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The Effects of Supplemental Vitamin C in Mandibular Fracture Patients: A Randomized Clinical Trial

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Abstract

Vitamin C is an oxidative stress mediator and essential cofactor in wound healing. The objective of this study was to investigate the clinical and biochemical effects of vitamin C supplementation on outcomes in patients undergoing mandibular fracture repair. We also aimed to evaluate the effects of sociodemographic, fracture, and treatment characteristics on post-operative clinical outcomes in these patients. The investigators conducted a double-blind, placebo-controlled, randomized clinical trial at Two Metropolitan, Level 1 Trauma Centers to prospectively evaluate the effects of vitamin C vs. placebo in a mandibular fracture population stratified by smoking and fracture status (open vs. closed). The study was conducted at two safety-net hospitals, enrolling a cohort of heavily underserved patients. Forty-five subjects were evaluated. We found decreased overall post-operative complications, decreased wound infection, and some improved bone healing outcomes in the vitamin C group compared to placebo, however, none of these outcomes reached statistical significance. Vitamin C intervention showed a signal of improved clinical and biological wound healing which was not statistically significant. Additionally, significant associations between patient characteristics and post-operative outcomes were identified. Older subjects and those with co-existent trauma were more likely to have increased healthcare utilization, and increased time from injury to surgery was significantly associated with frank infection. Prescription of additional opioids outside of standard practice was significantly associated with a need for additional wound care, increased emergency room visits, and any post-operative complication. Further investigation is needed to evaluate these findings in a larger study population, yet Vitamin C remains a low-risk, inexpensive potential means to improve wound healing outcomes after acute facial trauma.

Keywords
Mandibular fractures; ascorbic acid; postoperative complications; wound healing; healthcare disparities

1. Introduction

Mandibular fractures are a frequent pathology encountered by surgeons worldwide. These injuries can result from a variety of mechanisms, including motor vehicle collisions (MVCs) [1], assaults [2] or fall [3]. The cause of injury often determines the severity of the fracture [4], thus these entities are incredibly heterogeneous. Mandibular fractures are typically treated based on fracture type and anatomic location [5], and often require surgical intervention to reduce the risk of post-injury complications. Further, these injuries are physically and emotionally traumatic to patients, and prove to be costly for both the patient and the healthcare system [6]. Surgical repair technique has improved in recent years, and medical treatments have simultaneously been enhanced; yet the average overall complication rate remains approximately 25% [7, 8]. Complications following repair are associated with increased pain, diminished quality of life, and increased costs to patient and healthcare system. Approaches that improve these outcomes are needed. Additionally, there is a lack of prospective study surrounding the sociodemographic and treatment characteristics of the patient populations plagued by these injuries. It is critical that providers recognize factors that may be impacting a patient's ability to heal appropriately following surgery, especially with regards to lower socioeconomic characteristics.

Vitamin C (ascorbic acid) is an essential cofactor in wound healing [9]. Vitamin C is required to synthesize collagen, via hydroxylation of proline and lysine [10], and is an important component of all phases of wound/bone healing. Further, Vitamin C is a potent antioxidant to scavenge reactive oxygen species during normal physiology and wound healing [11]. Even moderate Vitamin C deficiency can manifest as poor soft tissue and bone healing [12]. However, most prior research indicating Vitamin C can improve bone healing is pre-clinical [13, 14]. Current evidence suggests that 8% of the general population is Vitamin C deficient, with greater deficiencies associated with lower socioeconomic status (SES), a frequent characteristic of patients with mandibular fracture patients [15].

Vitamin C deficiency typically occurs via two primary mechanisms: 1) inadequate intake (poor nutrition), and 2) excess oxidative stress demand [11], common in the setting of both smoking or trauma [16, 17]. Further, the higher prevalence of smoking among disadvantaged groups may put those with a lower SES at higher risk of Vitamin C deficiency [18]. Thus, patients with mandibular fracture may suffer from Vitamin C deficiency due to both of these mechanisms. Vitamin C supplementation is a low-risk intervention and has been shown to improve outcomes in patients that are undergoing surgery or are critically ill, but has not been studied in mandibular fracture [19-23]. Literature suggests that oral dosing alone of Vitamin C is insufficient to overcome heavy oxidative stress demands, and thus intravenous dosing is required [24].

While many conditions predispose to wound healing deficiencies, there is considerable evidence that tobacco smoke exposure increases surgical complications [25, 26]. Smoking impairs the inflammatory and proliferative phases of wound healing [27, 28], while increasing oxidative stress and hypoxia [29, 30]. Further, evidence of tobacco's detrimental effects on bone fragility are widespread [7, 31, 32]. At the same time, data suggests that cigarette smokers are Vitamin C deficient [17, 33], and thus may benefit from supplementation. Similar to tobacco smoking, a wealth of published literature indicates that socioeconomic disparities affect surgical outcomes [34-36]. However, most studies that have examined disparities within the context of mandibular fracture repair are retrospective, rather than prospective [37, 38]. Prior research has established that mandibular fractures most frequently occur in males; are most commonly the result of assaults; patients that are publicly-insured with concomitant orbital fractures undergo fewer facial fracture surgeries compared to patients that are non-publicly insured, and individuals with systemic medical conditions are more likely to experience post-operative complications [3, 5, 7, 37-39]. It has further been shown that patients with behavioral health disorders experience higher rates of facial trauma and in-hospital complications compared to those without behavioral disorders [40], and that these patients are predisposed to experiencing symptoms of depression following fracture repair [41]. Beyond these findings, the sociodemographic characteristics of patients with mandibular fracture are poorly characterized within a prospective context, and thus, we aimed to evaluate this population.

We conducted a double-blind, placebo-controlled, randomized clinical trial (RCT) to assess the benefit of Vitamin C supplementation in the setting of mandibular fracture with attention to smoking status. We prospectively and serially measured the clinical and biochemical effects of supplemental Vitamin C on post-surgical healing. We aimed to perform a robust evaluation of the effects of Vitamin C on wound healing after mandibular fracture to inform medical management and improve outcomes. Furthermore, we analyzed our secondary aim to prospectively characterize the sociodemographic, fracture, and treatment characteristics associated with patients who present with mandibular fracture to a safety-net hospital and their impact on post-operative outcomes. While past research is primarily cohort studies, our study is novel as a prospective RTC as well as by the patient population; to our knowledge, this therapy has not been prospectively evaluated in the setting of mandibular trauma.

