European Journal of Obstetrics & Gynecology and Reproductive Biology 199 (2016) 187–191

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Effect of intravenous ascorbic acid infusion on blood loss during laparoscopic myomectomy: a randomized, double-blind, placebo-controlled trial

Banghyun Lee [a,1], Kidong Kim [a,1], Hye Yon Cho [b], Eun Joo Yang [c], Dong Hoon Suh [a], Jae Hong No [a], Jung Ryeol Lee [a], Jung Won Hwang [d], Sang Hwan Do [d], Yong Beom Kim [a,e,*]

[a] Department of Obstetrics and Gynecology, Seoul National University, Bundang Hospital, Seongnam-Si, Gyeonggi-Do, Republic of Korea
[b] Department of Obstetrics and Gynecology, Hallym University, Dongtan Sacred Heart Hospital, Hwaseong-Si, Gyeonggi-do, Republic of Korea
[c] Rehabilitation Medicine Department, Seoul National University, Bundang Hospital, Seongnam-Si, Gyeonggi-Do, Republic of Korea
[d] Department of Anesthesiology and Pain Medicine, Seoul National University, Bundang Hospital, Seongnam-Si, Gyeonggi-Do, Republic of Korea
[e] Seoul National University, School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 15 October 2015
Received in revised form 16 January 2016
Accepted 11 February 2016

Keywords:
Ascorbic acid
Laparoscopy
Operative time
Surgical blood loss
Uterine myomectomy

ABSTRACT

Objective: Most interventions aimed at reducing bleeding during myomectomy lack sufficient evidence regarding their effectiveness. Recently, it was reported that intraoperative ascorbic acid administration effectively reduced blood loss during abdominal myomectomy. Therefore, this study aimed to investigate whether intravenous ascorbic acid infusion would affect intraoperative blood loss in women undergoing laparoscopic myomectomy.

Study design: A randomized, double-blind, parallel-group, placebo-controlled trial including 50 women undergoing laparoscopic myomectomy was conducted. Women with ≤4 myomas, ≤9 cm in maximum diameter were eligible. The study:control group ratio was 1:1. Starting 30 minutes before anesthesia, 2 g of ascorbic acid or a placebo were administered for 2 hours intraoperatively. Intraoperative blood loss, the primary endpoint, was calculated as the difference between the volume of fluids acquired from suction and that used for irrigation of the abdominal cavity during surgery using constant values.

Results: Among the 50 randomized women, 1 and 3 in the study and control groups, respectively, were excluded due to withdrawal of consent, cancelation of surgery, or non-measurement of the primary endpoint. The baseline and operative characteristics were similar between the study and control groups, as was the intraoperative blood loss (193 ± 204 mL vs. 159 ± 193 mL, $P = 0.52$). In addition, the operating time (95 ± 29 min vs. 110 ± 52 min; $P = 0.50$) and decrease in hemoglobin level after surgery (1.9 ± 1.31 g/dL vs. 1.4 ± 1.4 g/dL; $P = 0.24$) were similar between the study and control groups.

Conclusions: Intravenous ascorbic acid infusion did not reduce intraoperative blood loss in women undergoing laparoscopic myomectomy.

Clinical trial registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01715597.

Introduction

Myoma uteri is a very common gynecologic disease. In cases where surgical treatment is considered necessary, myomectomy is considered a safe alternative to hysterectomy in women who want to preserve their uterus [1]. However, myomectomy is associated with excessive bleeding, which may be life-threatening [2]. Although many interventions aimed at reducing bleeding during myomectomy have been suggested, most are lacking sufficient evidence of their effectiveness [1,2]. Recently, in a randomized trial, ascorbic acid (vitamin C) administration was reported to be effective in preventing excessive blood loss during abdominal myomectomy [3].

Scurvy, a disease resulting from ascorbic acid deficiency, is associated with impaired collagen synthesis and fragile capillaries, leading to abnormal bleeding [4]. Interestingly, increased coagulation time and reduced blood platelet aggregation have also been

* Corresponding author: Department of Obstetrics and Gynecology, Seoul National University, Bundang Hospital, 82, Gumi-ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea. Tel.: +82 31 787 7253; fax: +82 31 787 4054.
E-mail address: ybkimlh@snubh.org (Y.B. Kim).
[1] These authors contributed equally to this work and are co-first authors.

http://dx.doi.org/10.1016/j.ejogrb.2016.02.014
0301-2115/

noted in scurvy, suggesting a role of ascorbic acid in blood clotting [5,6]. Moreover, bleeding due to scurvy has been reported to be improved by ascorbic acid supplementation [7–9]. In addition, a previous study on smokers reported that combined administration of ascorbic acid and vitamin E improved endothelial function and resulted in decreased plasma levels of plasminogen activator inhibitor-1, von Willebrand factor, and the plasminogen activator inhibitor-1:tissue plasminogen activator ratio [10]. Thus, although there have been contradictory reports that ascorbic acid supplementation can reduce the risks of stroke, heart attack, and atherosclerosis, ascorbic acid administration might be effective in hemostasis [5–10].

