**Proposed study:**

Intra-operative intravenous tranexamic acid during laparoscopic surgery for severe endometriosis - a double-blinded randomized placebo controlled trial

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**Background:**

Tranexameic acid, an anti-fibrinolytic agent has been shown to significantly reduce surgical blood loss across a range of different specialties and procedures [1]. No increased incidence of thromboembolic events or other adverse effects have been reported with tranexamic acid use in the perioperative setting [1-4]. In obstetrics and gynaecology tranexamic acid use has been shown to reduce surgical bleeding at caesarean section[5], myomectomy [6] and at hysterectomy performed both abdominally and laparoscopically [7].

Laparoscopic surgery for treatment of severe endometriosis is a common, yet challenging, gynaecological surgical procedure. Part of what makes this type of surgery difficult is the small vessel bleeding, secondary to inflammation associated with active endometriosis and the large raw areas left behind after excision of the endometriosis. This general ‘ooze’ during surgery is difficult to control as there are multiple bleeding points from small vessel bleeders, which are often in close proximity to vital structures such as the ureter, bladder, bowel and other major blood vessels. It only takes 5ml of blood to completely obscure the view in some places, hence even a small reduction in blood loss during surgery is clinically significant from a surgical standpoint. Reducing blood loss at laparoscopy for severe endometriosis is not only an important end point itself, it may contribute to reduced operating times, reduced operative complications, reduced length of hospital stay and reduced need for blood transfusion. To date, no one has yet reported on the use of tranexamic acid in laparoscopic treatment of severe endometriosis.

**Primary Outcome:**

To compare weighed surgical blood loss between patients receiving intra- operative intravenous tranexamic acid versus placebo in those undergoing operative laparoscopy for severe endometriosis.

**Secondary Outcomes:**

To compare the following between patients receiving intra- operative intravenous tranexamic acid versus placebo:

* Operating time
* Intraoperative complications
* Postoperative complication, including thromboembolic events
* Surgeon’s assessment of how bleeding/ooze impacted on surgical operating conditions
* To compare different methods of estimating blood loss in surgery
  + Weighed loss from suction apparatus and packs used
  + Estimate by surgeon and anaesthetist
  + The modified Gross formula, using blood volume and initial, final and mean haematocrit levels (see below)
* Length of hospital stay
* Incidence of blood loss >500ml
* Need for blood transfusion

**Study hypothesis:**

Use of intravenous tranexamic acid during laparoscopic surgeries for severe endometriosis will reduce intraoperative blood loss.

**STUDY PROTOCOL**

**Study design:** Adouble-blinded randomized placebo controlled trial

**Study Unit:**

* Gynaecology 2 unit, Royal Women's Hospital

**Inclusion Criteria:**

* Suspected severe endometriosis (based on clinical or radiological evidence or findings at previous diagnostic laparoscopy)
* Proposed laparoscopic surgery to treat endometriosis of > 2 hours
* Planned surgery under level 6 gynaecological surgeons’ operating lists

**Exclusion Criteria:**

* Non consent
* Non English speaking
* Allergy or contraindication to tranexamic acid including: thrombophilia, previous/active thromboembolic disease, subarachnoid haemorrhage, malignancy or antithrombotic treatment
* Hysterectomy planned as part of procedure

**Patient identification, recruitment and informed consent:**

Study participants will be identified and recruited by the treating gynaecologist, gynaecology trainee or appointed research assistant in the Gynaecology 2 clinic of The Royal Women’s Hospital.

**Study schedule:**

Eligible patients will be approached pre-operatively to be recruited. Those consenting will be entered into the trial and have a trial number allocated. Prior to surgery, a computer-automated software will be used to randomly allocate each patient to one of the study arms. Randomisation will be stratified by which surgeon’s operating list they are booked to, in blocks of 4. Patients will be randomly assigned in a 1:1 ratio to receive either 1g intravenous tranexamic acid or a matched volume of intravenous placebo (Normal saline). This randomization process will be carried out in the pharmacy department and the appropriate trial medication brought labeled with the patient’s trial number to the operating theatre. It will be administered immediately following initial skin incision as this has been shown to have a small but greater effect of blood loss reduction [1]. Both patient and surgical team members (including anaesthetic team) will be blinded to the treatment received.

An initial haematocrit level [Hct (i)] will be performed via blood test once patient is under anaesthetic prior to commencement of surgery or this will be obtained from a full blood examination if performed on day of surgery (for example as per usual practice if a myomectomy is planned or if indicated due to medical comorbidities). A final haematocrit level will be performed at close of surgery [Hct (f)]. Euvolaemia will aim to be achieved as per usual practice with the use of intravenous crystalloid fluid. Patients not wishing to have these additional blood samples drawn whilst under anaesthetic will still be included in analysis but will not have a recorded modified Gross formula estimation of blood loss.

