Anesth Pain Med. 2021 October; 11(5):e119332.

doi: 10.5812/aapm.119332.

Published online 2021 November 8.

Research Article

The Effects of Intravenous Vitamin C on Stress Response Severity in Abdominal Hysterectomy Following Prolonged Fasting Time

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Received 2021 September 04; **Revised** 2021 October 18; **Accepted** 2021 October 26.

Abstract

Background: Inevitable prolonged fasting time before surgery leads to inflammatory reactions, surgery-related stress response, and consequently unfavorable outcomes; thus, developing strategies to mitigate these consequences is crucial.

Objectives: In this study, we evaluated the effect of ascorbic acid on stress response reduction in abdominal hysterectomy following prolonged fasting time.

Methods: Eligible women candidates for abdominal hysterectomy following prolonged fasting time were enrolled in the study and divided into 2 groups of vitamin C [group C; 1 g intravenously (IV) before surgery] and placebo (group P). Before induction of anesthesia, C-reactive protein (CRP), mean arterial pressure (MAP), heart rate (HR), and blood sugar (BS) were measured and compared between the 2 groups at 4-point times, 24 and 48 hours immediately after extubation.

Results: Finally, the data of 80 patients were included for the final analysis. A statistically significant difference was observed between the 2 groups in terms of CRP and BS values in T1 CRP serum levels; at the end of the study, CRP values were 0.5 $\pm$ 0.55 and 0.92 $\pm$ 0.69 in groups C and P, respectively (P = 0.012), and BS levels were 124.12 $\pm$ 18.11 and 152.0 $\pm$ 17.36 in groups C and P, respectively (P = 0.0001). However, this significant difference was not observed at T2 regarding CRP (P = 0.145) and BS (P = 0.135), as well as at T3 regarding CRP (P = 0.282) and BS (P = 0.213). However, according to both CRP and BS values, the trend of changes from T0 to T3 was significant in the 2 groups ($P < 0.0001$). Hemodynamic parameters were not significantly different between the 2 groups. No adverse event was reported in the 2 groups.

Conclusions: We found that ascorbic acid could induce short-term positive effects in abdominal hysterectomy following prolonged fasting time. Obviously, the optimal dosage, timing, and specific cases that benefit the most from this intervention should be investigated.

Keywords: Hysterectomy, Fasting, Metabolic Stress Responses, Vitamin C

1. Background

The policy of preoperative fasting time after midnight began in 1960 (1). This traditional fasting before surgery is recommended to prevent pulmonary aspiration. However, according to the American Society of Anesthesiologists (ASA) classification, the incidence of pulmonary aspiration during anesthesia is 1 in 7000-8000 cases in ASA classes I and II, and 1 in 400 cases in ASA classes III and IV (2). Contrary to popular perception, prolonged fasting time does not provide a safer condition for the patient and may increase the risk of pulmonary aspiration (3). In the clinical setting, the routine preoperative fasting time is recommended for both solids and liquids without attention to the different times of gastric emptying, which is 3-6 hours for solids and 2 hours for clear liquids (4-6).

Considering several complications due to prolonged preoperative fasting time (including dehydration, anxiety, increased postoperative pain, longer recovery time, and postoperative ileus) and based on current guidelines, the mentioned restricted protocols are no longer recommended (7-9).

On the other hand, it is well recognized that surgery itself and general anesthesia induce stress responses and inflammatory processes with different severities, depending on the type of surgery and anesthesia management (10, 11).

Furthermore, prolonged preoperative fasting time is associated with inflammatory cascade and stress responses, leading to intra- or postoperative complications (9). It should be noted that due to emergency surgeries, delays in transferring patients to the operating room or instrumental factors, and other reasons, prolonged preoperative fasting time might be inevitable. Therefore, protective strategies regarding these conditions are strongly recommended.

In this research, for the first time, the effects of ascorbic acid on stress response among patients undergoing abdominal hysterectomy following prolonged fasting time were assessed. Ascorbic acid is a water-soluble anti-inflammatory agent and has some beneficial effects on the immune system (12). It has been shown that ascorbic acid stimulates the immune system by enhancing T-lymphocyte proliferation in response to inflammation, leading to increased cytokine production and immunoglobulin synthesis. The underlying potential mechanism may be the inhibition of signaling pathways involved in T-cell apoptosis. Experimental studies have also shown that ascorbic acid selectively influences intracytoplasmic cytokine production in monocytes and lymphocytes (13). Based on strong evidence, the inflammatory process increases the production of reactive oxygen species (ROS), which may deplete antioxidant stores, including ascorbic acid (14). Ascorbic acid is structurally similar to glucose and can replace it in many chemical reactions and, thus, is effective in the prevention of non-enzymatic glycosylation of proteins.

