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The Efficacy of Vitamin C on Postoperative Outcomes after Posterior Lumbar Interbody Fusion: A Randomized, Placebo-Controlled Trial

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Background: Vitamin C has critical features relavant to postoperative pain management and functional improvement; however, no study has yet evaluated the effectiveness of vitamin C on improving the surgical outcomes for spine pathologies. Thus, this study aimed to explore the impact of vitamin C on postoperative outcomes after single-level posterior lumbar interbody fusion (PLIF) for lumbar spinal stenosis in prospectively randomized design. We conducted a 1-year prospective, randomized, placebo-controlled, double-blind study to evaluate the impact of vitamin C on the postoperative outcomes after PLIF surgery.

Methods: A total of 123 eligible patients were randomly assigned to either group A (62 patients with vitamin C) or group B (61 patients with placebo). Patient follow-up was continued for at least 1 year after surgery. The primary outcome measure was pain intensity in the lower back using a visual analogue scale. The secondary outcome measures were: (1) the clinical outcome assessed using the Oswestry Disability Index (ODI); (2) the fusion rate assessed using dynamic radiographs and computed tomography scans; and (3) complications.

Results: Pain intensity in the lower back was significantly improved in both groups compared with preoperative pain intensity, but no significant difference was observed between the 2 groups over the follow-up period. The ODI score of group A at the third postoperative month was significantly higher than the score of group B. After the sixth postoperative month, the ODI score of group A was slightly higher than the score of group B; however, this difference was not significant. The fusion rates at 1 year after surgery and the complication rates were not significantly different between the 2 groups.

Conclusions: Postoperative pain intensity, the primary outcome measure, was not significantly different at 1 year after surgery between the 2 groups. However, vitamin C may be associated with improving functional status after PLIF surgery, especially during the first 3 postoperative months.

Keywords: *Ascorbic acid, Spinal stenosis, Posterior lumbar interbody fusion, Treatment outcome*

The incidence and prevalence of spinal stenosis in the lumbar spine have both been increasing dramatically as the average life expectancy increases.[1] Posterior lumbar interbody fusion (PLIF) surgery is considered to be a cutting-edge surgical method for treating lumbar spinal stenosis (LSS),[2-5] but it also has some limitations, including the risk of intractable pain at the surgical site and unsatisfactory functional outcomes in the postoperative period.[4] Among these complications, intolerable postoperative pain in the lower back causes considerable suf-

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fering for a period of at least 1 week after surgery in most patients who undergo PLIF, even though the surgery is ultimately successful. Several approaches have been taken to alleviate intolerable postoperative pain after PLIF surgery;[5,6] however, none of these approaches has been particularly successful. Moreover, some of them even result in additional complications for the patient. Various methods for improving postoperative pain and functional status in other orthopedic territories have been well studied,[7,8] but spinal surgeons have little choice but to utilize opioids and nonsteroidal anti-inflammatory drugs due to the lack of suitable alternatives.

To date, the abilities of various types of drugs to alleviate postoperative pain and improve functional outcomes have been investigated. One of these drugs is ascorbic acid (vitamin C),[9-14] which has 2 critical attributes that may benefit patients who have received surgical treatment: (1) its ability to mediate pain management;[9-11,13] and (2) its antioxidant and neuroprotective properties.[15-25] We hypothesized that these features of vitamin C may allow to reduce postoperative pain intensity and improve functional outcomes for patients who undergo PLIF. However, the ability of vitamin C to impact PLIF outcomes has not yet been investigated.

Therefore, we conducted a 1-year prospective, randomized, placebo-controlled, double-blind study to evaluate whether vitamin C can influence positively the postoperative outcomes after single-level PLIF in terms of pain intensity, functional status, radiologic outcome, and complications. To the best of our knowledge, this is the first trial to investigate the ability of vitamin C to improve the outcomes of PLIF surgery.

METHODS

Participants

This was a prospectively randomized trial that investigated the impact of vitamin C on postoperative outcomes in LSS patients who underwent PLIF surgery. This study has been published at the ClinicalTrials.gov Protocol Registration System (trial No. NCT02127060).

This study was conducted with patients who met all of the following inclusion criteria: patients who (1) had been diagnosed with LSS using lumbar spine magnetic resonance imaging scans, and whose results were in agreement with the patient's clinical manifestations and physical examinations; (2) underwent single-level PLIF only at the L4–5 or L5–S1 level; (3) were between 40 and 60 years of age; and (4) underwent follow-up examinations for at least 1 year. Patients who met any of the following exclusion criteria were omitted from the study: patients who (1) exhibited fractures, infection, or tumors in the lumbar spine; (2) had a history of surgery in the lumbar spine; (3) underwent PLIF surgery at any lumbar segment other than L4–5 or L5–S1; and (4) underwent multi-level PLIF surgery. Prior to surgery, all patients were informed of the details of the PLIF procedure, including its difficulties and potential complications.

