



Does vitamin C supplementation improve rotator cuff healing? A preliminary study

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Abstract

Purpose One of the complications after rotator cuff repair is a tendon non-healing. It has already been posited in the literature that vitamin C (VC) promotes tendon healing through its antioxidant properties and its role as a cofactor in collagen synthesis. The aim of this study was to evaluate the effect of postoperative VC supplementation on the tendon healing following repair.

Methods This randomized monocentric prospective study included 98 patients who underwent arthroscopic rotator cuff repair in 1-year period and follow-up ultrasound 6 months postoperatively. The cohort was divided into two groups: the VC+ group (500 mg/day PO for 45 days postoperatively) and the VC– group (no supplementation). The evaluation criterion was tendon healing at 6 months postoperatively according to the Sugaya ultrasound classification. Preoperative and postoperative clinical evaluations were based on active mobilities, the Constant score and the subjective shoulder value.

Results There was no difference in term of postoperative outcomes between the two groups. At an average follow-up of 6.3 months, the non-healing rate in the overall population was 17%. This rate was higher in VC– compared to VC+, respectively, 23% vs. 11%, $p=0.2$.

Conclusion This study showed a trend to improve tendon healing after rotator cuff repair with VC supplementation. However, a prospective study with a larger patient population should be conducted to confirm this finding.

Keywords Rotator cuff · Tendon healing · Vitamin C · Antioxidant

Introduction

Rotator cuff injuries are among the three most common tendon injuries along with those of the flexor tendons of the hand and the Achilles tendon. Despite surgical procedures to reinsert these tendons, healing is long and difficult due to their hypocellular and hypovascular nature. The rates of non-healing and scarring defects remain very typical and the incidence ranges in the literature from 7 to 57% [1–3]. Certain risk factors have been identified, in particular the age of the patient at the time of the procedure, the size of the rupture and the associated muscle degeneration [1–4]. In order to improve tendon healing, biological strategies have been explored with autologous growth factors and in particular Platelet-rich Plasma and Stem Cells [5].

Vitamin C (VC) has already been suggested in the literature to promote not only bone consolidation, but also tendon and ligament healing [6, 7]. Because of its two major biological roles as an antioxidant and a cofactor in collagen synthesis, it could have a role in promoting tendon healing while limiting adhesion [8–11].

Tendon healing progresses in several overlapping phases which include the inflammatory, fibroblast and tenocyte proliferation, and tissue remodeling phases [12, 13]. Tendons are made of connective tissue composed of collagen fibers, a protein that provides mechanical strength. Tendon healing partly requires renewal and remodeling of collagen fibers.

In degenerative tendinopathies, these fibers are thinned, fragile, ruptured and disorganized [14]. Oxidative stress is one of the intrinsic factors responsible for tendon degeneration [15]. Through its antioxidant effect, VC contributes to the proliferation of fibroblasts and an increase in collagen production while increasing the diameter of collagen fibers [13, 16]. Recent studies in a mouse model seem to confirm the value of VC to limit rotator cuff tendon degeneration [15, 17].

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Our hypothesis was that VC may play a role in the tendon healing phase of repaired rotator cuff lesions and thereby increase the rate of healing.

Therefore, the aim of our study was to compare tendon healing after arthroscopic reinsertion with and without oral VC supplementation.

Materials and methods

Study design and patient selection

This is a prospective, monocentric randomized study approved by the local Ethical Committee (RnIPH 2020-150).

We included all patients who underwent arthroscopic a primary rotator cuff repair between January 1 and December 31 2018. The exclusion criteria were a retraction of at least one tendon superior or equal to grade 3, fatty degeneration of at least one muscle superior or equal to grade 3, an anatomically non-repairable tear, and an isolated injury of the subscapular (Ssc) tendon. Patients without a clinical and ultrasound evaluation at a minimum follow-up of 6 months were excluded.

The randomization process was carried out by year of birth: patients born in an even number year received postoperative VC supplementation at a dose of 500 mg per day orally for 45 days (VC+ group) and patients born in an odd number year received no supplementation (VC–group). Treatment adherence and adverse events were monitored at the follow-up consultation and documented in the medical record.