The anti-inflammatory properties of ascorbic acid could be explained by the ability to downregulate the hepatic messenger RNA (mRNA) expression for the tumor factors and interleukins, as well as by modulating the nuclear factor-κB (NF-κB) DNA binding activity (15). In addition, ascorbic acid has other benefits, including tissue and bone formation effect, antioxidant enzymes-activating effect, and iron absorption-enhancing effect, as well as nephronprotective, antioxidant, antidiabetic, and antimicrobial properties (6, 16-19).

The safety and efficacy of ascorbic acid have been examined in various inflammatory reactions rather than prolonged preoperative fasting time (20, 21). Additionally, it should be noted that a meta-analysis revealed that ascorbic acid concentrations were significantly depleted following surgery independent of the surgery type. Considering its anti-inflammatory properties, theoretically, prophylactic supplementation with ascorbic acid could restrict the stress response reactions (22, 23).

2. Objectives

Based on the above-mentioned evidence, in this study, the anti-inflammatory properties of ascorbic acid were investigated in abdominal hysterectomy cases suffering from the consequences of prolonged preoperative fasting time.

3. Methods

This double-blind, randomized clinical trial was conducted in Iran at Alzahra Hospital affiliated with Guilan University of Medical Sciences (GUMS) from October 2019 to May 2020. First, the aim of the study was explained to the patients; then, informed consent was obtained.

3.1. Sample Size

Based on the preliminary study, in 2 groups of 10 subjects who underwent exactly the study protocol, C-reactive protein (CRP) values were 0.54 $\pm$ 1.1 mg/dL and 1.5 $\pm$ 2.01 mg/dL in group C and group P, respectively. Considering d = 1.1, β = 10%, and $\propto$ = 0.05, a sample size of 40 in each group was calculated.

Women candidates for elective abdominal hysterectomy were screened for eligibility according to inclusion/exclusion criteria.

3.2. Inclusion Criteria

Women who were candidates for elective abdominal hysterectomy, aged 35 - 65 years (ASA classes I and II), and suffering from at least 12 hours preoperative fasting time were enrolled in this study.

3.3. Exclusion Criteria

Women with diabetes/history of insulin resistance, malignancy, and inflammatory or autoimmune diseases, as well as those who did not consent to participate or had corticosteroid therapy, were excluded from the study.

3.4. Randomization and Blinding

The method of the random allocation sequence was quadrant blocks using SAS version 9 (SAS Institute Inc, USA). The method of allocation concealment was based on 2 letters C and P. An anesthesia technician who was not aware of the study hypothesis prepared Vitamin C and normal saline in exactly the same 10 mL syringes. The patient and the investigator who documented the data were blinded to the study groups.

3.5. Intervention

In the treatment group, 1 g of vitamin C (Ampule, 500 mg/5 mL; Exir Company) was injected into 500 mL of normal saline serum within 20 minutes. In the placebo group, normal saline was injected into the serum in the same way. Based on some previous successful administered dosages of intravenous (IV) ascorbic acid (24-26) and considering the lack of similar studies on this issue, this dosage was selected. In order to measure CRP and blood sugar (BS) values, a peripheral blood sample was taken 4 times. The first measurement point time was before the induction of anesthesia (T0). The next times were immediately (T1), 24 (T2), and 48 hours (T3) after the patient was extubated. Moreover, mean arterial pressure (MAP) and heart rate (HR) were recorded at the mentioned point times, and any adverse effects were documented as well. Finally, the collected data were compared between the 2 groups.