Allocation and Randomization

Patients were randomly assigned to either group A, to which vitamin C was administered orally, or group B, to which placebo pill was administered. In group A, vitamin C treatment was initiated on the first postoperative day and administered each following morning for 45 days. This dosage and treatment duration were chosen to be consistent with 2 previous studies of vitamin C.[19,26] The treatment allocation was blinded to both the surgeon and the patient; thus, this was a double-blinded study.

Randomization was conducted by a computer-generated allocation program (nQuery Advisor PPS 6.01; Statistical Solutions Ltd., Saugus, MA, USA), which assigns numbers in strict chronological sequences and enters regular sequences for each study group. Randomization was stratified *via* 3 variables: (1) age (40s vs. 50s); (2) smoking status (smoker vs. nonsmoker); and (3) surgical level (L4–5 vs. L5–S1). Each study participant was allocated a unique randomization number upon completion of the screening process.

Surgical Procedure and Postoperative Protocol

All operations were performed using the same surgical technique. After performing posterior decompression, 2 polyetheretherketone (PEEK) cages (Capstone; Medtronic Sofamor Danek, Memphis, TN, USA) for interbody fusion and posterior stabilization with pedicle screws and rods (Legacy System; Medtronic Sofamor Danek) were utilized in all patients. To improve bone fusion, a mixture of a locally-harvested autograft obtained during posterior decompression and a demineralized bone matrix (Korea Bone Bank, Seoul, Korea) was packed inside and outside the PEEK cages.

All patients were managed with the same postoperative medications and rehabiliation program protocols. Patients wore a lumbo-sacral orthosis for 3 months after the surgery and were allowed to ambulate on the first day post-surgery. Patients were not permitted to sit for long periods of time for the first month after surgery, and at 3 months post-surgery, patients were allowed to resume normal activities.

Outcome Measures

The primary outcome measure was pain intensity in the lower back around the surgical site. Pain intensity at the lower back was recorded using a visual analogue scale (VAS), whose scores were obtained before surgery and then again at 1, 3, 6 months, and 1 year post-surgery. Patients were instructed to mark a horizontally-oriented, 10-point VAS ranging from "no pain, zero points" at the far left to "greatest pain, ten points" at the far right. Patients were not allowed to review their previous scores.

The secondary outcome measures included: (1) clinical outcome; (2) fusion rate; and (3) complications. Clinical outcomes were evaluated using the Oswestry Disability Index (ODI). Similar to above, values were obtained before surgery and then again at 1, 3, 6 months, and 1 year post-surgery. Patients were not allowed to review their previous scores. Questionnaires, chart data, and clinical records were analyzed by 1 surgeon who was not otherwise involved in this study. Fusion status was determined at 1 year post-surgery using dynamic radiographs and computed tomography (CT) scans. Fusion was defined as: (1) a difference of 2° or less in Cobb angles that were taken in flexion and in extension, as viewed in dynamic lateral radiographs and (2) the presence of a definitely continuous fusion mass, either inside the cage or outside the cage, as viewed by CT images. The status was denoted as nonunion if the Cobb angles differed by more than 2° or if the fusion mass on the CT scans was discontinuous or insufficient. All dynamic radiography and CT measurements were performed by an orthopedic spine surgeon who was not involved in patient treatment. In addition, all complications such as any surgery-related problems and drug-related side effects, including vitamin C, were carefully recorded.

Statistical Analysis

The independent student *t*-test or the analysis of variance (ANOVA) test was used for continuous variables such as pain intensity (VAS score) and ODI score, The Fisher exact test was used for proportional variables such as fusion rate, smoking, diabetes mellitus (DM), and hypertension (HTN). All analyses were performed using IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Patient Demographics

A total of 123 eligible patients who qualified for this study were randomly assigned either to group A (with vitamin C, 62 patients) or to group B (with placebo, 61 patients) (Fig. 1). No significant differences were observed between any of the demographic characteristics of the 2 groups, including age, sex, height, weight, body mass index, comorbidities such as DM and HTN, smoking status, and surgical level (Table 1).