The surgery will then proceed as per the patient’s needs and surgeon’s usual practice. Surgery will not be affected by the trial. Blood products may be used according to usual practice. Other intraoperative details will be recorded (see below).

Standard practice with use of calf-thigh intermittent pneumatic compression devices intra-operatively, followed by graduated compression stockings with a prophylactic dose of dalteparin (unless contraindicated) during the postoperative hospital stay will be followed. Other postoperative inpatient details will be recorded (see below).

A postoperative outpatient check will be scheduled between 4-6 weeks postoperatively with details regarding complications recorded.

*Intra-operative details:*

* Operation performed
* Operating time (from skin incision to close)
* rASRM stage of endometriosis
* Intraoperative complications, including conversion to laparotomy
* Use of intraoperative blood products
* Estimated blood loss by weight:
  + Once the laparoscopy has commenced any fluid already in the peritoneal cavity will be sucked out and discarded (e.g. pre-existing free fluid and/or fluid that has entered the peritoneal cavity from hysteroscopy performed prior to laparoscopy)
  + Bags of irrigation fluid to be weighed prior to use (= irrigation fluid weight prior)
  + At the end of the case irrigation bags used weighed with any remaining fluid (= irrigation fluid weight post)
  + Irrigation fluid in = irrigation fluid weight prior – irrigation fluid weight post
  + Thorough suction of all fluid out of peritoneal cavity at end of case (including tilting patient head up to allow suctioning of all possible fluid). Irrigation fluid out weighed.
  + Blood loss (grams) = (fluid out – fluid in) + (weight of packs/swabs used – dry weight of packs/swabs) – estimated volume of ovarian cyst fluid (if present) as per ultrasound and clinical findings.
  + Convert to ml of blood by 1.050g/mL (specific gravity of blood at 37 degrees Celsius)
  + The surgical team will be responsible for weighing irrigation bags, suction bags and packs/swabs.
* Estimated blood loss by surgeon (to be made prior to blood loss weighed)
* Estimated blood loss by anaesthetist (to be made prior to blood loss weighed)
* Estimated blood loss by modified Gross formula[8]
  + Acutal blood loss (ABL) = BV [Hct (i) – Hct (f)/Hct (m)]
    - BV (blood volume) = body weight (kgs) x 70mgkg
    - Hct (i) = haematocrit initial
    - Hct (f) = haematocrit final
    - Hct (m) = mean of initial and final haematocrits
* Questions posed to surgeon at close of case
  + “How much did bleeding/ooze impair the surgical operating conditions? No impairment/Small impairment/Moderate impairment/Large impairment”
  + “Do you think tranexamic acid was used in this case? Yes/No”

*Post-operative inpatient details:*

* Immediate post-operative complications
* Postoperative use of blood products
* Length of stay

*Post-operative outpatient details:*

* Any postoperative complication including any incidence of VTE.

Consenting participants will be allocated a trial number and all data will be recorded in a de-identified manner using the study number.

All information will be kept secure: all paperwork from the project will be kept in a locked room and all computerised information will be kept in a database that is password protected. All information will be kept for a period of 7 years after the project is completed, at which time hard copy records will be shredded and computer files deleted.

In any publication, information will be provided in such a way that particpipants cannot be identified. This will be ensured by providing summarised data or else by referring to individual results by their study number.

**Sample size calculations:**

Topsoee et al published in 2016 a randomized control trial comparing tranexamic acid with placebo in benign hysterectomies (all modes – open, vaginal and laparoscopic) [7]. The results showed EBL of 100ml vs 166ml, a 40% reduction.

Roman et al performed a randomized control trial comparing bowel shave versus bowel resection in severe endometriosis[9]. Their study showed a median EBL of 200ml in both groups.

Based on these previous studies, we assume average EBL for severe endometriosis surgeries to be 200ml and the use of TA will reduce this by 40%. Using STATA version 11 with two-tailed calculation, power of 0.80 and p of 0.05, the sample size needed is 100 in each arm. Therefore, the final total sample size will be 200.

We plan to conduct an interim analysis after 80 cases have been recruited to assess what the average blood loss in our surgeries is and if this requires the sample size to be re-calculated.

**Study timeframe:**

We will keep recruiting until we have 100 cases in each arm (unless the interim analysis changes this figure). There are approximately 8-10 cases of laparoscopic treatment of severe endometriosis per month. Allowing for patients who choose not to participate in the study, cancelled lists and drop-outs (estimated to be 20%) we calculate we would need 2-2.5 years to reach our goal of 200 patients.

**Funding:**

Funding is currently being sought via application of grants from independent bodies. Recruitment will not commence until funding has been confirmed.

**Conflict of interest:** None

**References:**

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