Institutional review board (IRB) approval was obtained from both Hennepin Healthcare Research Institute IRB (#17-4279, approved on 2/8/2017) and HealthPartners Institute IRB (19-057, approved on 4/3/2019) in compliance with the Declaration of Helsinki. Informed consent was collected from all participants prior to conducting any research procedures. ClinicalTrials.gov Identifier: NCT03938584.

https://clinicaltrials.gov/ct2/show/NCT03938584?term=vitamin+C&cond=Mandible+Fracture&cntry=US&state=US%3AMN&city=Minneapolis&draw=2&rank=1.

2. Materials and Methods

2.1 Study Procedures

2.1.1 Participant Enrollment

Participants were enrolled from two level-1 trauma centers, Hennepin County Medical Center (Minneapolis, MN) and Regions Hospital (St. Paul, MN) between October 12th, 2017 and March 17th, 2020. The RCT was stopped early due to the COVID-19 pandemic. Participants were recruited from the Otolaryngology and Oral-Maxillofacial Departments and underwent surgical repair by 1 of 13 surgeons. The enrollment schema for the randomized controlled trial is depicted in Figure 1. All patients received standard of care treatment including antibiotics intraoperatively. Current smokers were offered non-pharmacological tobacco treatment.

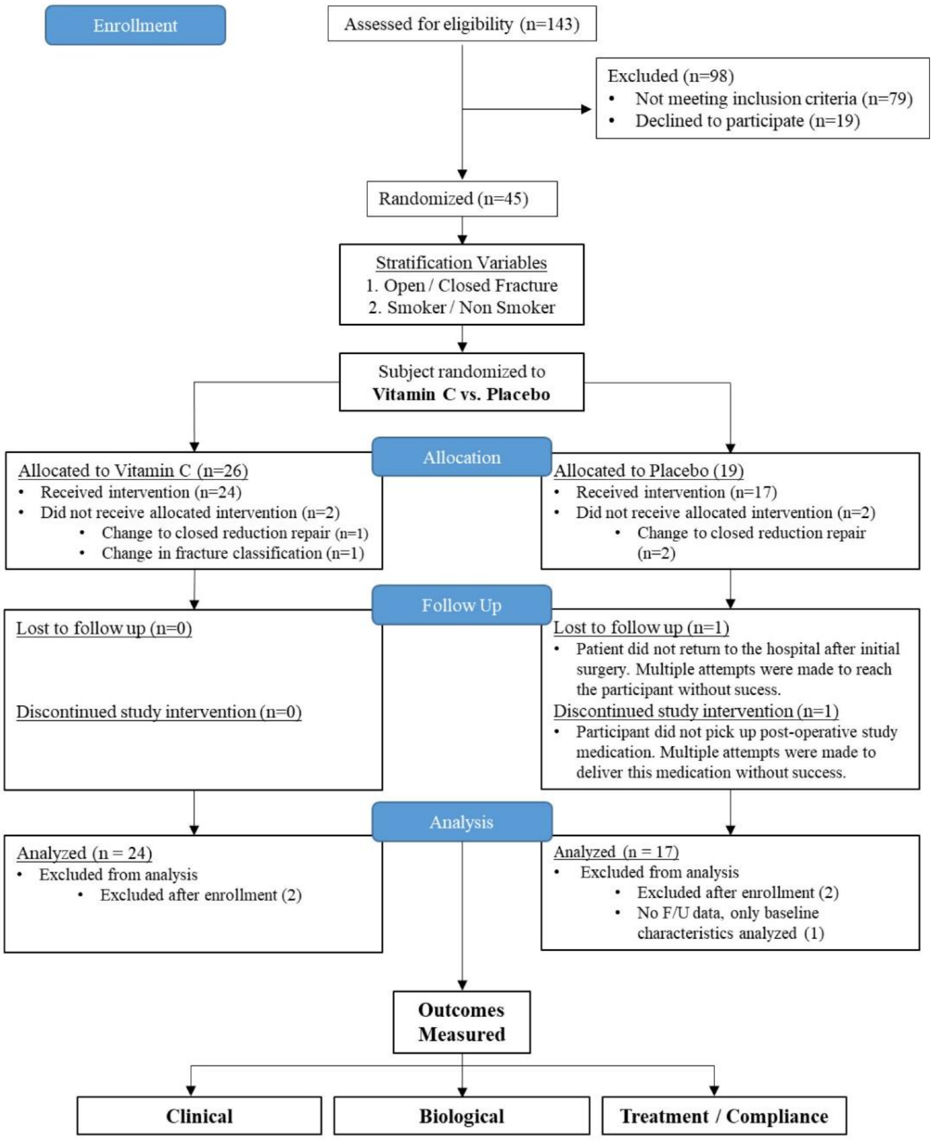

Figure 1 CONSORT Flow Diagram of RCT. The CONSORT Flow diagram indicates the number of patients screened, randomized, allocated to each treatment group, lost to follow up, discontinued study intervention, and analyzed for final analysis.

All study participants underwent mandibular fracture repair in the operating room (OR). Inclusion criteria were: age >18, *de novo* mandibular fracture, repair via an intra-oral incisional approach with plating, and surgery within 7 days of injury. Exclusion criteria were: cognitive impairment limiting ability to provide informed consent, pregnancy, nursing, comminuted fractures or isolated subcondylar fractures, history of renal insufficiency, or allergy to Vitamin C/placebo components. Isolated subcondylar fracture status was not added to criteria until after trial commencement to minimize fracture variability. Tobacco use was quantified by the PhenX-Toolkit tobacco questionnaire. Smoking status was classified as follows: Current smokers smoked within the past 30 days; Nonsmokers smoked <100 lifetime cigarettes or smoked >100 cigarettes but none in the month before presentation. Pain was assessed via the Numerical Rating Scale. Subject characteristics and sociodemographic variables (sex, race, age, BMI, comorbidities, insurance type, homelessness etc.), fracture characteristics (time between injury and surgery, fracture type, fracture side, anatomic location, and mechanism of injury) and treatment characteristics (surgeon, use of mandibulo-maxillary fixation (MMF), types of plates used) were collected. A routine pre-operative CT scan was completed before surgery.

2.1.2 Randomization & Treatment Initiation

Participants were randomized to treatment groups by a digital randomization program designed by the study statistician, using a stratified block design. They were stratified by smoking (current versus nonsmoker) and fracture status (open versus closed) to ensure balanced group characteristics. Randomization was completed by the research coordinator prior to operative intervention and carried out in REDCap, a secure database [42]. The clinical team was blinded to randomization status. A baseline venous blood sample was collected in the OR, prior to study interventions.

Participants initiated treatment or placebo in the OR as follows: the Intervention Group was administered a single intravenous (IV) dose of Vitamin C, 66 mg/kg/hr over 2 hours, just after induction of anesthesia. The Placebo Group received IV placebo (normal saline) identically packaged to the intervention by the same protocol. Beginning on post-operative day 1, the intervention group received a 4-week prescription of liquid Vitamin C, 500 mg, while the placebo group received the aqueous solution base without active Vitamin C, to be taken by mouth twice daily [11, 12]. Subjects were given written and verbal instructions on standard post-operative clinical recommendations and study requirements. All participants were instructed to avoid dietary supplements that include Vitamin C, to log daily nutrition and medication intake for the duration of the study. Participants were also asked to avoid non-steroidal anti-inflammatory drugs (NSAIDs) for 3-5 weeks following surgery, as NSAIDs may alter cytokine response during wound healing [43]. When possible, subjects were sent two daily text message medication reminders. Post-operative characteristics were prospectively recorded: length of hospital stay, time in MMF, unfilled prescriptions (including study medication), need for additional opioids beyond standard, pattern of opioid use, compliance with no-chew diet, smoking status after surgery, ER visits, return to OR, readmission, clinic nursing calls for pain, and missed appointments. Standard practice in our group was a 7-day post-operative prescription of 5 mg oxycodone used Q4-6 hours prn pain. Any requests or hospital visits for additional pain control that resulted in additional pain prescriptions were deemed “additional opioids beyond standard.” A pattern of opioid abuse was defined by a documented past history of abuse within the medical record or a provider suspicion requests for opioids was not due to mandibular fracture (i.e. mandible was healing appropriately, but patient repeatedly presented to clinic visit or ER asking for pain medication).

2.1.3 Post-Operative Assessment

The study included 1 and 3-5 week post-operative visits. Participants were compensated at each visit. At these visits, assessments were made by clinicians blinded to treatment group using study-specific forms. Staff completed the tobacco, nutrition and pain scale questionnaires with the participant and recorded applicable post-operative characteristics. At the second follow-up visit questionnaires were repeated, and a venous blood sample was obtained.

Post-operative outcomes were collected prospectively via clinic visits and medical record review at three timepoints: early (<3 weeks), late (3-12 weeks), and long term (>12 weeks). Outcomes were documented by the blinded, treating physician and included: overt signs of infection (frank purulence, abscess), any evidence of post-operative wound infection (additional antibiotics received beyond standard of care, fever, dehiscence, hardware exposure w/signs of infection such as purulence or pain, osteomyelitis), fever (temperature ≥100.5°F), incision dehiscence (open or dehisced wound), hardware exposure (visible hardware), lack of bony fusion, malocclusion (premature contact of teeth on either side or open bite that differed from premorbid bite), malunion/nonunion (noted as nonunion, fracture line still present, or non-healing fracture), loose hardware (noted as lucency present/loose hardware on CT or X-Ray) and need for post-discharge active wound care outside the standard (additional care needed for dehiscence or exposed hardware). All participants underwent post-operative CT scan.

2.1.4 Biomarker Evaluation:

Serum extracted from venous blood was stored in a -80-degree Celsius (C) freezer for biomarker evaluation. Only specimens from participants with baseline and follow-up samples were analyzed via ELISA and multiplex (Luminex) assays at the UMN Cytokine Core. The following biomarkers were measured: 1) Collagen synthesis: pro-collagen-1-alpha; 2) Inflammatory: C-reactive protein (CRP), interferon gamma (IFNγ), interleukins (IL) 1b, IL-6, IL-8, IL-13, tumor necrosis factor alpha (TNFα), neutrophil elastase-2 (ELA2), matrix metalloproteinases (MMPs) 1, 2, and 9; 3) Bone healing: bone-specific alkaline phosphatase (BAP), Tartrate-resistant acid phosphatase isoform 5b (TRAP5b), osteoprotegerin (OPG), osteocalcin (OC), C-telopeptide of type I collagen (CTX-1), procollagen type III N-terminal propeptide (PIIINP); and 4) Oxidative stress: 8-isoprostane, DNA/RNA oxidative damage, 1 alpha 1-nitrite, nitrate + nitrite, TBARS/TEAC.

2.2 Statistical Methods

The planned primary outcome measure was change in procollagen-1-alpha, a biomarker of collagen production, from baseline to follow-up [44, 45]. A blocking design assured similar variability among the two groups. We planned for 42 subjects per group, to give a statistical power >80% to detect a difference in procollagen between groups if the treatment group increases 50% or more. This two-sided comparison has a significance level of 0.05. Planned secondary outcomes included clinical and biological measures.

The change in biomarker levels from surgery to follow-up was compared between groups with a two-sample test. The non-parametric Wilcoxon rank sum test compared the pre-post differences in the biomarkers between arms. Categorical and ordered clinical outcomes were compared between treatment arms using chi-square tests and Wilcoxon rank sum tests. This included binary and ordinal clinical measures. Cohen's D analysis was also performed for our primary outcome, pro-collagen-1-alpha. Smaller sample sizes than expected limited the inclusion of additional covariates using a multiple regression approach to adjust for possible confounding effects. However, we did not expect large imbalances between arms for other covariates due to randomization.

Whole cohort demographic, patient, and treatment characteristics were compared with post-operative clinical outcomes at any time point during the study period. Any characteristic that was observed in more than 15% of the patients and any outcome that occurred in more than 10% of the patients were included in these comparisons. Comparisons that resulted in a p-value ≤ 0.10, are reported. Because opioid use could predate mandibular trauma or indicate a post-operative complication, "need for additional opioids" was analyzed both as a treatment variable as well as a potential post-operative outcome along with the other documented clinical outcomes. Binary clinical outcomes occurring at any time during the study period were evaluated by categorical characteristics using the chi-square or Fisher's exact tests and by ordinal and continuous variables with the Wilcoxon rank sum test. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary NC).

3. Results

3.1 Cohort Characteristics

In sum, 45 subjects were enrolled. Following randomization, four patients were excluded: one due to change in fracture classification, and three due to intraoperative change to closed reduction repair. Therefore, we present data on 41 patients, 17 randomized to placebo and 24 to Vitamin C. One subject in the placebo arm was lost to follow-up, with only baseline data collected.

Cohort characteristics are shown in Table 1, stratified by placebo and Vitamin C arms. The majority of subjects were young, male, and black/African American. Insurance coverage assessments suggested low SES in both study arms, with 54.1% and 70.5% having public or no insurance in the Vitamin C and placebo groups respectively. Approximately 25% of subjects in both groups had unstable housing and transportation difficulty. Subjects had few medical comorbidities other than mental health problems (25.0% Vitamin C vs 47.1% placebo), most commonly anxiety, depression, bipolar disorder, and substance abuse. The majority of subjects were current smokers (62.5% Vitamin C vs 64.7% placebo) and commonly presented while intoxicated with alcohol (25% Vitamin C vs 35.3% placebo). There were no significant differences in baseline subject characteristics or demographics between study arms.

Table 1 Cohort Characteristics.

	Whole Cohort n = 41 (%)	**Placebo n = 17 (%)**	**Vitamin C n = 24 (%)**	***P* value [a]**
Age, years ± SD	30.9 ± 8.4	30.5 ± 6.4	31.1 ± 9.7	0.812 [b]
BMI ± SD	24.7 ± 4.4	25.4 ± 4.6	24.2 ± 4.3	0.385 [c]
Sex				1.000
Male	36 (87.8)	15 (88.2)	21 (87.5)	
Female	5 (12.2)	2 (11.8)	3 (12.5)	
Race/Ethnicity [d]				0.321
American Indian/Alaska Native	1 (2.4)	1 (5.9)	0 (0.0)	
Black or African American	23 (56.0)	11 (64.7)	12 (50.0)	
Hispanic/Latino	2 (4.9)	1 (5.9)	1 (4.2)	
White	14 (34.1)	4 (23.5)	10 (41.7)	
More than one race	1 (2.4)	0 (0.0)	1 (4.2)	
Insurance				0.480
Private	16 (39.0)	5 (29.4)	11 (45.8)	
Public	19 (46.3)	10 (58.8)	9 (37.5)	
None	6 (14.6)	2 (11.8)	4 (16.7)	

Alcohol Intoxication Upon Emergency Room Arrival				0.507
Yes	12 (29.3)	6 (35.3)	6 (25.0)	
No	29 (70.7)	11 (64.7)	18 (75.0)	
Diabetes Diagnosis				0.166
Yes	2 (4.9)	2 (11.8)	0 (0.0)	
No	39 (95.1)	15 (88.2)	24 (100.0)	
Homeless/Unstable Housing				1.000
Yes	10 (24.4)	4 (23.5)	6 (25.0)	
No	31 (75.6)	13 (76.5)	18 (75.0)	
Coexistent Trauma/Critical Illness/Sepsis				0.421
Yes	7 (17.1)	4 (23.5)	3 (12.5)	
No	34 (82.9)	13 (76.5)	21 (87.5)	
Previous Treatments (Radiation/Chemotherapy)				0.502
Yes	2 (4.9)	0 (0.0)	2 (8.3)	
No	39 (95.1)	17 (100.0)	22 (91.7)	
Immunosuppression				0.166
Yes	2 (4.9)	2 (11.8)	0 (0.0)	
No	39 (95.1)	15 (88.2)	24 (100.0)	
Vascular Disease				1.000
Yes	1 (2.5)	0 (0.0)	1 (4.2)	
No	40 (97.6)	17 (100.0)	23 (95.8)	
Hypertension				1.000
Yes	3 (7.3)	1 (5.9)	2 (8.3)	
No	38 (92.7)	16 (94.1)	22 (91.7)	
Mental Health Problem				0.189
Yes	14 (34.1)	8 (47.1)	6 (25.0)	
No	27 (65.9)	9 (52.9)	18 (75.0)	
Addiction Medicine Inpatient Consult				0.373
Yes	6 (14.6)	1 (5.9)	5 (20.8)	
No	35 (85.4)	16 (94.1)	19 (79.2)	
Transportation Difficulty				1.000
Yes	11 (26.8)	5 (29.4)	6 (25.0)	
No	30 (73.2)	12 (70.6)	18 (75.0)	
Pre-Surgical Smoking Status [e]				1.000
Cigarette Smoker	26 (63.4)	11 (64.7)	15 (62.5)	
Former Smoker	6 (14.6)	2 (11.8)	4 (16.7)	
Never Smoker	9 (22.0)	4 (23.5)	5 (20.8)	
Post-Surgical Smoking Status [e]				0.728
Cigarette Smoker	15 (36.6)	5 (29.4)	10 (41.7)	
Former Smoker	6 (14.6)	2 (11.8)	4 (16.7)	
Never Smoker	9 (22.0)	4 (23.5)	5 (20.8)	

Temporary Cessation	6 (14.6)	4 (23.5)	2 (8.3)	
Missing Status	5 (12.2)	2 (11.8)	3 (12.5)	
Long-Term Smoking Status [e]				0.356
Cigarette Smoker	17 (41.5)	5 (29.4)	12 (50.0)	
Former Smoker	2 (4.9)	1 (5.9)	1 (4.2)	
Never Smoker	5 (12.2)	3 (17.6)	2 (8.3)	
Missing Status	17 (41.5)	8 (47.1)	9 (37.5)	

Abbreviations: BMI, Body Mass Index; SD, Standard Deviation.

[a] Fisher's exact test, comparing between Control and Vitamin C arms

[b] Mann-Whitney U Test

[c] Independent t-test

[d] Compared White to non-White

[e] Grouped into current and non-current smoking status for analysis

The treatment groups were balanced with regards to fracture and treatment characteristics (Table 2). In our cohort, more fractures were open (66.7% Vitamin C vs 70.6% placebo), and approximately half of subjects in both arms presented with bilateral fractures. The etiology of injury was assault in most subjects (58.3% Vitamin C vs 76.5% placebo), and premorbid dentition was largely fair-poor in both arms. Patients typically underwent surgical repair within 48 hours of presentation (1.9 days Vitamin C vs 1.8 placebo). More than half of subjects in both groups missed a clinical follow-up appointment.

Table 2 Fracture and Treatment Characteristics.

	Whole Cohort n = 41 (%)	**Placebo n = 17 (%)**	**Vitamin C n = 24 (%)**	***P* value [a]**
Fracture Type				1.000
Open	28 (68.3)	12 (70.6)	16 (66.7)	
Closed	13 (31.7)	5 (29.4)	8 (33.3)	
Fracture Laterality				1.000
Unilateral	20 (48.8)	8 (47.1)	12 (50.0)	
Bilateral	21 (51.2)	9 (52.9)	12 (50.0)	
Fracture Location [b]				N/A
Angle	22	10	12	
Body	12	5	7	
Parasymphyseal	17	8	9	
Subcondylar	8	3	5	
Parasymphyseal + Subcondylar	2	0	2	
Body + Subcondylar	1	0	1	
Teeth Noted as Fractured Before Surgery				0.512
Yes	14 (34.1)	7 (41.2)	7 (29.2)	
No	27 (65.9)	10 (58.8)	17 (70.8)	
Mechanism of Injury				0.513
Assault	27 (65.9)	13 (76.5)	14 (58.3)	

Fall	4 (9.8)	2 (11.8)	2 (8.3)	
MVA	6 (14.6)	1 (5.9)	5 (20.8)	
Other	4 (9.8)	1 (5.9)	3 (12.5)	
State of Premorbid Dentition				0.527
Good	12 (29.3)	4 (23.5)	8 (33.3)	
Fair	16 (39.0)	6 (35.3)	10 (41.7)	
Poor	13 (31.7)	7 (41.2)	6 (25.0)	
Number of Premorbid Adult Teeth, Mean ± SD	28.7 ± 3.8	28.9 ± 4.8	28.6 ± 2.8	N/A
Time (Days) Between Initial Injury and Surgery, Mean ± SD	1.9 ± 1.3	1.8 ± 1.3	1.9 ± 1.3	N/A
NSAID Use Prior to Surgery				0.422
Yes	14 (34.1)	5 (29.4)	9 (37.5)	
No	27 (65.9)	12 (70.6)	15 (62.5)	
MMF Use				0.358
Yes	23 (56.1)	8 (47.1)	15 (62.5)	
No	18 (43.9)	9 (52.9)	9 (37.5)	
Non-Compliance with Non-Chew Diet				0.154
Yes	10 (24.4)	5 (29.4)	5 (20.8)	
No	29 (70.7)	10 (58.8)	19 (79.2)	
Unknown	2 (4.9)	2 (11.8)	0 (0.0)	
Completed Closeout Study Visit?				1.000
Yes	24 (58.5)	10 (58.8)	14 (58.3)	
No	17 (41.5)	7 (41.2)	10 (41.7)	
Missed Any Post-Operative Appointments?				1.000
Yes	23 (56.1)	10 (58.8)	13 (54.2)	
No	18 (43.9)	7 (41.2)	11 (45.8)	

Abbreviations: MMF, Mandibulo-maxillary fixation; MVA, Motor Vehicle Accident; N/A, Not Applicable; NSAID, Non-Steroidal Anti-Inflammatory Drug; SD, Standard Deviation.

[a] Fisher's exact test, comparing between Control and Vitamin C arms

[b] Patients may have presented with fractures to multiple locations

3.2 Outcomes by Treatment Group

We sought to evaluate associations between clinical outcome variables and treatment groups. While no differences between groups were statistically significant, there were some relevant signals to highlight (Figure 2, A-D). We evaluated both groups for post-operative complications at any time point, and these were lower in the intervention group (62.5%) than the placebo group (68.8%). Analysis of soft tissue healing identified some outcomes (e.g. post-operative wound infection) which were better in the intervention group (25.0% vs. 31.3% in placebo); however, dehiscence (25.0% vs. 18.8% in placebo) and frank signs of wound infection (16.7% vs. 12.5% in placebo) were more common in the intervention group. We evaluated bony healing metrics and observed trends toward improved outcomes with Vitamin C supplementation in the assessments of malocclusion (20.8% vs. 31.3% in placebo), loose hardware (12.5% vs. 18.8% in placebo), and hardware exposure (8.3% vs. 12.5% in placebo). Fracture stratification variables were not associated with the clinical outcomes.

Finally, we observed that the placebo group had a greater rate of return to the emergency room (ER) (29.2% in Vitamin C vs. 43.8% in placebo), but the Vitamin C cohort returned to the OR more frequently (29.2% vs. 18.8% in placebo). The median (range) for length of hospital stay was 2 (0-7) vs 1 (0-10) day for placebo and intervention groups respectively.

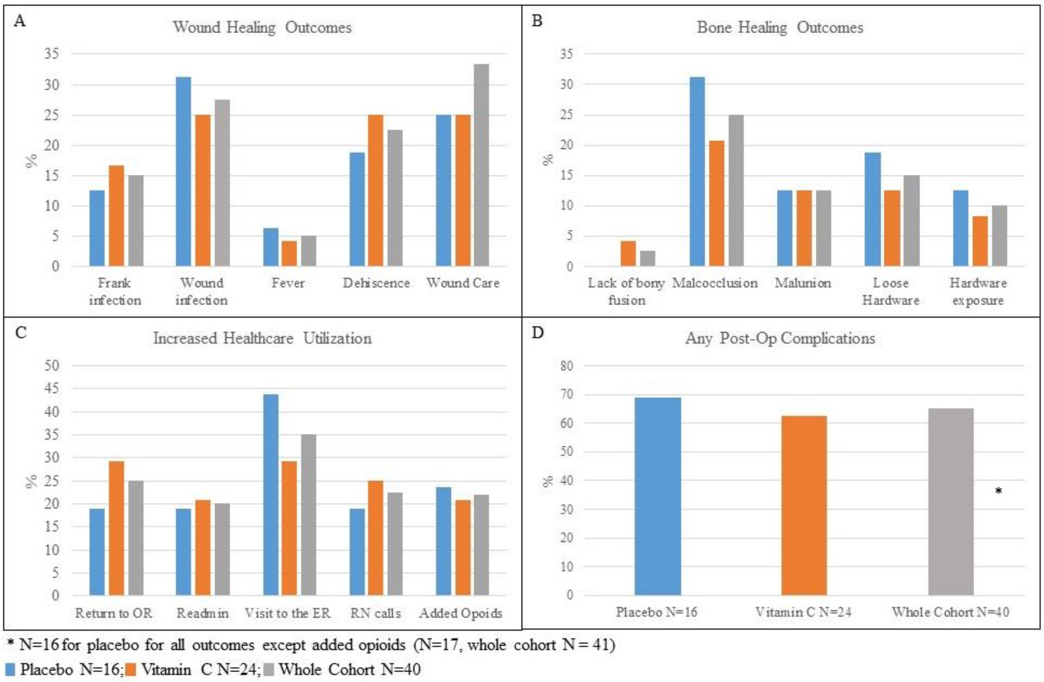

Figure 2 Outcomes. Post-operative outcomes including any complication (a), wound healing outcomes (b), bone healing outcomes (c), and increased healthcare utilization outcomes (d) by treatment group (Placebo (blue); N = 16, Vitamin C (Orange); N = 24) and the cohort as a whole (Grey: N = 40). *N = 16 for placebo for all outcomes except added opioids (N = 17, whole cohort = 41).

3.3 Patient and Treatment Characteristics by Clinical Outcome

We next evaluated how subject demographic, fracture, and treatment characteristics influenced wound healing, bone healing, and healthcare utilization outcomes within the whole cohort (Table 3). Many associations approached significance ($p \leq 0.10$) or were significant ($p < 0.05$). Most notably, we found that the addition of opioid medications *(as a treatment variable)* were associated with poorer clinical outcomes including increased post-operative complications (p = 0.016), visits to the ER (p < 0.001), and the requirement for post-discharge wound care (p = 0.003). Patients with coexistent trauma (those with fractures other than that of the mandible) were more likely to visit the ER (p = 0.039) and be prescribed additional opioids (p = 0.031). Further, we found an association between increased days from injury to surgery and increased frank infection (p = 0.044). Additionally, the median age of subjects who returned to the ER post-discharge (35.0) was higher than the median age of subjects who did not (28.5) (p = 0.033). Finally, those that returned to the OR and had wound dehiscence present at any time were more likely to have a higher number of follow up appointments, p = 0.005 and p = 0.009, respectively.

Table 3 Categorical and Continuous Demographic, Patient and Treatment Characteristics by Clinical Outcome [a].

Demographic/Patient/Treatment Characteristic Clinical Outcome	**Category 1, 2 or 3 N (%) or [Median]**			**P-value**
Categorical Characteristics				
Sex	**Male**	**Female**		
Frank Infection	4 (11.1)	2 (50)		0.10
Race	**Non White**	**White**		
Loose Hardware	6 (23.1)	0 (0.0)		0.074
Insurance Type	**None**	**Public**	**Private**	
Loose Hardware	2 (33.3)	4 (21.1)	0 (0.0)	0.092
Visit to the ER	2 (33.3)	10 (52.6)	2 (13.3)	0.058
Added opioids *(as an outcome)*	1 (16.7)	7 (36.8)	1 (6.3)	0.088
Homeless	**No**	**Yes**		
Malunion	2 (6.7)	3 (30.0)		0.089
Dehiscence of Incision	9 (30.0)	0 (0.0)		0.081
Post-operative wound Infection	6 (20.0)	5 (50)		0.100
Coexistant Trauma	**No**	**Yes**		
Visit to the ER	9 (27.3)	5 (71.4)		**0.039**
Added opioids *(as an outcome)*	5 (14.7)	4 (57.1)		**0.031**
Fracture Type	**Closed**	**Open**		
Nursing Calls	5 (41.7)	4 (14.3)		0.097
Added Opioids *(as a treatment variable)*	**No**	**Yes**		
Post-operative wound infection	6 (19.4)	5 (55.6)		0.083
Need for additional wound care	4 (12.9)	6 (66.7)		**0.003**
Visit to the ER	6 (19.4)	8 (88.9)		**<0.001**
Any post-operative complication	17 (54.8)	9 (100)		**0.016**
Non Compliance w/No Chew Diet	**No**	**Yes**		
Visit to the ER	7 (24.1)	6 (60.0)		0.056
Continuous Characteristics				
Days from Injury to Surgery	**No**	**Yes**		
Added Opioids *(as an outcome)*	32 [2]	9 [1]		0.084
Malocclusion	20 [2]	10 [1]		0.084
Frank Infection	34 [1]	6 [2.5]		**0.044**
Age	**No**	**Yes**		
Visit to the ER	26 [28.5]	14 [35]		**0.033**
Post discharge wound care	30 [29]	10 [33]		0.059
BMI	**No**	**Yes**		
Post-operative wound Infection	28 [25.4]	11 [22.8]		0.057
Any post-operative complication	14 [26.6]	25 [23.7]		0.098
Total Follow Up Appointments	**No**	**Yes**		
Return to OR	31 [2]	10 [5]		**0.005**

Readmission to Hospital	32 [2]	8 [4.5]	0.084
Dehiscence of Incision	31 [2]	9 [4]	**0.009**
Any post-operative complication	14 [1]	26 [3]	0.100

[a] Added opioids were analyzed as a treatment variable and as an outcome.

3.4 Biomarker Analysis

Of the 41 patients included in this study, 23 had complete hematologic specimen sets used for biomarker analysis. The median change in biomarker (follow-up minus baseline) was compared between treatment groups (Figure 3). The change in biomarkers of collagen synthesis (Figure 3A), inflammation (Figure 3B-K), bone healing (Figure 3L-Q), and oxidative stress (Figure 3R-V) were not statistically significantly associated with treatment group. Notably, pro-collagen-1-alpha was different between the two groups at baseline ($p = 0.024$) with placebo having a higher median value than the treatment group; the follow-up value was not different between groups. Cohen's D analysis for effect size was performed for our primary outcome, change in pro-collagen-1-alpha, and Vitamin C supplementation was found to have a medium to large effect ($d = 0.61$ 95% CI [-0.24–1.4]).

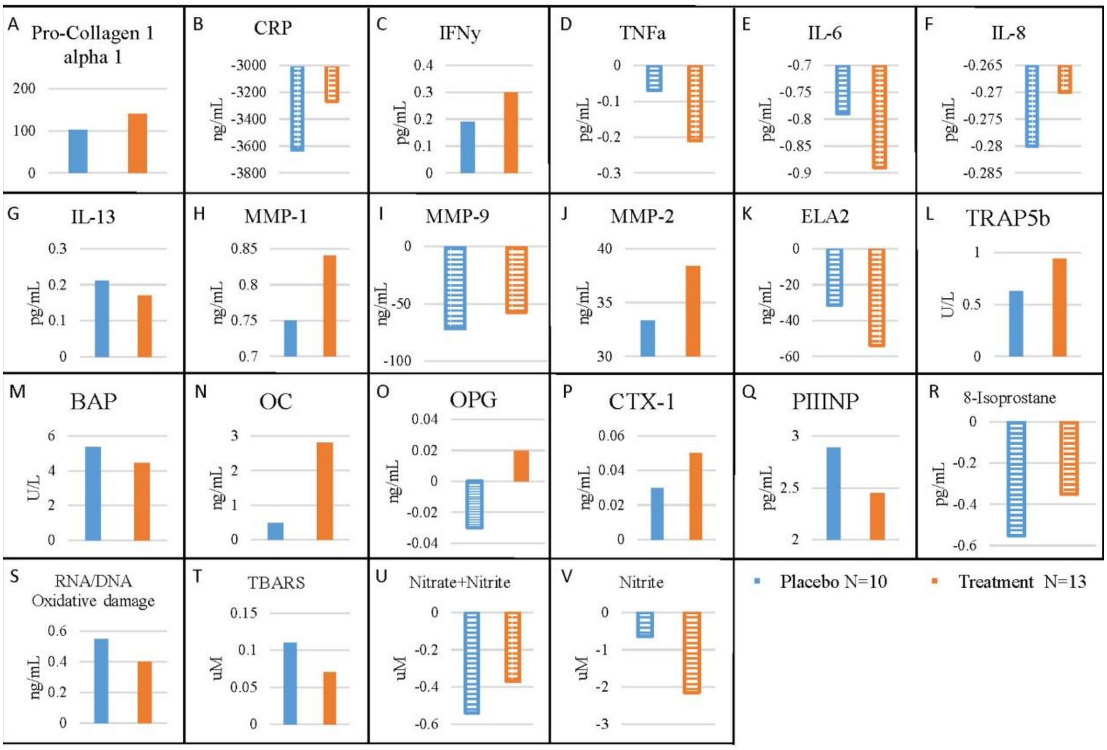

Figure 3 Median change (follow up minus baseline) in biomarkers of (A) collagen synthesis including pro-collagen 1 alpha one, (B-K) inflammation including CRP, INFγ, TNFα, IL-6,-8,-10,-13, MMP-1,-9,-2 and ELA2, (L-Q) bone healing including TRAP5b, BAP, OC, OPG, CTX-1, and PIIINP, and (R-V) oxidative stress including 8-isoprostane, RNA/DNA oxidative damage, TBARS, Nitrate + Nitrite, and Nitrite by treatment group[1] (Placebo (blue); N = 10, Vitamin C (Orange); N = 13). A positive number reflects an increase from baseline and a negative number is a decrease.

[1] A positive number reflects an increase from baseline and a negative number is a decrease.

4. Discussion

Mandibular fracture is a frequent, yet heterogenous pathology resulting from a variety of mechanisms and leading to multiple treatment approaches [1, 2, 4, 5]. Patients with this type of injury frequently come from underserved communities and are at elevated risk for post-operative complications. Despite technical and device-related advances, complication rates remain high. Diminished soft tissue and bone healing lead to suboptimal post-operative outcomes [7, 8]. Vitamin C is a low-risk supplement that mediates oxidative stress, known to be high in the setting of traumatic and surgical injury [16, 19, 20], as well as a necessary co-factor for collagen synthesis [10]. Vitamin C has been evaluated in both preclinical and clinical settings and was found to improve acute wound healing of soft tissues and bone [46]. As interventions are needed to improve mandibular fracture outcomes, we conducted a double-blind, placebo-controlled, randomized clinical trial to evaluate Vitamin C supplementation in this setting. Furthermore, we prospectively evaluated the sociodemographic and treatment characteristics our mandibular fracture cohort as a whole.

Similar to previous retrospective epidemiological studies, this cohort was largely male, had a mean age of ~30 years old, and presented with a mandibular fracture due to assault [5, 37, 38]. Our study population consisted of subjects largely coming from underserved backgrounds, likely complicating their ability to access follow-up care. The mean age of this cohort was well below the Medicare enrollment age of 65, yet the majority (61.0%) of patients had public or no insurance at all, and nearly 25% of patients had some form of unstable housing. Prior literature suggests that factors such as insurance status or race do not affect the method of fracture repair (open vs. closed) [47], but these sociodemographic characteristics have been shown to be associated with outcomes and limited care post-hospitalization [48, 49]. Within our cohort, sociodemographic factors (non-white race, females, homeless individuals or those with public or no insurance) trended toward higher rates of post-operative complications, although these findings were not significant. Further, older patients (mean age 35 years) visited the ER significantly more than younger patients (mean age 28.5 years). The high proportion of subjects coming from disadvantaged communities likely contributed to our cohort's poor follow up rate, with over half of patients missing at least one standard of care follow-up visit. Given that poor follow up is associated with poorer surgical outcomes [8, 50], it is crucial that surgeons involved in the care of patients with mandibular fracture recognize the social determinants of health behind their patients' injuries and respond accordingly. Research has shown that removing barriers to transportation [51] and providing financial incentives [52] has improved patient follow up compliance.

With regards to clinical outcomes by treatment arm, there were no statistically significant associations. However, there were some signs of potential improvement in clinical outcomes associated with Vitamin C supplementation. These included a small decrease in all post-operative complications in the intervention group as well as a decreased rate of wound infection in the intervention group, both considered key clinical outcomes. A small number of treatment arm subjects had more severe clinical signs of infection (frank infection). With regards to bone healing clinical outcomes, the Vitamin C arm exhibited lower rates of malocclusion, loose hardware, and hardware exposure. When assessing healthcare utilization outcomes, the placebo group had higher rates of return to the ER, but the intervention group returned to the OR more frequently. The remainder of healthcare utilization measures were mixed in direction between groups. However, when analyzing the cohort as a whole, we observed multiple significant associations between the addition of opioids and post-operative outcomes. Statistical analysis showed that patients who had opioids added to their treatment regimen beyond standard were more likely to have visited the ER, needed additional wound care, and experienced any post-operative complication. While these associations do not indicate causation, it is important to recognize the role that opioids may play in post-operative outcomes in this population, particularly in light of the current opioid epidemic. It has been widely documented that underserved populations are disproportionately impacted by the opioid crisis, and that increased prescription of opioids is associated with higher rates of opioid substance use disorder [53]. Risk factors for opioid use disorder in patients that underwent surgery include having a history of mental health disorders, being male, or having a history substance or alcohol misuse [54], all of which are characteristics observed in our patient cohort. Thus, great caution should be exhibited when prescribing opioids in patient with mandibular fracture, particularly in underserved communities which have been shown to be at greater risk to experience mandibular fracture [55]. Other options do exist: for example, a recent RTC found that patients who underwent mandibular nerve block before mandibular surgery consumed significantly less opioids post-operatively [54], posing a potential intervention to limit the use of opioids.

Regarding other treatment characteristics that affect post-operative outcomes in this population, significant associations were found. Those with co-existent trauma tended to visit the ER more frequently (0.039) and were prescribed more opioids ($p = 0.031$). Understandably, those with additional traumas not related to the mandible have an inherently higher likelihood of being in pain and having suboptimal outcomes needing prompt attention. Not surprisingly, those that returned to the OR and had wound dehiscence had more follow up appointments than those that did not ($p = 0.004$, $p = 0.009$, respectively), as poor post-operative outcomes require increased healthcare [6]. Further, contrary to previous literature which found no significance between time of surgery and post-operative complications [56-61], our results showed that increased time to surgery was significantly associated with frank infection. Conversely, decreased time to surgery signaled a greater likelihood of malocclusion and additional opioids prescribed beyond standard practice.

We subsequently explored biochemical outcomes to assess for effects of Vitamin C on biomarkers of collagen synthesis, inflammation, bone healing, and oxidative stress. Although sample size was especially limited for these metrics and none reached statistical significance, these mediators give important information on the molecular mechanisms or pathogenesis of wound healing in the setting of Vitamin C or placebo supplementation. As Vitamin C is an essential cofactor in collagen synthesis [9], our primary outcome was change in procollagen-1-alpha from baseline to follow-up, and we observed a greater but not statistically significant increase in pro-collagen-1-alpha in the intervention group than placebo. As we did not reach our planned sample size, we performed a Cohen's D assessment which revealed a medium-large effect size for Vitamin C supplementation on procollagen levels, supporting the potential use and utility of further study.