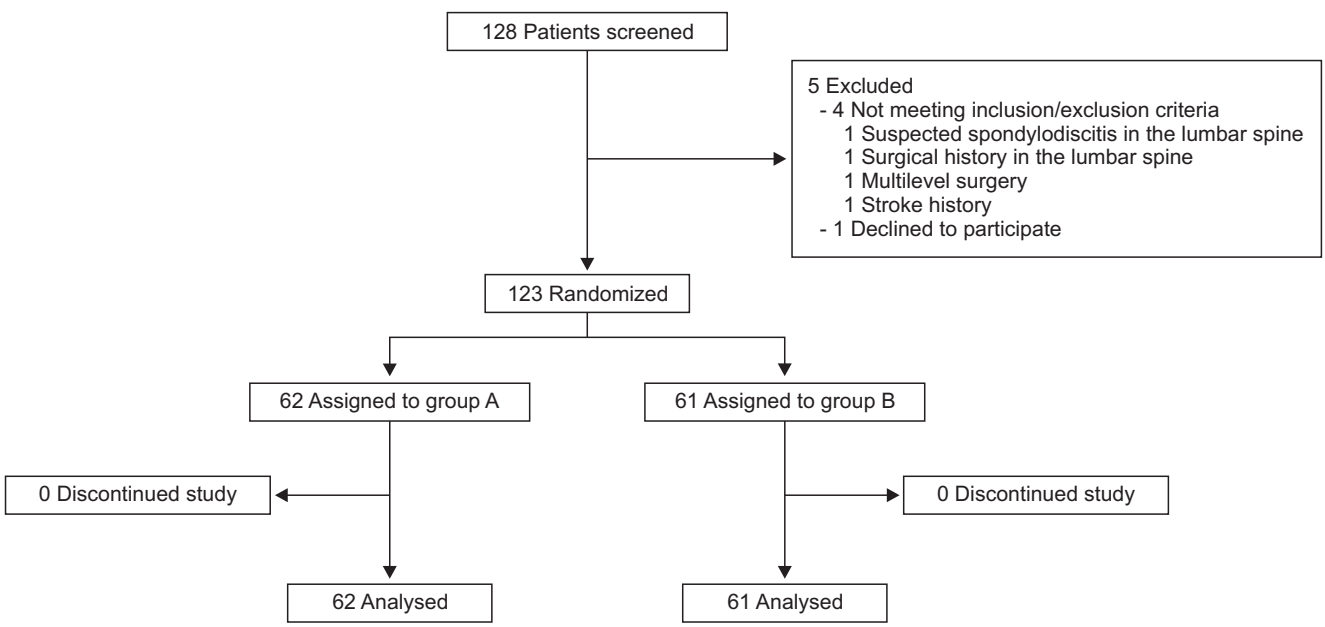

Fig. 1. Flow diagram of patient enrollment.

Primary Outcome Measure

Pain intensity scores for the lower back 1 year post-surgery improved significantly in both groups; the mean score decreased from a preoperative value of 7.8 ± 2.1 to a 1-year postoperative value of 1.9 ± 1.0 in group A and from 7.9 ± 1.8 to 2.0 ± 1.3 in group B ($p < 0.0001$ and $p < 0.0001$, respectively). No significant differences were observed between the 2 groups regarding the pain intensity scores for the lower back. This observation was true for the preoperative scores and also for the scores obtained at all time points during follow-up (Table 2).

Table 1. Demographic Data

Demographic	Group A	Group B	*p*-value
Case	62	61	-
Age (yr)	54.7 ± 13.1	53.2 ± 12.7	0.83
Sex (male/female)	41/21	38/23	0.52
Height (cm)	169.3 ± 29.2	167.2 ± 25.1	0.78
Weight (kg)	74.2 ± 16.5	77.1 ± 13.9	0.41
Body mass index (kg/m^2)	26.3 ± 10.2	27.1 ± 11.3	0.54
Diabetes mellitus	8 (13)	9 (15)	0.62
Hypertension	6 (10)	6 (10)	0.73
Smoking status			0.79
Smoker	19 (31)	20 (33)	
Nonsmoker	43 (69)	41 (67)	
Surgical level			0.86
L4–5	30 (48)	31 (51)	
L5–S1	32 (52)	30 (49)	

Values are presented as mean ± standard deviation or number (%).
Group A: vitamin C was administered orally, Group B: placebo was administered.

