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Intravenous ascorbic acid (vitamin C) administration in myomectomy: a prospective, randomized, clinical trial

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Abstract
Background To assess the usefulness of using ascorbic acid (vitamin C) administration in abdominal myomectomy.
Materials and methods A total of 102 patients were divided two groups in this prospective, clinical trial. Group A had received 2 g of ascorbic acid during a myomectomy, and group B had a myomectomy without any interventions. The operative time, blood loss, days of hospitalization, post-operative complications and rate of blood transfusions were compared between the two groups.
Results The blood loss (521.44 ± 199.24 vs. 932.9 ± 264.38 ml; p value <0.001), duration of the operation time (42 ± 13.9 vs. 68 ± 21.7 min; p value <0.001), days of hospitalization (2.7 ± 0.69 vs. 3.1 ± 0.59 days; p value 0.002) in group A were significantly less than in group B (p value 0.001). The chance risk ratio of a blood transfusion in group A was 0.4 (7.7 vs. 18% 95% CI of 0.1–1; p value 0.07). There was a significant correlation between the volume of bleeding and post-operative complications in both groups (p value in group A = 0.03; in group B = 0.004).
Conclusion The administration of ascorbic acid (vitamin C) in abdominal myomectomy could reduce the blood loss during the procedure, operation time and days of hospitalization.

Keywords Platelet · Ascorbic acid · Vitamin C · Myomectomy

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Introduction

The management of uterine myoma in reproductive-age women is always a challenge. Some non-invasive treatments, like GnRH agonists [1], aromatase inhibitors [2] and progesterone antagonists (i.e. mifepristone) [3], have been proposed. In addition, minimally invasive techniques, such as: uterine artery embolization (UAE) [4], high-intensity focused ultrasound (HIFU) [5], and magnetic-resonance-guided focused ultrasound surgery (MRgFUS) [6] have also been used. Despite these many options, abdominal myomectomy remains the standard therapeutic choice.

The greatest operative risk, which makes the operation even higher risk than a hysterectomy and requires an experienced surgeon, is uncontrolled intraoperative bleeding with life-threatening complications. The risk of a blood transfusion after abdominal myomectomy has been reported to be 20%, and there exits 2% having convert the operation to an undesirable and unplanned outcome: a hysterectomy [7].

Inside a fibroma vascularisation is poor but the surrounding myometrium has a rich vascular plexus. Due to the mechanical pressure of the myoma on the peripheral myometrium, the dilatation of vessels and blood congestion can lead to significant bleeding after myoma enucleation; consequently, efficient haemostasis is the cornerstone of a myomectomy. There are some interventions used to reduce bleeding. One of the oldest techniques is to use clamps or tourniquets [8, 9]; uterine artery ligation has also been attempted [10]. Various chemical haemostatic agents, such as: intramyometrial vasopressin [11], intravenous tranexamic acid [12], intravaginal misoprostol [13], and intravenous oxytocin [14] have been used. However, according to a Cochrane review [15], none of the above efforts demonstrate acceptable results.

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Ascorbic acid (AA), or vitamin C, has a known role in tissues repair. Due to its properties (water-soluble), vitamin C is not stored in the body and, when depleted, the bleeding tendency will increase due to dysfunctional connective tissue production in vessel wall. In addition to the familiar regenerative role of AA, it has some important functions in platelets; such as, antioxidizing activity and reducing the level of reactive oxygen species (ROS) [16]. AA accumulates in platelets [17]. During the first phase of haemostasis, platelets are activated and aggregated to form a haemostatic plug. Then, after thrombin activation, once the fibrin clot has been established, "secondary haemostasis" [18], free radicals or ROS are produced that dissolve platelets [19]. From another perspective, during platelet activation and aggregation, AA is consumed, resulting in greater sensitivity to ROS [20]. Therefore, at that stage, exogenous AA administration might compensate for the functional, secondary thrombocytopenia (due to thrombin production) [19]. In addition, in the post-aggregation phase, AA could increase platelet–fibrin clot stability and strength [16].

The aim of our prospective study was to compare the usefulness of AA administration during an abdominal myomectomy and to evaluate its effect on blood loss and other complications.

Materials and methods

A prospective comparative randomized clinical trial was performed in the obstetrics and gynecology ward of Imam Khomeini Teaching Hospital in Ahvaz, Iran.

From October 2009 to August 2010, women ($n = 102$) at reproductive age who were admitted for an abdominal myomectomy were randomly assigned to group A ($n = 52$), received ascorbic acid or group B ($n = 50$), no ascorbic acid.