Surgical technique

All surgeries were performed by the same surgeon specialized in shoulder surgery (NB), under combined locoregional and general anesthesia, with the patient in the beach chair position. Using four arthroscopic approaches, the glenohumeral joint was first explored and tendon retraction was evaluated according to the Patte classification. Tenotomy or tenodesis of the long head biceps (LHB) was performed if a pathology was identified (tenosynovitis, instability or hourglass biceps). After bursectomy, an acromioplasty was systematically performed using a motorized burr. Before performing the tendon repair, the footprint was freshened and the end of the tendon was debrided. Cuff repair was performed using a single-row tension band technique or a double-row suture bridge technique using Fixit® screw anchors (SBM, Lourdes) [18]. In case of partial thickness tear, the tear was first completed, then repaired. Acromioclavicular resection was performed in case of painful degenerative joint disease prior to surgery.

Postoperative protocol

In postoperative care, all patients followed the same rehabilitation protocol. The limb was partially immobilized for 45 days with a sling in internal rotation. Pendular shoulder exercises were started as of the early days after surgery and passive range of motion supervised by a physiotherapist starting on the 15th day. Active exercises could be initiated on the 45th day, then progressive muscular reinforcement as of the 3rd month. A return to professional activities requiring heavy lifting was not allowed before the 6th month after surgery.

Clinical evaluation

A detailed interview concerning the main epidemiological characteristics was carried out when the patients were included.

Preoperatively, then at 45 days, 3 months and 6 months postoperatively, active mobility was measured in anterior elevation, external rotation, internal rotation and abduction using a goniometer. Constant (Cst) and subjective shoulder value (SSV) functional scores were established preoperatively and at 6 months [19, 20].

Complications were identified and entered in the medical record at each stage of follow-up.

Radiological evaluation

Preoperatively, the diagnosis of rotator cuff injury was established either by Magnetic Resonance Imaging ($n=47$; 48%) or by Arthro-CT scan ($n=51$; 52%). Through this examination, fatty muscle degeneration was analyzed according to the Goutallier classification.

At 6 months postoperative, tendon healing according to the Sugaya classification was evaluated by ultrasound by a radiologist specialized in osteoarticular imaging [21, 22]. Tendon integrity was then classified into two categories: intact (corresponding to Sugaya types I and II) or unhealed (Sugaya types III, IV and V) [23, 24].

Statistical analysis

Descriptive statistics (mean, maximum, minimum and standard deviation for continuous variables and frequencies with proportions for categorical data) were used to summarize recorded variables. Student (parametric test) or Wilcoxon Rank Sum (non-parametric test), and Pearson's Chi-Square (parametric test) or Fisher's exact tests were used to test univariate differences across groups (VC+ versus VC–) in

continuous and categorical variables, respectively. The statistical significance was set at $p < 0.05$. The statistical analysis was carried out with the StatiS[®] software.

Results

Description of the population

Ninety-eight patients were included during the period of the study. 8 patients were excluded because of lost to follow-up, leaving 46 patients in VC+ and 44 patients in VC- group available for statistical analysis (Fig. 1).

The mean age at the time of surgery was 60.8 years (range, 45–75 years) and 56% ($n = 50$) were female. The mean Cst score was 49.7 points (range, 16–82), and the mean SSV was 41.7% (range, 0–100) preoperatively. Fifteen patients were off work prior to the intervention (17%) and 35 were retired (39%). The population epidemiological data are provided in Table 1. There was no significant difference between the 2 groups.

The tendon injury was degenerative with a progressive onset in 50 cases (56%). The Supraspinatus tendon was minimally retracted (stage 1) in the majority of cases ($n = 57$; 63%). Data on the type of injury and repair are

presented in Table 2. The two groups were comparable in terms of these data, except for the associated Subscapularis tendon repair which was more frequent in the VC- group.

Clinical outcomes

In the VC+ group, functional scores improved significantly at an average follow-up of 6.4 months (5.5–8). The average SSV was 39% (10–100) preoperatively and 88% (50–100) at the last follow-up ($p = 0.001$). The mean Cst score was 50 points (18–82) preoperatively and improved to 71.8 points (33–100) 6 months postoperatively ($p = 0.001$).

In the VC- group, the average preoperative SSV of 44.7% (0–80) improved significantly to 83% (50–100) at an average follow-up of 6.3 months (5.5–10) ($p = 0.001$). The mean preoperative Cst score at 49.4 points (16–82) also improved significantly 6 months postoperatively to 72.5 points (38–92) ($p = 0.001$).