Secondary Outcome Measures

The mean ODI scores of both groups were not significantly different at baseline, with values of 37.6 ± 12.1 in group A and 38.7 ± 16.2 in group B ($p = 0.74$) (Table 3). The ODI scores of patients in both groups were markedly improved after 1 year of follow-up compared with their baseline values. The 1-year follow-up ODI scores were 16.4 ± 10.7 in group A and 18.1 ± 13.6 in group B. Interestingly, the ODI score of group A at the third postoperative month was significantly higher than the corresponding score of group B ($p = 0.04$); moreover, the mean ODI score of group A after the sixth postoperative month was slightly higher than the corresponding score of group B, although this difference was not significant.

The fusion rate was evaluated with dynamic radiographs and CT scans 1 year post-surgery. According to our fusion criteria, solid fusion was achieved in 87.1% (54/62) of the patients in group A and 86.9% (53/61) of the patients in group B; these rates were not significantly different between groups ($p = 0.79$).

The complications that occurred in each of the groups are summarized in Table 4. Regarding surgery-related complications, 4 patients (4/62, 6.5%) in group A and 4 patients (4/61, 6.6%) in group B experienced a complication. Specifically, postoperative neurologic deterioration occurred in 2 patients and a superficial infection also occurred in 2 patients in group A. On the other hand, a superficial infection occurred in 2 patients, postoperative neurologic deterioration occurred in 1 patient, and a deep infection occurred in 1 patient in group B. With respect

Table 2. Pain Intensity

VAS on the LBP	Group A (n = 62)	Group B (n = 61)	*p*-value
Preoperative	7.8 ± 2.1	7.9 ± 1.8	0.83
1-Month postoperative	3.9 ± 1.5	3.8 ± 1.7	0.81
3-Month postoperative	2.6 ± 0.9	2.8 ± 1.3	0.47
6-Month postoperative	1.8 ± 1.0	2.0 ± 1.1	0.32
1-Year postoperative	1.9 ± 1.0	2.0 ± 1.3	0.75

Values are presented as mean ± standard deviation.
VAS: visual analogue scale, LBP: lower back pain, Group A: vitamin C was administered orally, Group B: placebo was administered.

Table 3. Functional Outcome

ODI score	Group A (n = 62)	Group B (n = 61)	*p*-value
Preoperative	37.6 ± 12.1	38.7 ± 16.2	0.74
1-Month postoperative	21.3 ± 7.4	20.6 ± 9.7	0.53
3-Month postoperative	16.3 ± 5.9	19.6 ± 10.3	0.04*
6-Month postoperative	15.2 ± 8.4	17.7 ± 9.4	0.07
1-Year postoperative	16.4 ± 10.7	18.1 ± 13.6	0.07

Values are presented as mean ± standard deviation.
ODI: Oswestry Disability Index, Group A: vitamin C was administered orally, Group B: placebo was administered.
*Significant difference between groups ($p < 0.05$).

Table 4. Complications

Variable	Group A (n = 62)	Group B (n = 61)	*p*-value
Surgery-related complication	4	4	0.89
Postoperative neurologic deterioration	2	1	
Superficial infection	1	2	
Deep infection	1	1	
Drug-related side effect	14	13	0.87
Epigastric discomfort	7	8	
Gastric erosion	2	1	
Gastric ulcer	1	0	
Diarrhea	2	3	
Constipation	2	1	
Hepatotoxicity	0	0	
Total	18	17	0.90

Group A: vitamin C was administered orally, Group B: placebo was administered.

to drug-related side effects, 14 patients (14/62, 22.6%) in group A and 13 patients (13/61, 21.3%) in group B experienced a drug-related side effect. Specifically, in group A, 7 patients experienced epigastric discomfort, 2 patients experienced gastric erosion, 2 patients experienced constipation, 2 patients experienced diarrhea, and 1 patient experienced a gastric ulcer. In group B, 8 patients experienced epigastric discomfort, 1 patient experienced gastric erosion, 3 patients experienced diarrhea, and 1 patient experienced constipation. The incidences of surgery-related and drug-related complications were not significantly different between the 2 groups ($p = 0.89$ and $p = 0.87$, respectively).