3.6. Standard General Anesthesia Protocol

Arriving in the operating room, standard monitoring, including non-invasive blood pressure (NIBP), pulse oximetry, and oxygen saturation (SO_2), was performed; then, the infusion of normal saline was started. Intraoperative fluid therapy was performed based on the standard guidelines to prevent hypovolemia or volume overload, leading to a stable status. A standard protocol of general anesthesia was considered for all cases in both groups. Fentanyl 4 μ/kg and midazolam 0.05 mg/kg were administered as premedication, and anesthesia was induced by propofol 1 mg/kg; 3 minutes after injection of atracurium 0.5 mg/kg, the trachea was intubated. Anesthesia maintenance was provided by isoflurane (1 MAC) and 60% N_2O. To reverse the effects of muscle relaxant, atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were administered at the end of surgery. In order to unify the patients in terms of influencing factors on the degree of the stress response, just one surgeon performed all the surgeries. At the end of surgery, patients were transferred to the recovery room in a stable hemodynamic status. Oral intake was performed after the return of bowel function almost within 8 - 10 hours, and the patient's mobilization was started 12 hours following surgery.

3.7. Ethical Consideration

First, the study protocol was approved by the Local Ethics Committee of GUMS (code: IR.GUMS.REC.1397.379) and then registered on the Iranian Registry of Clinical Trials (IRCT) website (code: IRCT20130814014359N5).

3.8. Statistical Analysis

SPSS version 21 (SPSS Inc, Chicago, Ill, USA) was used to analyze the data. Repeated measurement, 1-way analysis of variance (ANOVA), t, chi-square, and Friedman tests were used as well. Statistically, a P value < 0.05 was considered significant.

4. Results

Finally, the data of 80 patients were analyzed. Baseline characteristics of cases in the 2 groups had no significant difference (Table 1). Based on CRP and BS values, no expected harmful effects of long-term preoperative fasting were observed at baseline (T0), as these items were presented in the normal range, group C (0.27 ± 0.23), group P (0.36 ± 0.28), and group C (97.8 ± 9.3), group P (98.97 ± 10.0), respectively. A statistically significant difference was observed between the 2 groups in terms of CRP and BS values in T1 CRP serum levels; at the end of the study, CRP values were 0.5 ± 0.55 and 0.92 ± 0.69 in groups C and P, respectively (P = 0.012), and BS levels were 124.12 ± 18.11 and 152.0 ± 17.36 in groups C and P, respectively (P = 0.0001). However, this significant difference was not observed at T2 regarding CRP (P = 0.145) and BS (P = 0.135), as well as at T3 regarding CRP (P = 0.282) and BS (P = 0.213). According to both CRP and BS values, the trend of changes from T0 to T3 was significant in the 2 groups (P < 0.0001). Hemodynamic parameters were not significantly different between the 2 groups at 4 measurement point times (Table 2). No adverse event was reported in the 2 groups, and all of our patients were discharged on the third day after surgery.

5. Discussion

Studies have shown that abdominal hysterectomy (as the second most common major gynecological procedure after cesarean section) is associated with significant stress response and cytokine release; in this regard, some preventive strategies have been introduced (27-33). Recently, prolonged preoperative fasting time has been recognized as an additional stressor for surgery-related inflammatory cascade. Despite numerous efforts to develop optimal management of surgery patients regarding physiological and pharmacological management, the impact of preoperative nutritional strategies on metabolic stress response has not been sufficiently focused on (26). Studies have shown that metabolic state during surgery is directly associated with surgery stress response (25). It has been confirmed that insulin resistance following prolonged fasting time is associated with cytokine release and increased metabolic rate and catabolism, similar to what happens in surgery-related stress response (13, 14).

Moreover, studies have indicated that in prolonged preoperative fasting time, the patient remains in catabolic status, despite nutrition starts. In addition, anxiety, headache, and hemodynamic instability due to fasting could be precipitating factors (15). It has been demonstrated that patients with higher preoperative reserve could better cope with surgical stress (24). In this regard, recent studies have shown that traditionally, fasting time before surgery is not only unnecessary but also harmful

Table 1. Characteristics of the Patients and Surgery

Variables	Group C	Group P	P Value
Age	48.6 ± 3.5	48.52 ± 4.16	0.931 [a]
ASA class			
I	29 (72.5)	28 (70)	0.805 [b]
II	11 (27.5)	12 (30)	
BMI	29.3 ± 2.49	29.05 ± 3.19	0.697 [a]
Surgery duration (min)	170.85 ± 7.98	127.27 ± 10.85	0.506 [a]
Fasting time (h)	13.31 ± 2.07	13.27 ± 1.89	0.736 [a]

Abbreviations: ASA class, the American Society of Anesthesiologists classification; BMI, body mass index.
[a] *t* test.
[b] Chi-square test.

