td>1/-0.23 = -0.5</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

In the Kouides and Kripilani studies, participants experienced some unfavorable adverse effects from Tranexamic Acid and their controls. In the Kouides study, of the 90 patients who used either medications 14% (n=13) reported in side effects, 7 to IN-DDVAP and 6 to TA. The most commonly reported side effects among those taking both IN-DDAVP and TA were headaches as a result of treatment. Other symptoms of complaint were experiences of transient double vision, dizziness and vomiting. Both patients with complaints of dizziness, double vision vomiting and headache withdrew from the study. In the Kripilani study, side effects were noted in 8 (16.3%) cases with TA and 15 (33.3%) cases with MPA. Like, the Kouides study, the majority of patients with adverse effects after taking TA were headaches (6.1%). Other reactions included gastrointestinal upsets and giddiness. Of those patients who took MPA, 11.1% had intermittent bleeding, 4.4% for headaches, GI upset, and breast tenderness. One patient had to discontinue treatment after having an allergic reaction to TA.

**DISCUSSION**

Based on the three Randomized controlled Trials in this review, the efficacy and safety of Tranexamic Acid to reduce MBL with women dealing with menorrhagia has been proven. All three trials showed increased improvement with TA compared to placebo or other
pharmaceuticals used for menorrhagia prior to TA. Reduction of MBL to a PBAC of <100 has been studied and verified and can now be recommended as the first line therapy to treat women with increased blood flow. Xanodyne Pharmaceuticals received approval from the US Food and Drug Administration (FDA) for the drug in late November 2009 and Ferring Pharmaceuticals acquired Lysteda from Xanodyne Pharmaceuticals on May 10, 2010. Tranexamic acid is the first nonhormonal product approved by the FDA for use in treating menorrhagia.

Women who took tranexamic acid for heavy menstrual bleeding experienced significant improvements in quality of life after 3 cycles and improvement of quality of life. Women were more able to participate in social, leisure, physical, and social activities after taking the medication, according to the American Congress of Obstetricians and Gynecologists (ACOG). Adverse reactions to Tranexamic Acid are still present, headaches more commonly, however the benefits can outweigh the potential risks. The combination of tranexamic acid and hormonal contraceptives can increase the risk for blood clots, stroke, and heart attack. For women who can't take hormonal medications, such as those with increased risk of strokes or migraines who take estrogen medications, tranexamic acid might be one alternative. Tranexamic acid in the form of brand name Lysteda is already being used as a standard, first line treatment for menorrhagia and is readily available prescription medication.

CONCLUSION

Tranexamic Acid is a safe and effective pharmaceutical to reduce menstrual blood loss in women with menorrhagia or IUD induced MBL. This was proven through the numerous statistically significant reductions and/or improvements of QOL throughout the three studies reviewed. It is another option and options are good for management of a problem that can truly be life changing for many women with menorrhagia instead of reverting to hysterectomies.
Currently, there are no clinical trial data on the risk of thrombotic events with the concomitant use with hormonal contraceptives, women using hormonal contraception should take Lysteda only if there is a strong medical need, and if the benefit of treatment will outweigh the potential increased risk. Some limitations of the studies were smaller study sizes, doesn’t access long term safety. Areas for further study could include the effectiveness of subjects with menorrhagia/IUD induced bleeding for long term effects.
References:


