Journal of the Korea Academia-Industrial cooperation Society
Vol. 22, No. 2 pp. 434-439, 2021

https://doi.org/10.5762/KAIS.2021.22.2.434
ISSN 1975-4701 / eISSN 2288-4688

Effect of intravenous ascorbic acid administration on fatigue after laparoscopic myomectomy: A randomized, double-blind, placebo-controlled trial

Woo Yeon Hwang, Kidong Kim*
Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

복강경 자궁근종절제술을 받은 여성에서 정맥 내 아스코르브산 투여가 피로에 미치는 영향: 무작위 배정 양측맹검 위약대조 임상시험

황우연, 김기동*
분당서울대학교병원 산부인과

Abstract We assessed the effects of intravenous (IV) ascorbic acid administration on fatigue in women undergoing laparoscopic myomectomy. We analyzed the secondary endpoint results of a randomized, double-blind, placebo-controlled trial . Fifty patients undergoing laparoscopic myomectomy received IV ascorbic acid (2g) or placebo (randomly 1:1 ratio) intravenously during surgery. On day 2 post-surgery, we measured the level of fatigue using the Brief Fatigue Inventory-Korean version. Forty-five women (experimental arm 23, control arm 22) were eligible for analysis after 5 women (experimental arm 2, control arm 3) were excluded due to withdrawal of consent, cancellation of surgery or non-measurement of the endpoints. The baseline and operative characteristics were similar between arms and the global fatigue score of the experimental arm (4.56 ± 2.63) was not significantly different from that of the control arm (5.21 ± 2.02, P = 0.351). However, the fatigue score of the experimental arm tended to be lower than that of the control arm in most domains. IV ascorbic acid administration did not significantly reduce the level of fatigue in women undergoing laparoscopic myomectomy as compared to placebo. More research is needed to better understand the effects of ascorbic acid on fatigue in surgical patients.

요 약 본 논문은 복강경 자궁근종절제술을 받은 여성에서 정맥 내 아스코르브산 주입이 피로에 미치는 영향 알아보고자 하였다. 우리는 무작위 배정 양측맹검 위약대조 임상시험의 2차 평가변수의 결과를 분석하였다. 복강경 자궁근종절제술을 받은 환자 50명은 수술 중 아스코르브산 (2g)이나 위약을 수술 중 투여받았다. 환자 비율은 임의로 1:1 비로 하였다. 수술 후 2일차에는 간이 피로 평가지 (Brief Fatigue Inventory-Korean version, BFI-K)을 사용하여 피로수준을 평가하였다. 대상자가 동의를 철회하거나 수술을 취소한 경우 또는 평가변수가 측정되지 않은 5명은 제외되어 총 45명 (시험군 23명, 대조군 22명)을 대상으로 분석하였다. 분석에 포함된 대상자의 임상적 특성은 실험군과 대조군간의 차이가 없었으며, 전체 피로도 점수도 실험군 (4.56 ± 2.63). 대조군 (5.21 ± 2.02 P = 0.351)으로 두 군간에 차이를 보이지 않았다. 그러나 대조군의 피로도 점수는 대부분의 영역에서 대조군의 피로도 점수보다 낮은 경향을 보였다. 결론적으로 복강경 자궁근종절제술을 시행받은 여성에서 정맥 내 아스코르브산 주입은 피로도를 크게 줄이지 못했으며, 추가적인 연구가 필요하다.

Keywords : Ascorbic Acid, Fatigue, Intravenous Infusion, Laparoscopic Myomectomy, Placebo

본 논문은 분당서울대학교병원 연구과제로 수행되었음.
*Corresponding Author : Kidong Kim(Seoul National University Bundang Hospital)
email: kidong.kim.md@gmail.com
Received October 12, 2020 Revised November 4, 2020
Accepted February 5, 2021 Published February 28, 2021

1. Introduction

Fatigue is one of the most common symptoms patients experience after surgery[1]. Postoperative fatigue has a significant impact on the well-being of a patient after surgery[2]. Although this topic has received little interest, surgeons have now begun to realize its importance following surgery, giving it a label of "postoperative fatigue"[3]. This fatigue is in response to a series of physiologic changes that are caused by surgical trauma, as well as the duration of the surgery[4,5].

In the immediate postoperative period, patients undergoing major abdominal and gynecological surgeries were all found to suffer from a large increase in fatigue[6]. Oxidative stress is thought to be an integral part of the surgical stress response, which may cause fatigue[7,8]. Ascorbic acid is an antioxidant that scavenges free radicals and may thereby prevent further oxidative damage[9]. Several studies have reported that intravenous ascorbic acid treatment alleviates fatigue among terminal cancer patients[10] and even in healthy office workers[11]. However, there is still a lack of randomized controlled studies evaluating the efficacy of intravenous ascorbic acid[12] in reducing fatigue, especially after surgery.

Previously, we reported the effect of intravenous ascorbic administration on blood loss during laparoscopic myomectomy[13]. One of the secondary endpoints included whether intravenous ascorbic acid administration reduces fatigue as reported in several previous studies[10,11]. Therefore, our study aimed to assess the effect of intravenous ascorbic acid on fatigue in patients undergoing laparoscopic myomectomy as an ancillary analysis of a randomized controlled trial.

2. Materials and methods

2.1 Overview

In this randomized, double-blind, placebo-controlled trial, we randomly assigned patients undergoing laparoscopic myomectomy in a 1:1 ratio to receive either 2g of intravenous ascorbic acid or placebo starting 30 minutes before anesthesia. Additional details regarding this trial overview, including inclusion and exclusion criteria, efficacy assessment, randomization, and adverse event, are provided in a previous paper[13]. This study was approved by the Institutional Review Board of our university hospital (No. B-1208/166-007) on September 28, 2012.

2.2 Intervention

The study group received 2g of ascorbic acid with 500mL of 0.9% sodium chloride (normal saline) 30 minutes before the start of anesthesia, while the placebo group was administered 500mL of 0.9% sodium chloride for 2 hours intraoperatively. In most patients, the ascorbic acid was fully infused before the operation was completed. The clinical trial drugs were administered intravenously using a separate line from those used for other medications during the surgery.

2.3 Measurement of fatigue

Previous study have shown that ascorbic acid reduced fatigue at two hours, and persisted for one day[11]. Therefore we decided to measure fatigue on postoperative day 2. We measured fatigue using the Brief Fatigue Inventory-Korean version (BFI-K)[14], which consists of 9 questions. Fatigue and its interference were measured by participants on a numerical rating scale from 0 to 10, ranging from "no fatigue" (0) to "fatigue as bad as you can imagine" (10). The first 3 items evaluated the level of fatigue and the next 6 items described the level of interference fatigue has caused in their daily life during the previous 24 hours. The global score for the BFI

was calculated as the mean value of all questions. We compared the global score and individual item scores between the ascorbic acid and placebo groups.

2.4 Statistical analyses

Power calculations were not performed because this study is exploratory research of a secondary endpoint of a previous study. All statistical analyses were performed using SPSS version 25 (IBM Corporation, Inc., Chicago, IL, USA). Continuous variables were analyzed using the independent t test or Mann-Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher's exact test. A P value of ⟨0.05 was considered statistically significant.

3. Results

Figure 1 represents the flow diagram of this randomized study. Among the 50 randomized women, 2 participants in the study group were excluded due to non-measurement of the primary and secondary endpoint, while 3 participants in the control group were excluded due to cancellation of surgery, withdrawal of consent, and non-measurement of the primary endpoint. Therefore 23 and 22 patients were included in the study and control groups, respectively.