Table 2. The Trend of Changes of Blood Sugar, C-reactive Protein, Mean Arterial Pressure, and Heart Rate from T0 to T3

Groups	T0	T1	T2	T3	P Value	F	P Value	F
Group C								
BS	97.8 ± 9.3	124.12 ± 18.11	119.42 ± 11.21	100.82 ± 5.6	0.0001	66.33	0.0001 [a]	32.01
Group P	98.97 ± 10.0	152.0 ± 17.36	122.7 ± 7.87	102.6 ± 6.96	0.0001	226.4		
P value	0.588	0.0001	0.135	0.213				
t	0.544	7.02	1.51	1.25				
Group C								
CRP	0.27 ± 0.23	0.54 ± 0.96	2.51 ± 0.68	3.2 ± 3.29	0.0001	26.33	0.443 [b]	0.89
Group P	0.36 ± 0.28	1.4 ± 2.07	3.3 ± 2.79	3.98 ± 2.89	0.0001	36.63		
P value	0.136	0.022	0.16	0.263				
t	1.5	2.36	1.41	1.12				
Group C								
MAP	74.77 ± 3.97	75.35 ± 3.73	75.37 ± 3.82	75.17 ± 3.82	0.516	0.638	0.884 [a]	0.116
Group P	74.6 ± 5.45	74.82 ± 4.52	75.05 ± 3.52	75 ± 3.67	0.72	0.317		
P value	0.87	0.573	0.671	0.835				
t	0.164	0.566	0.426	0.209				
Group C								
HR	76.37 ± 6.13	77.77 ± 4.66	78.4 ± 3.96	77.87 ± 5.65	0.166	1.88	0.562 [a]	0.431
Group P	78.65 ± 6.94	78.97 ± 5.35	79.52 ± 4.75	79.22 ± 4.94	0.66	0.525		
P value	0.125	0.289	0.254	0.259				
t	1.55	1.06	1.15	1.13				

Abbreviations: BS, blood sugar; CRP, C-reactive protein; MAP, mean arterial pressure; HR, heart rate.
[a] Repeated measurement 1-way ANOVA.
[b] Friedman test.

(7). It has been emphasized that anesthesiologists' practice and attitude should be revised (34). In other words, fasting time exacerbates stress response following surgery; also, avoidance of 6 - 8 hours fasting limits the severity of stress response and insulin resistance (35). Consistent with the present study, several studies have shown that by preoperative infusion of glucose or oral carbohydrate-rich fluids, insulin resistance and consequently the inflammatory cascade are reduced (34, 36).

Furthermore, studies have assumed that the association between preoperative fasting time and stress response could be due to a mechanism other than insulin resistance. Nygren found that perioperative nutritional support led to a better nitrogen balance and fewer inflammatory reactions (37). Based on the current literature, this study, for the first time, evaluated the effects of IV ascorbic acid on stress response severity in abdominal hysterectomy cases suffering from the consequences of prolonged preoperative fasting time. Although indicating the novelty of the work, it restricts the challenging comparisons.

In the following, we will discuss some studies indicating the anti-inflammatory properties of ascorbic acid in various conditions. In a supporting study, Fowler et al reported that IV ascorbic acid could effectively reduce inflammatory reaction in severe sepsis and significantly improve some outcomes, including sequential organ failure assessment (SOFA) score, CRP values, endothelial injuries, and organ failure compared to the placebo group. This could be justified by the difference between studies regarding the higher dosage and longer duration of infusion (38). Diomede et al also demonstrated the anti-inflammatory effects of ascorbic acid on cell homeostasis (39). Gęgotek et al found the antioxidative effects of ascorbic acid on skin fibrosis caused by UV radiation (40). Sun et al concluded that diabetic patients could benefit from the anti-inflammatory properties of ascorbic acid in wound healing (41). Consistent with previous studies, we also found that abdominal hysterectomy led to a significant stress response (42).