DISCUSSION

Many alternative drugs, interventions, and multimodal approaches have recently been studied in the context of alleviating postoperative pain and improving functional outcomes; one of these drugs is vitamin C. The pathomechanism of vitamin C for alleviating pain intensity has not been fully established. Based on the review of literature, one factor in the generation of pain, especially persistent, recurrent, or neuropathic pain, has been elucidated as reactive oxygen species (ROS) such as superoxide and certain radicals, and the ROS can be managed by antioxidant materials, including vitamic C.[9,11,17] Vitamin C is an essential nutrient that acts as an antioxidant in human and has been acknowledged as a ROS scavenger.[12,13,16,19,24] Considering the positive benefits of vitamin C, we presumed that it may be beneficial to patients who undergo PLIF surgery. First, vitamin C appears to alleviate pain; and second, vitamin C exerts neuroprotective and antioxidant effects.[9-29] For instance, one study reported that oral supplementation with vitamin C significantly decreased morphine consumption after laparoscopic cholecystectomy, indicating that vitamin C reduces acute pain.[11] In addition, the plasma concentration of vitamin C has been shown to decrease after surgery, and the requirement for vitamin C increases in surgical patients. These 2 observations could be explained by a greater demand for vitamin C caused by increased oxidative stress.[14,15,17] Some clinical and/or experimental reports have suggested that vitamin C leads to functional improvements of damaged nerves.[15-17,22,23,28] The meaningful possibility that vitamin C may reduce the intensity of postoperative pain and improve functional outcomes following spine surgery formed the motivation for the current study.

We prospectively analyzed 123 patients (group A with vitamin C, 62 patients; group B with placebo, 61 patients) who underwent single-level PLIF and had follow-up for at least 1 year. The pain intensity in the lower back, primary endpoint, was significantly improved in both groups compared with preoperative score ($p < 0.0001$ and $p < 0.0001$, respectively); however, the extents of pain improvement in the two groups was not significantly different at any of the follow-up time points. This study had

3 secondary endpoints: clinical outcome based on ODI, fusion rate, and complications. The ODI score of group A at 3 months postoperatively was significantly higher than the corresponding score of group B ($p = 0.04$). Similarly, the ODI score of group A was slightly higher than the corresponding score of group B after 6 postoperative months, although this difference was not significant. The fusion rates at 1 year after surgery were not significantly different between the groups based on the dynamic radiographs and CT scans ($p = 0.79$). The complications in both groups, including surgery-related complications and drug-related side effecst, were also similar. Previous articles have reported that long-term intake of vitamin C might be associated with some adverse side effects such as gastric discomfort and ulcers.[11-14,19,20] However, patients were given vitamin C for 45 days in the present study. Due to this period of administration, no serious side effects were observed at any of the follow-up examinations. The present study indicates that vitamin C may be associated with improved functional status after surgery, especially during the first three postoperative months, although it does not significantly alleviate postoperative pain in 1 year after surgery.

The current study had some limitations. First, it was conducted without a sufficient sample size, as assessed by sample size estimation; moreover, it did not have enough follow-up time points for a comprehensive evaluation of the effects of vitamin C. The study had a small sample size and few time points because it was intended to be a pilot study for the evaluation of vitamin C. Since no previous study had reported the effectiveness of vitamin C in improving the outcomes of PLIF surgery, we conducted the current study as an initial (pilot) clinical trial. A second limitation of the current study was that it used randomized allocation of the enrolled patients into the 2 groups, blinded to both the surgeon and the patient. Although we did not provide any information regarding vitamin C intake to the patients in both groups, the patients might have detected that they were being given vitamin C based on the drug's morphology or by some other characteristics. However, since no patient asked the surgeon about the characteristics of vitamin C, we believe that the patients were properly blinded to their allocation group. Third, this study was conducted only on patients who underwent single-level PLIF surgery at the L4–5 or L5–S1 level, without performing a dual-energy X-ray absorptiometry (DEXA) study to evaluate whether the patients exhibited osteoporosis. Thus, the results of this study cannot be fully generalized to patients who underwent multilevel fusion surgery, surgery on other lumbar segments, or who had osteoporosis. Finally, we did not evaluate other factors that can influence postoperative pain and clinical outcomes, such as psychologic status and a degree of social stress.

Despite these limitations, the current study has some unique strengths. First, this was the first clinical trial with a prospective randomized study design to evaluate the effectiveness of vitamin C in improving clinical and radiological outcomes of PLIF surgery. Second, all enrolled patients (n = 123) were evaluated throughout the duration of the follow-up period, with no patient loss during this period. In addition, the patients in the current study were relatively homogenous regarding their participation in sports and levels of physical activity, since the study was performed at an armed forces hospital. This high degree of population homogeneity reduces the potential for confounding factors on outcome variables. In addition, due to the lack of any previous studies regarding the potential of vitamin C in improving outcomes of spine surgery, this study can be considered a cornerstone for further research.

In conclusion, based on the results of the current study, vitamin C may be associated with improvement of functional status after PLIF surgery, especially during the first 3 postoperative months. However, the postoperative pain intensity, the primary outcome measure, was not significantly different at 1 year after surgery between the 2 groups.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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