No differences were observed in the demographic and clinical characteristics between the ascorbic acid group and placebo group (Table 1). The mean age, body mass index (BMI), number and diameter of uterine myoma, and previous abdominal operation history were well balanced between the 2 groups. The surgical outcomes, including operation time, preoperative and postoperative hemoglobin levels, and the decrease in hemoglobin levels after surgery were similar between the groups. In addition, the

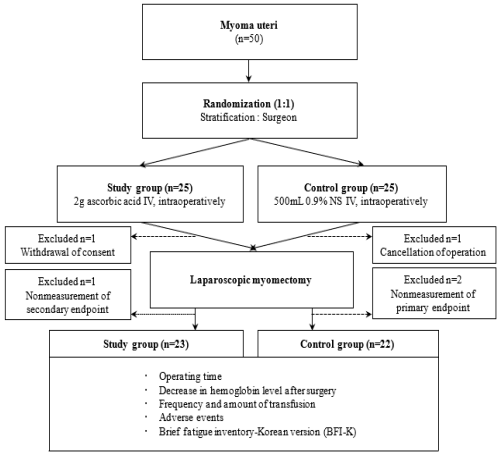


Fig. 1. Study flow chart. This diagram shows the flow of this randomized, double-blind, parallel-group, placebo- controlled study.

transfusion rate was similar in both case. One patient in the ascorbic acid group had grade 3 nonspecific abdominal pain for 2 days, but no adverse events related to ascorbic acid were detected, and oxalate was not detected in the urine of any patient. No hemostatic drugs were used in either group.

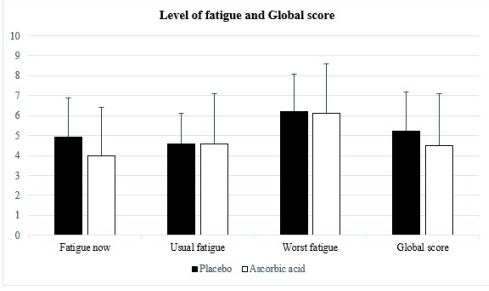


Fig. 2A. Level of fatigue and global score of BFI-K in each group (mean ± standard deviation)

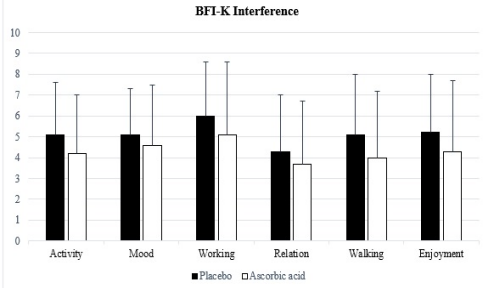


Fig. 2B. The BFI-K interference in each group (mean ± standard deviation)

Table 1. Comparison of the parameters between the study and control groups

Characteristics	Study group (n=23)	Control group (n=22)	*P* value
Age (years)	42.3 ± 6.0	40.3 ± 6.2	0.344
BMI (kg/m^2)	23.1 ± 3.1	22.5 ± 2.49	0.543
Number of myomas	1.3 ± 0.5	1.5 ± 0.8	0.429
Diameter of the largest myoma (cm)	6.9 ± 1.3	6.7 ± 1.7	0.651
Previous abdominal surgery	5 (21.7)	5 (22.7)	>0.999
Cesarean section	3	4	
Unilateral salpingectomy			
Laparotomy	1	0	
Laparoscopic	1	0	
Operating time (min)	95.0 ± 30.0	105.6 ± 50.1	0.717
Hemoglobin level (g/dL)			
Preoperative	12.5 ± 1.61	11.7 ± 1.94	0.087
Postoperative	10.8 ± 1.54	10.3 ± 1.67	0.301
Preop-Postop	1.75 ± 1.28	1.41 ± 1.37	0.266
Transfusion	1 (4.35)	3 (13.6)	0.346
Adverse events related to ascorbic acid administration	0	0	
Oxaluria	0	0	

BMI, body mass index; The data were expressed as the mean ± standard deviation or number (%). A P value of less than 0.05 was considered to be statistically significant.

Table 2. BFI-K score of each group

Scales/Items	Study group (n=23)	Control group (n=22)	*P* value
Level of Fatigue			
Fatigue currently	4.0 ± 2.4	4.9 ± 2.0	0.193
Usual fatigue	4.6 ± 2.5	4.6 ± 1.5	0.990
Worst fatigue	6.1 ± 2.5	6.2 ± 1.9	0.900
BFI-K interference			
Activity	4.2 ± 2.8	5.1 ± 2.5	0.245
Mood	4.6 ± 2.9	5.1 ± 2.2	0.577
Working	5.1 ± 3.5	6.0 ± 2.6	0.482
Relation to others	3.7 ± 3.0	4.3 ± 2.7	0.474
Walking	4.0 ± 3.2	5.1 ± 2.9	0.207
Enjoyment of life	4.3 ± 3.4	5.2 ± 2.8	0.360
Global score	4.5 ± 2.6	5.2 ± 2.0	0.351

BFI-K, Brief Fatigue Inventory-Korean version; The data were expressed as the mean ± standard deviation. A P value less than 0.05 was considered statistically significant.