No significant difference was noted in the overall Cst score and the postoperative SSV when the two groups were compared. There were no significant differences regarding active mobility either.

These results are presented in Table 3.

Fig. 1 Flow diagram

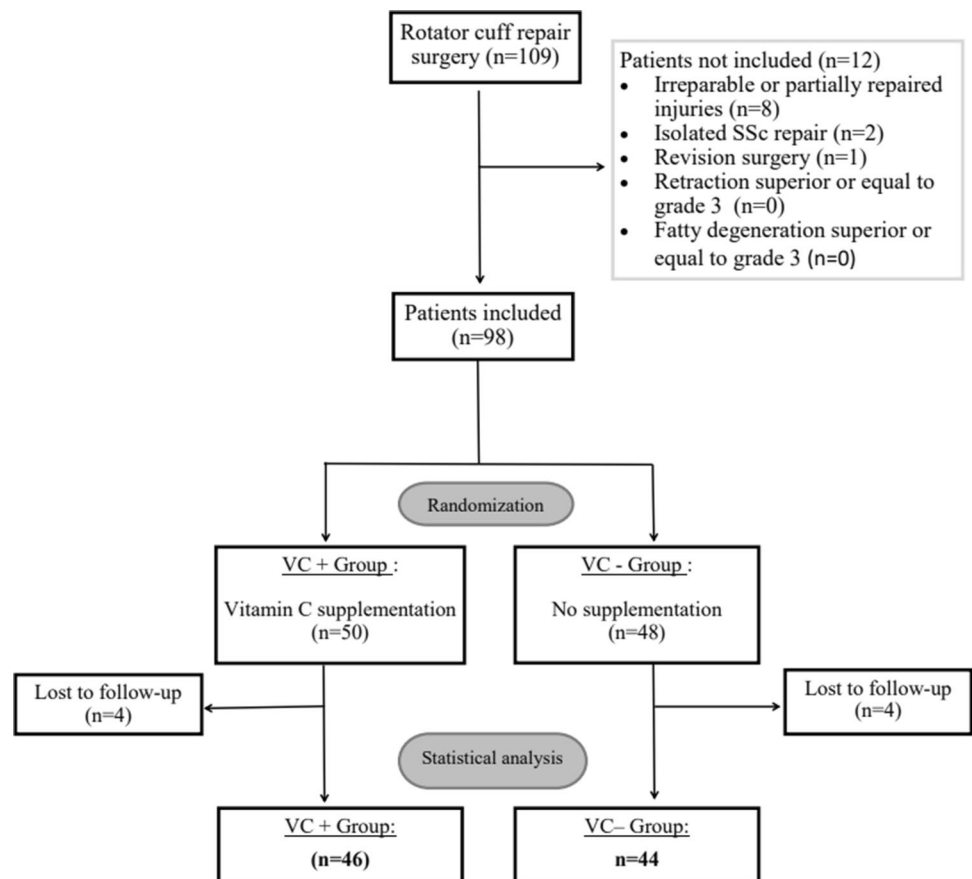


Table 1 Comparison of the population demographics and clinical data

	Overall population <i>n</i> = 90	VC+ group <i>n</i> = 46	VC- group <i>n</i> = 44	<i>p</i> value
Age at the time of surgery, (years) mean (SD; min–max)	60.8 (7.4; 45–75)	60 (7; 46–74)	62 (7.8; 45–75)	0.2
Female gender, <i>n</i> (%)	50 (56%)	27 (59%)	23 (52%)	0.9
Dominant side, <i>n</i> (%)	72 (80%)	35 (76%)	37 (84%)	0.5
Professional activity, <i>n</i> (%)				0.1
Unemployed	1 (1%)	0 (0%)	1 (2%)	
Sedentary work	22 (24%)	12 (26%)	9 (19%)	
Moderate manual work	24 (27%)	8 (17%)	16 (37%)	
Hard physical work	43 (48%)	26 (57%)	18 (42%)	
Sick leave, <i>n</i> (%)	15 (17%)	11 (24%)	4 (9%)	0.2
Retired, <i>n</i> (%)	35 (39%)	16 (35%)	19 (44%)	0.2
Preoperative evaluation mean (SD; min–max)				
Global <i>Cst</i> score (100 pts.)	49.7 (16.5; 16–82)	50 (17.2; 18–82)	49.4 (16; 16–82)	0.9
Pain (15 pts.)	6.9 (2.5; 0–13)	6.7 (2.6; 0–13)	7.1 (2.4; 2–11)	0.4
Activity level (20 pts.)	8.1 (3.6; 0–16)	8.1 (3.8; 0–16)	8.2 (3.5; 0–16)	0.9
Mobility (40 pts.)	27.3 (8.7; 1–40)	28 (8.7; 8–40)	26.9 (8; 4–38)	0.5
Anterior elevation (10 pts.)	7.7 (2.3; 0–10)	7.8 (2.3; 2–10)	7.6 (2.2; 2–10)	0.6
Abduction (10 pts.)	6.4 (2.6; 0–10)	6.4 (2.6; 0–10)	6.3 (2.7; 0–10)	0.8
External rotation (10 pts.)	7.2 (2.6; 0–10)	7.4 (2.8; 0–10)	7.1 (2.4; 2–10)	0.6
Internal rotation (10 pts.)	6.2 (2.3; 0–10)	6.3 (2.5; 2–10)	6.1 (2.1; 0–10)	0.7
Strength (25 pts.)	2.7 (3.1; 0–13)	3.3 (3.5; 0–13)	2 (2.4; 0–9)	0.2
SSV (%) mean (SD; min–max)	41.7 (22.3; 0–100)	39 (21; 10–100)	44.7 (24; 0–80)	0.3
Comorbidities				
Smoking, <i>n</i> (%)	14 (15.6%)	6 (13%)	8 (18.2%)	0.9
Type II diabetes, <i>n</i> (%)	6 (6.7%)	2 (4.3%)	4 (9.1%)	0.3
Dyslipidemia, <i>n</i> (%)	12 (13.3%)	7 (15.2%)	5 (11.4%)	0.9
Dysthyroidism, <i>n</i> (%)	10 (11.1%)	7 (15.2%)	3 (6.8%)	0.5
Depression ± anxiety, <i>n</i> (%)	9 (10%)	7 (15.2%)	2 (4.5%)	0.2
History of CRPS1, <i>n</i> (%)	4 (4.4%)	3 (6.5%)	1 (2.3%)	0.9
Duration of follow-up (months), mean (SD; min–max)	6.3 (0.7; 5.5–10)	6.4 (0.7; 5.5–8)	6.3 (0.8; 5.5–10)	0.6

n absolute value, *SD* standard deviation, *min* minimum, *max* maximum, *pts* points, *Cst* constant, *SSV* subjective shoulder value, *CRPS* complex regional pain syndrome

Radiographic results

At an average follow-up of 6.3 months (5.5–10), the overall rate non-healing was 17% (*n* = 15) (Sugaya III: *n* = 10; Sugaya IV: *n* = 1; Sugaya V: *n* = 4). This rate was lower for patients in the VC+ group (*n* = 5; 11%) than for those in the VC- group (*n* = 10; 23%) (*p* = 0.2).

The results are presented in Table 3. Ultrasound pictures of a healed and an unhealed tendon at 6-month follow-up are reported in Fig. 2.

Discussion

The main outcome of the study was the effect of VC on rotator cuff tendon healing after transosseous repair at 6 months of follow-up. The second outcome was the effect on postoperative functional improvement.

Table 2 Comparison of the type of injury and surgical management

	Overall population <i>n</i> = 90	VC+ group <i>n</i> = 46	VC– group <i>n</i> = 44	<i>p</i> value
Type of injury				
<i>Appearance of injuries, n (%)</i>				0.9
Progressive	50 (56%)	25 (54%)	25 (57%)	
Trauma	40(44%)	21 (46%)	19 (43%)	
<i>Stage of SS retraction, n (%)</i>				0.9
Stage 1	57 (63%)	28 (61%)	29 (66%)	
Stage 2	27 (30%)	15 (33%)	12 (27%)	
Stage 3	6 (7%)	3 (6%)	3 (7%)	
<i>Type of SS injury, n (%)</i>				1
Partial tear	23 (25%)	12 (26%)	11 (25%)	
Full thickness tear	67 (75%)	34 (74%)	33 (75%)	
Associated IS injury, <i>n (%)</i>	43 (48%)	22 (48%)	21 (48%)	1
Associated SSc injury, <i>n (%)</i>	25 (28%)	12 (26%)	13 (30%)	0.9
<i>LHB injury, n (%)</i>				0.9
Subluxation	32 (36%)	15 (33%)	17 (39%)	
Tenosynovitis	35 (39%)	19 (41%)	16 (36%)	
Peroperative data				
<i>Type of repair, n (%)</i>				0.5
Single-row	54 (60%)	26 (57%)	28 (64%)	
Double-row	36 (40%)	20 (43%)	16 (36%)	
<i>Associated procedures, n (%)</i>				
LHB tenotomy	68 (64.5%)	27 (59%)	31 (71%)	0.3
LHB tenodesis	30 (33.5%)	18 (39%)	12 (27%)	0.3
Ssc repair	9 (10%)	0 (0%)	9 (21%)	0.01*
Acromioclavicular resection	20 (22%)	11 (24%)	9 (21%)	0.9