Similar to in abdominal myomectomy, it can be hypothesized that ascorbic acid administration would be effective in reducing bleeding during laparoscopic myomectomy. Therefore, this study aimed to investigate whether intravenous ascorbic acid infusion would affect the intraoperative blood loss in women undergoing laparoscopic myomectomy. The associations between ascorbic acid administration and other surgical outcomes were also evaluated.

Materials and methods

Overview

Our randomized, double-blind, parallel-group, placebo-controlled study included 50 women who enrolled in a clinical trial at our tertiary university hospital from January 1, 2013 to June 30, 2014. This study was approved by the Institutional Review Board of our university hospital (No. B-1208/166-007) on September 28, 2012.

The inclusion criteria were as follows: women who were given clinically diagnoses of myoma, those scheduled for laparoscopic myomectomy, those with $\leq$4 myomas with a largest diameter $\leq$9 cm, and those who provided voluntary consent for the present clinical trial. The exclusion criteria were as follows: women who were scheduled for myomectomy and other surgeries simultaneously, and those with abnormal coagulation test results; hypersensitivity to ascorbic acid; hyperoxaluria, renal calculi (oxalate), thalassemia, gout, or cystinuria; glucose-6-phosphate dehydrogenase deficiency; a disease or taking a medication influencing coagulation; a serum creatinine level $>$1.5 mg/dL; and who were considered ineligible for the clinical trial by a physician.

Efficacy assessment

Efficacy assessments were performed in all randomized patients, excluding the dropouts. The primary endpoint was the amount of intraoperative blood loss. Secondary endpoints included the operating time, decrease in hemoglobin level after surgery, frequency and amount of transfusion, and adverse events (AEs). Additionally, we assessed the association between urinary outcomes and ascorbic acid using an exploratory design; these data will be reported in the near future.

The amount of intraoperative blood loss was calculated as follows: fluid that drained into the suction pump – fluid that was put into the abdominal cavity + fluid that remained within laparoscopic instruments and the abdominal cavity (constant value = 160). We defined this constant value as the average value of 3 surgeries with a lower amount of bleeding, such as laparoscopic unilateral salpingo-oophorectomy.

The operating time was defined as the time interval between when the skin incision was made and when skin closure was completed.

The decrease in hemoglobin level after surgery was calculated as follows: preoperative hemoglobin level – hemoglobin level on postoperative day 1 + hemoglobin level increased by transfusion [calculated as 1 g/dL per 1 unit of packed red blood cells].

Study setup and outcome assessment

At our hospital, pelvic examination and transvaginal ultrasound are usually performed to clinically diagnose myoma uteri. Pelvic examination findings indicating myoma uteri include an enlarged, irregularly shaped, firm, and non-tender uterus [11]. The ultrasound findings indicating myoma uteri are variable, but often include symmetric, well-defined, hypoechoic, and heterogeneous masses [11]. If myomectomy is chosen as the treatment method, a laparoscopic or abdominal approach is selected according to the preference of the patient and the physician based on the number, size, and position of the myomas.

At study enrollment, all participants were assessed for eligibility. Written informed consent was provided by the participants after an explanation about the current trial, including the possible benefits and adverse effects of intravenous ascorbic acid infusion. They were allowed adequate time before deciding to participate in this trial.

Screening process

Preoperative tests, including hemoglobin and coagulation, were performed, followed by randomization. Participants with abnormal preoperative coagulation test results were excluded.

Randomization

Stratified randomization according to the surgeon and block randomization were performed by a statistician who had no direct contact with the participants. The statistician created sequence tables to randomize. Two copies of the randomization list were prepared. One was kept by the statistician and the other copy was kept as a confidential document. After each participant was enrolled, allocation was performed by the statistician and the assignments were delivered to the pharmacist. The participants were randomly assigned to either the study or control group in a 1:1 ratio. The size of the block unit was not disclosed to prevent the investigators from predicting the participants' assignments. The participants and investigators were not informed regarding whether a participant was assigned to the study or control group. After each participant was enrolled, the investigators delivered the patient information, such as the participant' number defined for this trial, admission date, and operation date, to the pharmacist.

Interventions

Starting 30 minutes before anesthesia, 2 g of ascorbic acid with 500 mL 0.9% sodium chloride (normal saline) or 500 mL 0.9% sodium chloride were administered to the study and control groups, respectively, for 2 hours intraoperatively. In most participants, all ascorbic acid was fully infused before completion of the surgery. The clinical trial drugs were administered intravenously using a separate line from those used for medication during the surgery. Laparoscopic myomectomy was performed, and the intraoperative blood loss was estimated. Intramyometrial injection of vasopressin was performed according at the surgeon's discretion.

Progress

On postoperative day 1, the hemoglobin and urinary oxalate levels, which may be increased by ascorbic acid administration [12], were assessed at least 12 hours after surgery. On postoperative day 2, the frequency and amount of blood transfusion and any