The inclusion criteria were the following: (1) at least one non-cavitary fibroma $\geq$40 mm^3 in size; (2) a normal coagulation profile (bleeding time, clotting time, platelet number, prothrombin time and activated partial thromboplastin time); (3)non-smoker; (4) no history of chronic illness (renal failure, drug abuse, haemoglobinopathy or respiratory, liver or heart disease); (5) no history of recent hospitalization; (6) regular consumption of fresh fruit or vegetables at least once a day and (6) no history of glucose 6-phosphatase dehydrogenase (G6PD) deficiency [21].

After receiving institutional ethical committee approval and participant informed consent, the study began. In all patients age, BMI, marital status, parity, duration of infertility (if present), size and number of myoma on recent ultrasonography, basic haemoglobin (Hb) and haematocrit (Hct) were recorded. Patients with Hb $\leq$8 (mg/dl) received one unit of packed red cells pre-operatively. One surgical team performed all of the operations and the patient's grouping was masked from the operating team.

The abdominal wall was opened with a Millard incision. After reaching the uterus but before the myomectomy, in group A patients, the first ascorbic acid ampule (500 mg in 5 ml, Aboorihan Company, Iran) was infused in 15 ml normal saline at a rate of 50 μg/min. The second ampule was administered during myoma enucleation, and the third was administered during wound closure; all three were infused in the same manner. The last ampule was infused during the serosal closure. After the operation, 2 additional ascorbic acid ampules were infused at a rate of 20 μg/min over the first 12 h postoperatively. The control group was not given AA. In both groups, the myomectomy method was the same and no other interventions, such as ligation or tourniquets, were used. The abdominal closure was performed similarly between groups.

In both groups, the size and number of myoma were recorded after removing all myoma. The duration of the operation was measured from incision of the first myoma to serosal closure of the last myoma wound. Bleeding was measured by adding the blood collected via suction with the number of soaked surgical 4×4-cm gauze (each one assigned a value of 5 ml blood) and towels (each one was assigned a value of 50 ml blood), used during the myomectomy.

Hb and Hct were rechecked 6 h after the operation. In any patient with a >2 units drop in Hb with clinical symptoms or with bleeding >1,100–1,200 ml during the myomectomy, a blood transfusion was administered. Other complications were recorded during the hospitalization period.

The statistical analysis was performed using SPSS 16.0 for Windows. A *t* test, paired *t* test, Chi-square test, Fisher exact test and Pearson correlation index were used for data analysis. Significance was defined at $p < 0.05$.

Results

In total, 102 patients were enrolled in the study (52 patients in group A, and 50 patients in group B). The basic demographic characteristics were similar in the two groups (Table 1). The duration of the procedure, amount of bleeding and days of hospitalization (after the operation) were significantly less in group A. The total size and number of myoma seen on pre-operative ultrasonography in both groups were similar, but the total size of the removed myoma was higher in group A (Table 2). In group A, there was a 74 and 71.4% increase in the number and size of the removed, respectively, in group B, there was 45 and 36% increase, respectively.

Table 1 Maternal demographic and clinical characteristics in treated group (A) and non-treated group (B)

Characteristics	Group A	Group B	*p* value
Age (year)	32 ± 4.5	30.4 ± 6.5	0.15
BMI (kg/m^2)	22.6 ± 2.4	22.9 ± 2.1	0.48
Duration of infertility	3.2 ± 3.9	4.1 ± 3.6	0.26
Married[a]	42	36	0.3
Single[a]	10	14	
No pregnancy[b]	35	35	
History of abortion[b]	12	8	0.58
At least one child[b]	5	7	
Mean Hb (mg/dl)	10.12 ± 0.9	10.05 ± 1	0.52
Mean Hct (%)	32.29 ± 2.6	31.26 ± 2.3	0.81

[a] Marital status

[b] Parity status

In addition, differences between the pre-operative and post-operative haemoglobin and haematocrit levels in both groups were not significant (Table 2).

There was a direct correlation between the duration of the myomectomy and the amount of bleeding (Pearson correlation index 0.59, *p* value <0.001). In both groups, the relationship between bleeding and the rate of post-operative complications was significant (*p* value in group A, 0.03; in group B, 0.004). The relationship between the duration of the operation and complications was not significant (*p* value in group A, 0.16; in group B, 0.14).

In group A, 14 patients had single myoma and 38 patients had multiple myoma; in group B, there were 11 patients with a single and 39 patients with multiple myoma. After the analysis between the two groups, the duration of the myomectomy and the amount of bleeding, was significantly less in group A than group B (Table 3).