We next investigated biomarkers of inflammation and noted a decrease in neutrophil elastase in the intervention group relative to placebo, indicating a systemic decrease in neutrophil bactericidal activity and thus infectious or inflammatory activity [62]. Likewise, decreases in acute inflammatory markers TNFα and IL-6 [63] were seen in the intervention group. However, some inflammatory markers such as CRP and IL-8 [26] decreased more in the placebo group. Matrix metalloproteinases MMP-1 and MMP-2, enzymes critical to the maturation of the acutely healing wound [64], were found to increase in the intervention group relative to placebo. Along the same lines, MMP-9, a critical mediator of acute wound healing as a stimulator of angiogenesis [64], decreased less in the intervention group. In sum, these results point to potentially positive physiologic effects of Vitamin C on inflammatory response, especially seen with proteases, and warrant further investigation.

Like bone healing outcomes, biomarkers of bone repair showed a more consistently positive effect in the intervention group. OC, an osteoblast-secreted, key marker of bone formation for which low levels are associated with delayed union [65], showed the largest margin of increase in the intervention group relative to placebo of all biomarkers assessed. Previous research has shown a marked increase in OC in patients given post-operative antioxidant supplementation (including Vitamin C) after surgical repair consistent with our results [66]. PIINP, a bone formation and collagen synthesis biomarker and known indicator of poor fracture healing [67], was higher in placebo group than Vitamin C, also supporting a positive effect on bone healing. Markers of bone resorption TRAP5b and CTX-1 increased more in the Vitamin C group, indicating an improvement, as low levels of these markers have been associated with delayed fracture healing [68]. OPG, another marker of bone resorption activity [69], increased in the Vitamin C group but decreased in placebo which is consistent with animal models [70]. These findings suggest biochemical improvement in bone repair in the Vitamin C group which parallel the bone clinical outcomes, and suggest that Vitamin C supplementation may play a positive role in fracture healing.

In this RCT we found some trends of Vitamin C supplementation improving clinical and biological wound healing outcomes, but no findings were statistically significant. While this lack of significant findings may indicate no benefit of Vitamin C supplementation in this setting, a significant limitation of the study is that power was reduced due to not reaching planned sample size. Furthermore, we successfully characterized the sociodemographic, treatment and biological characteristics in a severely disadvantaged population drawn from two safety net hospitals. Significant associations between baseline characteristics and post-operative outcomes when analyzing the cohort as a whole. Most importantly, we showed that additional opioid prescription outside of standard practice was associated with poorer post-operative outcomes. Within the context of the current opioid crisis, this should be of the utmost importance to surgeons repairing mandibular fractures.

Our study, as with many others [71], was prematurely halted due to the COVID-19 pandemic, preventing further recruitment. Our patient population was recruited from two safety-net hospitals, and subjects were severely disadvantaged as evidenced by the high rates of public/no insurance, unstable housing, and transportation difficulty. They were also observed to have high rates of mental illness, alcohol intoxication, and cigarette smoking, indicating a baseline risk of poor health outcomes. Furthermore, many subjects lacked access to reliable communication and thus were difficult to retain for the full study duration. The subjects also had some difficulty with medical compliance, such as adhering to no-chew diet and surgeon instructions, potentially confounding results. Although vitamin C was not significantly associated with post-operative outcomes in the RTC, when assessing the cohort as a whole, it could potentially confound the results. Next, the individuals included in this study may not be representative of the overall population experiencing mandible trauma, since the participants were compensated which could cause selection bias. Also, the mandible fractures studied did not include all types of fractures: specifically, we excluded isolated subcondylar fractures as these fractures are typically repaired by very different methods than other mandible fractures studied and thus could not be reliably compared. Further, 13 surgeons operated on these patients who likely have their own unique technique, skills, and perioperative management strategies which could confound these results. As each mandible fracture is unique, there is not a uniform protocol established for repair, and large multicenter studies support the heterogenicity in treatment protocols and patterns for mandibular fracture [5]. Despite this variability, surgeons in our center share common management principles, and treatment approaches are honed via multidisciplinary bi-weekly trauma conferences and continuous collaborative care of patients. Finally, other limitations include that only 23 patients had complete hematologic specimen sets used for biomarker analysis, limiting complete analysis.

While this study was significantly limited by the above factors, it presents numerous strengths. This investigation was a multi-site, double-blind, placebo controlled, randomized clinical trial conducted with integrity and attention to detail. Experimental procedures including placebo appearance and blinding were completed with success. Further, our study affirmed that Vitamin C may be useful the healing of mandibular or other traumatic fractures, improving some clinical outcomes as well biochemical markers of healing, especially in bone repair. Further, we were provided the unique opportunity to assess characteristics and post-operative outcomes among a disadvantage subject population due to our enrollment locations. Thus, the demographic composition of our cohort is likely similar to that of other safety-net hospitals throughout the nation and can serve as the foundation for further investigation of mandibular fracture in this population.

5. Conclusions

We conducted a double-blind, placebo-controlled, randomized clinical trial to assess the effect of supplemental Vitamin C versus placebo on clinical and biochemical wound healing outcomes in a mandibular fracture population. Additionally, we sought to establish the effects of sociodemographic, fracture, and treatment characteristics on post-operative clinical outcomes in patients undergoing mandibular fracture repair. While we were unable to reach our planned sample size, there was evidence of a signal of improvement in outcomes associated with Vitamin C. As Vitamin C represents a low-risk and inexpensive therapeutic, further investigation is warranted for potential use in this setting. Furthermore, we found numerous significant associations between patient characteristics and post-operative outcomes, including increased complications with increasing time from injury to surgery and age. Notably, additional opioids prescribed outside of standard practice was significantly associated with a need for additional wound care, increased emergency room visits, and any post-operative complication. Further investigation is needed on mitigation strategies for these patient characteristics and treatment risk factors in mandibular fracture populations in order to improve patient outcomes.

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Author Contributions

AAL: Conceptualization, methodology, funding acquisition, data curation, supervision, writing – original draft, writing - review and editing. AW: data curation, investigation, writing –original draft, writing - review and editing, project administration. WJ: Formal analysis, writing –original draft, writing - review and editing. AJ: Conceptualization, writing - review and editing; BL: Conceptualization, formal analysis, writing - review and editing. RO: Conceptualization, supervision, writing - review and editing.

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Competing Interests

The authors have declared that no competing interests exist.

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