The BFI global scores of the ascorbic acid and placebo groups were similar (mean ± SD, 4.56 ± 2.63, 5.21 ± 2.02, respectively, P = 0.351) (Table 2). However, the global and item scores of the ascorbic acid group tended to be lower than those of the placebo group (Fig 2).

4. Conclusion

In this randomized trial, we found that intravenous infusion of ascorbic acid in women undergoing laparoscopic myomectomy tended to reduce fatigue levels. Unfortunately, there were no significant differences between the study and control groups. However, we believe that this is

meaningful research leading to a need for future studies.

There are some possible explanations for the lack of significant differences in the fatigue level between the 2 groups. First, the power of this study may be insufficient. Specifically, this research lacked sample size calculation because of its exploratory nature. Second, women who undergo laparoscopic surgery may not have much fatigue. Several studies have shown that postoperative fatigue appears to be less after laparoscopic surgery than after open procedures[1,6,15]. The fatigue level of women in this trial was just moderate based on their fatigue severity categorization[14]. Therefore, the difference in fatigue between the groups may not have been great enough to detect a significant decrease in fatigue due to the effect of intravenous ascorbic acid. Third, the dosage of ascorbic acid may be insufficient. For example, in a previous Korean study, injection of 10 g ascorbic acid intravenously twice a day with a 3-day interval significantly improved fatigue in inpatients with terminal cancer[10].

There are some limitations of our study. First, we did not measure the baseline level of fatigue prior to surgery. Therefore, we have not measurement of fatigue increase after surgery. Second, this study may have been underpowered as previously mentioned.

In summary, intravenous administration of ascorbic acid in women undergoing laparoscopic myomectomy tended to reduce fatigue levels. Additional studies with an increased number of patients are required to examine the clinical significance. In addition studies exploring fatigue after open surgeries, where higher levels of fatigue are noted, and the effect of ascorbic acid administration are needed.

References

[1] Schwenk, W., B. Bohm, and J.M. Muller, *Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial.* Surgical Endoscopy, 1998. **12**(9): p. 1131-6 DOI: https://dx.doi.org/10.1007/s004649900791

[2] Zargar-Shoshtari, K. and A.G. Hill, *Postoperative fatigue: a review.* World Journal of Surgery, 2009. **33**(4): p. 738-45 DOI: http://dx.doi.org/10.1007/s00268-008-9906-0

[3] Oliveira, M., G. Oliveira, J. Souza-Talarico, and D. Mota, *Surgical Oncology: Evolution of Postoperative Fatigue and Factors Related to Its Severity.* Clinical Journal of Oncology Nursing, 2016. **20**(1): p. E3-8 DOI: http://dx.doi.org/10.1188/16.CJON.E3-E8

[4] Christensen, T. and H. Kehlet, *Postoperative fatigue.* World Journal of Surgery, 1993. **17**(2): p. 220-5 DOI: http://dx.doi.org/10.1007/BF01658930

[5] Yu J, Zhuang CL, Shao SJ, Liu S, Chen WZ, Chen BC, et al. Risk factors for postoperative fatigue after gastrointestinal surgery. J Surg Res. 2015. **194**(1): p. 114-9. DOI: http://dx.doi.org/10.1016/j.jss.2014.09.041

[6] Rubin, G.J., R. Hardy, and M. Hotopf, *A systematic review and meta-analysis of the incidence and severity of postoperative fatigue.* Journal of Psychosomatic Research, 2004. **57**(3): p. 317-26 DOI: http://dx.doi.org/10.1016/S0022-3999(03)00615-9