Bold value corresponds to significant *p* value

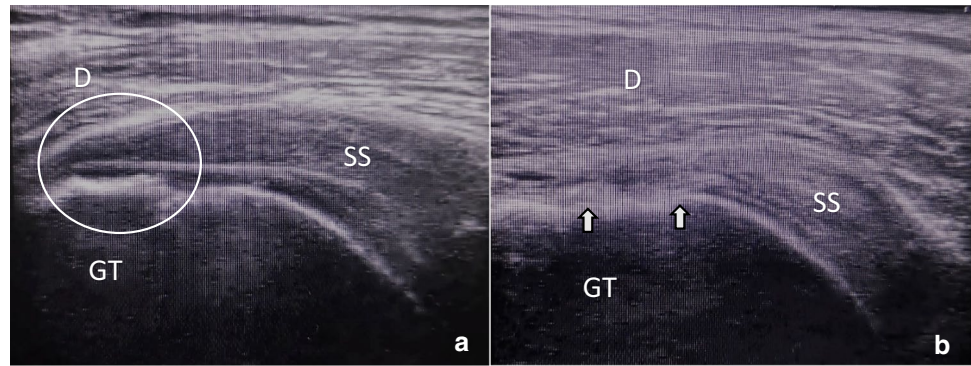
* *n* absolute value, *SD* standard deviation, *SS* SupraSpinatus, *IS* InfraSpinatus, *SSC* SubScapularis, *LHB* long head biceps

Table 3 Results of the univariate statistical analysis

Variables	Overall population <i>n</i> = 90	VC+ group <i>n</i> = 46	VC– group <i>n</i> = 44	<i>p</i> value
Postoperative Cst (pts.), mean (SD; min–max)	72 (15; 33–100)	71.8 (15; 33–100)	72.5 (11.5; 38–92)	0.8
<i>Mobility (pts.), mean (SD; min–max)</i>	35 (5.7; 16–40)	35 (6.4; 16–40)	35 (4.9; 18–40)	0.9
Anterior elevation (°), mean (SD; min–max)	153 (18.2; 90–180)	154 (17.8; 110–180)	153 (18.9; 90–180)	0.9
Abduction (°), mean (SD; min–max)	144 (22.8; 90–180)	146 (24.4; 90–180)	144 (21.4; 90–170)	0.7
External rotation (°), mean (SD; min–max)	47 (15.6; 10–80)	46 (13.9; 20–70)	48 (17.3; 10–80)	0.7
Internal rotation (pts.), mean (SD; min–max)	8 (2.1; 2–10)	8.3 (2.2; 2–10)	8.1 (1.9; 4–10)	0.7
Postoperative SSV (%), mean (SD; min–max)	86 (14.5; 50–100)	88 (14.1; 50–100)	83 (14.7; 50–100)	0.1
<i>Ultrasound evaluation of tendon healing, n (%)</i>				0.2
Healed (Sugaya 1, 2)	75 (83)	41 (89%)	34 (77%)	
Unhealed (Sugaya 3,4, 5)	15 (17)	5 (11%)	10 (23%)	

n number, *SD* standard deviation, *min* minimum, *max* maximum, *pts* points

Fig. 2 Ultrasound pictures of tendon at 6-month follow-up **a** healed tendon; Sugaya 1, **b** unhealed tendon; Sugaya 5



D: Deltoid, SS: Supraspinatus tendon, GT: Greater Tuberosity of humerus, Circle: healed tendon, Arrow: defect

Healing defect

In our study, the tendon healing defect rate was 17%, which is similar to the rates indicated in the literature. Le et al. [3] found a rate of 17% 6 months postoperatively, while a Korean study in 2017 found a rate of 7% in the same postoperative period [1]. This rate remains unchanged at 24 months after surgery and was 15% in the study by Kim et al. [25].