The post-operative complications, between two groups were not statistically significant (*p* value 0.7) (Table 4). In group A, 55.8% (29 patients) and in group B, 52% (26 patients) had no problem. None of the operations were converted to a hysterectomy.

Table 3 Comparison of the number of myoma between women who received vitamin C and no received vitamin C during operation

Variable	Group A	Group B	*p* value
Single myoma[a]	33.7 ± 8.3	50.6 ± 10.5	0.001*
Multiple myomas[a]	45 ± 14.4	73.9 ± 21.3	0.001*
Single myoma[b]	420 ± 135	711.3 ± 299.6	0.001*
Multiple myomas[b]	558.8 ± 207	995.3 ± 240.9	0.001*

[a] Duration of myomectomy(min)

[b] Amount of bleeding (ml)

Discussion

A deficiency of ascorbic acid (AA) in surgical patients with normal coagulation profiles has been proposed [22], which is related to the integrity of the vascular wall. In another survey, vitamin C supplementation in clinically ill patients after cardiac or gastrointestinal surgery demonstrated clinical benefits; because of the reduction of oxidative stress [23]. In addition, these advantages have been observed in patients with major trauma and subarachnoid haemorrhage [24]. In these cases, the clinical value of AA administration is due to its antioxidant ability. However, as mentioned before, AA also has an important role in platelet function. Vitamin C plays a crucial role in aggregating platelets and preventing platelet depletion during haemostasis. This specific role has been observed in patients undergoing cardiopulmonary bypass surgery [25].

However, in none of mentioned clinical situations did patients have any risk factors for vitamin C deficiency; rather, it is suggested that subclinical AA deficiency might be more common than previously thought. The recommended daily allowance (RDA) for vitamin C for adults is 60 mg/day, but 20–30% of adults in the United States ingest less than the recommended amount [26]. In addition, another published study reported that, 80% of adults consumed fruits and vegetables, fewer than two times a day [27] and that 16% of college students had a vitamin C deficiency [28].

Table 2 The results obtained after operation in treated group (A) and non-treated group (B)

Variable	Group A	Group B	*p* value
Hb differences (mg/dl)	−0.91 ± 0.83	−0.77 ± 1	0.45
Hct differences (%)	−2.3 ± 1.6	−1.6 ± 1.7	0.26
Number of myomas before operation	1.96 ± 1.04	2.36 ± 1.56	0.13
Number of removed myomas after operation	3.44 ± 2.57	3.34 ± 2.31	0.83
Size of myomas before operation	111.94 ± 50.51	109.6 ± 46.13	0.08
Size of removed myomas after operation	175.63 ± 82.54	142.2 ± 52.6	0.02*
Duration of operation (min)	42 ± 13.9	68 ± 21.7	<0.001*
Amount of bleeding (ml)	521.44 ± 199.24	932.9 ± 264.38	<0.001*
Days of hospitalization	2.7 ± 0.69	3.1 ± 0.59	0.002*

Table 4 The rate of complications after operation in treated group (A) and non-treated group (B)

Complications	F	T	V	C	P	F + P	F + V	V + P	F + T
Group A: Count (%)	9 (17.3)	4 (7.7)	2 (3.8)	0 (0)	4 (7.7)	2 (3.8)	1 (1.9)	1 (1.9)	0 (0)
Group B: Count (%)	5 (10)	9 (18)	1 (2)	1 (2)	2 (4)	2 (4)	1 (2)	0 (0)	3 (6)

F fever, *T* blood transfusion, *V* vomiting, *C* constipation, *P* sever pain needing pethidine

In our study, the duration and the amount of bleeding was reduced in the vitamin C-treated group, which also correlated with fewer complications after the operation. Due to the small sample size in our study, the rate of complications between the two groups was not statistically significant; but, the chance of a blood transfusion was almost 2.5 times greater in the control group. In addition, the differences between pre and post-operative Hb and Hct levels were not significant. In this study, if we had checked the plasma level of AA before the operation, the study could have been more evidence based; but, because of our restricted inclusion criteria, none of the participations had any risk factors for vitamin C deficiency.

Based on these results, we use AA routinely in surgeries, like a hysterectomy. Also, in cases of post-partum haemorrhage in patients without obstetrical problems, we use ascorbic acid administration with excellent clinical results.

In conclusion, even if we do not believe that, subtle vitamin C deficiency is more prevalent than previously reported, AA administration either as a prophylactic agent, or as a therapeutic option could be useful in all gynaecologic or obstetrics procedures without any serious side effects. It is time to re-examine older substances: vitamin C.

Conflict of interest The authors declare no conflict of interest in the study.

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