Despite the attempt to maintain a suitable depth of anesthesia using appropriate anesthetic drugs, considering any fluctuations in hemodynamic parameters, and performing surgery by an experienced surgeon, stress reactions occurred, presenting in BS and CRP values. Therefore, protective interventions seem necessary against these adverse reactions. It should be noted that this study was designed with the assumption that prolonged preoperative fasting time leads to insulin resistance and BS disturbance (43, 44); an expectation that was not observed in our cases, as baseline BS and CRP values were normal. This finding indicates that the issue may need more attention among older patients with higher ASA classes, who were routinely scheduled early morning; these cases were excluded from the present study.

It should also be considered that the mentioned adverse reactions might occur following longer preoperative fasting times, or other inflammatory markers should be examined. Therefore, in normal baseline BS values, the exact site of action of the positive anti-inflammatory effects of ascorbic acid could not be determined. In our study, the beneficial effects of ascorbic acid were only observed after surgery—but not in the next measurement point times. The trend of BS changes from T0 to T3 was significant in both groups, with the highest values at T1. Comparing the 2 groups, the difference was statistically significant only at T1, although at other point times, T2 and T3 BS values were higher in group P. In terms of CRP values, the same pattern was observed; higher values were in group P but significantly differed only at T1.

It seems that ascorbic acid induced positive effects for this purpose; however, a higher dosage or infusion might be required to achieve more beneficial effects. In terms of CRP values, the same pattern was observed; higher values were in group P but significantly differed only at T1. It seems that ascorbic acid induced positive effects for this purpose; however, a higher dosage or infusion might be required to achieve more beneficial effects. In terms of hemodynamic parameters, patients in both groups were kept stable status with no significant difference. It was expected because our cases were candidates for elective surgery, optimized after a preoperative visit and scheduled in stable conditions. On the other hand, ASA classes III and IV patients were not enrolled in the study. This study provided valuable and informative results and, despite some limitations, could be served as a model for future studies. As ascorbic acid is a safe, available, easy to use, and cost-effective agent, it is worth planning future works based on the results of this study (45).

Obviously, this paper raised several questions: (1) whether better results could be achieved by a higher dosage or infusion of ascorbic acid?; (2) are the positive effects of the drug due to the depletion of ascorbic acid following surgery?; (3) are patients in good health significantly affected by prolonged fasting time?; (4) are there additional stress indicators (besides BS and CRP) that should be evaluated and may yield different results?; (5) is fasting time longer than 12 hours clinically harmful?; (6) The mean preoperative fasting time in our study was 13 hours, while other studies have demonstrated much longer preoperative fasting times; therefore, the suppressing effects of our intervention might be exerted on surgery stress responses rather than the inflammatory process due to prolonged preoperative fasting time. Overall, future studies are needed to address these ambiguities and find the optimal timing and dosage of ascorbic acid, as well as specific cases that benefit the most from this intervention.

5.1. Limitations

We acknowledge some limitations of this paper. It was a single-center trial with a limited sample size. Furthermore, our evaluation was limited to CRP and BS values. If other inflammatory markers [such as tumor necrosis factor α (TNF-α) or interleukin 10 (IL10)] were evaluated, different results might be achieved. The other limitation of this study was the exclusion of high-risk patients in ASA classes III and IV. Moreover, the depth of anesthesia was not assessed based on the bispectral index (BIS).

5.2. Conclusion

According to the promising results of this study, it seems that ascorbic acid could be an effective and safe option for stress response reduction in abdominal hysterectomy cases after prolonged fasting time, which presents itself in CRP and BS values. However, in a single dosage, only short-term benefits were achieved. In order to confirm these results and be able to recommend this strategy in clinical practice, further well-designed clinical trials are required.

Acknowledgments

The authors would like to thank Anesthesiology Research Center members Mrs Mohadese Ahmadi and Ms Mahin Tayefeh Ashrafie for their collaboration in this study.

Footnotes

Authors' Contribution: All the authors were involved in the manuscript preparation process.

Clinical Trial Registration Code: The study protocol was registered on the Iranian Registry of Clinical Trials (IRCT) website (code: IRCT20130814014359N5).

Conflict of Interests: The authors declare no conflict of interest.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Ethical Approval: The study protocol was approved by the Local Ethics Committee of GUMS (code: IR.GUMS.REC.1397.379).

Funding/Support: The authors declared nothing regarding funding.

Informed Consent: The aim of the research was explained to the patients; then, informed consent was obtained.

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