[7] Ruzic, B., I. Tomaskovic, D. Trnski, O. Kraus, M. Bekavac-Beslin, and N. Vrkic, *Systemic stress responses in patients undergoing surgery for benign prostatic hyperplasia.* BJU International, 2005. **95**(1): p. 77-80 DOI: https://doi.org/10.1111/j.1464-410X.2004.05276.x

[8] Kucukakin, B., I. Gogenur, R.J. Reiter, and J. Rosenberg, *Oxidative stress in relation to surgery: is there a role for the antioxidant melatonin?* Journal of Surgical Research, 2009. **152**(2): p. 338-47 DOI: http://dx.doi.org/10.1016/j.jss.2007.12.753

[9] Popovic, L.M., N.R. Mitic, D. Miric, B. Bisevac, M. Miric, and B. Popovic, *Influence of vitamin C supplementation on oxidative stress and neutrophil inflammatory response in acute and regular exercise.* Oxidative Medicine and Cellular Longevity, 2015. **2015**: p. 295497 DOI: http://dx.doi.org/10.1155/2015/295497

[10] Yeom, C.H., G.C. Jung, and K.J. Song, *Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration.* Journal of Korean Medical Science, 2007. **22**(1): p. 7-11 DOI: http://dx.doi.org/10.3346/jkms.2007.22.1.7

[11] Suh, S.Y., W.K. Bae, H.Y. Ahn, S.E. Choi, G.C. Jung, and C.H. Yeom, *Intravenous vitamin C administration reduces fatigue in office workers: a double-blind randomized controlled trial.* Nutrition Journal, 2012. **11**: p. 7 DOI: http://dx.doi.org/10.1186/1475-2891-11-7

[12] Padayatty, S.J. and M. Levine, *New insights into the physiology and pharmacology of vitamin C.* CMAJ: Canadian Medical Association Journal, 2001. **164**(3): p. 353-5.

[13] Lee, B., K. Kim, H.Y. Cho, E.J. Yang, D.H. Suh, J.H. No, J.R. Lee, J.W. Hwang, S.H. Do, and Y.B. Kim, *Effect of intravenous ascorbic acid infusion on blood loss during laparoscopic myomectomy: a randomized, double-blind, placebo-controlled trial.* European Journal of Obstetrics, Gynecology, and Reproductive Biology, 2016. **199**: p. 187-91
DOI: http://dx.doi.org/10.1016/j.ejogrb.2016.02.014

[14] Yun, Y.H., X.S. Wang, J.S. Lee, J.W. Roh, C.G. Lee, W.S. Lee, K.S. Lee, S.M. Bang, T.R. Mendoza, and C.S. Cleeland, *Validation study of the korean version of the brief fatigue inventory.* Journal of Pain and Symptom Management, 2005. **29**(2): p. 165-72
DOI: http://dx.doi.org/10.1016/j.jpainsymman.2004.04.013

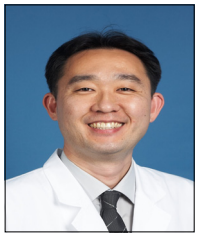
[15] Hill, A.G., P. Finn, and D. Schroeder, *Postoperative fatigue after laparoscopic surgery.* Australian and New Zealand Journal of Surgery, 1993. **63**(12): p. 946-51
DOI: http://dx.doi.org/10.1111/j.1445-2197.1993.tb01724.x

Woo Yeon Hwang [Regular member]

- Feb. 2014 : Kyung Hee Univ., School of Medicine, M,D.
- Mar. 2015 ~ Feb. 2019 : Kyung Hee Univ. Hospital, Dept. of Obstetrics & Gynecology, Residency
- Mar. 2019 ~ current : Seoul National Univ. Bundang Hospital, Gynecologic Oncology Fellowship

〈Research Interests〉
Gynecologic Cancer, Clinical trial

Kidong Kim [Regular member]



- Feb. 2006 : Seoul National University College of Medicine, MS
- Aug. 2012 : Seoul National University College of Medicine, PhD
- Mar. 2011 ~ current : Seoul National University Bundang Hospital, Dept. of Obstetrics and Gynecology, Professor

〈Research Interests〉
Gynecologic cancer, Clinical trial, Bioinformatics