Several perioperative factors may increase the rate of non-healing after rotator cuff repair. Muscle atrophy, fat infiltration, tendon retraction, the length and thickness of the rupture, and the quality and type of sutures used are predictive factors reported in the literature [1, 3]. Saccomanno et al. [4] showed that advanced age was a major factor in the risk of healing defects. Microvascularization of the footprint played an essential role in healing. It is also important to consider smoking and postoperative rehabilitation.

Vitamin C supplementation

In our study, VC could have a favorable effect on healing since 55% of the patients with a healed rotator cuff on ultrasound were in the VC+ group versus 45% in the VC- group. However, the test did not reach the 5% significance threshold. Nonetheless, since the Chi-squared test was close to significance, this means that by including more patients, statistical significance would probably be achieved.

VC has already been used in numerous studies to evaluate the efficacy after musculoskeletal injury [6, 26]. The effect on bone, tendon and ligament healing was explored in animal model [9–11, 15, 17]. The study of Sarisozen et al. [27] suggested that VC supplementation accelerates fracture healing of tibia in rat model. Omeroglu et al. [9] reported that high-dose vitamin C supplementation stimulates effects on the Achilles tendon healing in rat model. Souza et al. [10] showed that local VC injections administered into the paratendinous region can also have a beneficial effect on

the recovery of function of the Achilles tendons of rats by accelerating tissue organization.

Recent human studies have been focused on the link between vitamin C and risk of fracture. Torbergesen et al. [28] suggested that low serum concentration of VC was associated with a higher risk of hip fracture. The link between VC supplementation and osteoporosis has also been studied in humans. Kim et al. [29] showed an association between higher vitamin C intake levels and lower risk of osteoporosis in Korean adults aged over 50 with low level of physical activity.

Morikawa et al. [15, 17] on mice addresses the subject of rotator cuff healing. The authors demonstrated that VC administration attenuates the rotator cuff degeneration [15, 17].

However, to our knowledge, no study was conducted in humans regarding rotator cuff tendons healing.

Oxidative stress

Oxidative stress leads to premature degeneration of healthy tissue. Morikawa et al. [15, 17] analyzed SS tendons of mice with a deficiency in an important intracellular antioxidant enzyme. They found histological signs of early rotator cuff degeneration similar to those found in humans. In addition, they noted collagen fiber disorganization resulting in a loss of connective tissue elasticity. Oral administration of VC to these mice could attenuate the histological changes described above by the antioxidant effect.

Collagen production

VC has a role in the production of collagen proteins and proteoglycans that enable tendon regeneration [6, 8].

In their study of ruptured Achilles tendons in rats, Omeroglu et al. [9] showed that high-dose oral VC supplementation increased angiogenesis and collagen production leading to significant acceleration of healing.

Impact on postoperative clinical scores

In this study, the postoperative Cst score was not significantly impacted by VC supplementation. Nevertheless, the postoperative SSV was higher in the VC+ group. Therefore, VC could improve patients' subjective and global postoperative sensations without having an impact on the objective elements (strength, mobility) of the Constant score.

Limitations

One of the limitations of our study was the lack of strict control of treatment compliance as the data was gathered from patient interviews. No assays were performed to assess VC concentration, and dietary habits were not examined.

Eight patients were lost to follow-up. Given the equivalent distribution of those lost to follow-up between the two groups, this bias should not impact our statistical analysis.

Finally, for this preliminary study, only a few subjects were included and this resulted in a lack of power that did not allow us to obtain statistically significant results. The power of the study with respect to the main hypothesis was calculated a posteriori. We estimated that with 117 eligible patients per group (a total of 234 patients), we would have a power of 80% to detect a clinically significant difference of 12% in the mean proportion of patients with an unhealed rotator cuff, assuming a level of significance of 0.05. Therefore, a subsequent study with a sufficient number of patients should be conducted.

Conclusion

This study showed a trend to improve tendon healing after rotator cuff repair with postoperative VC supplementation. However, a prospective study with a larger patient population achieving satisfactory power should be conducted to confirm this finding.

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Declarations

Conflict of interest The authors declared that they have no conflicts of interest to declare.

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