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Randomized Control Trials

Perioperative supplementation with a fruit and vegetable juice powder concentrate and postsurgical morbidity: A double-blind, randomised, placebo-controlled clinical trial

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SUMMARY

Background & aims: Surgical trauma leads to an inflammatory response that causes surgical morbidity. Reduced antioxidant micronutrient (AM)[a] levels and/or excessive levels of Reactive Oxygen Species (ROS)[b] have previously been linked to delayed wound healing and presence of chronic wounds. We aimed to evaluate the effect of pre-operative supplementation with encapsulated fruit and vegetable juice powder concentrate (JuicePlus+®) on postoperative morbidity and Quality of Life (QoL)[c].

Methods: We conducted a randomised, double-blind, placebo-controlled two-arm parallel clinical trial evaluating postoperative morbidity following lower third molar surgery. Patients aged between 18 and 65 years were randomised to take verum or placebo for 10 weeks prior to surgery and during the first postoperative week. The primary endpoint was the between-group difference in QoL over the first postoperative week, with secondary endpoints being related to other measures of postoperative morbidity (pain and trismus).

Results: One-hundred and eighty-three out of 238 randomised patients received surgery (Intention-To-Treat population). Postoperative QoL tended to be higher in the active compared to the placebo group. Furthermore, reduction in mouth opening 2 days after surgery was 3.1 mm smaller (95% CI 0.1, 6.1), the mean pain score over the postoperative week was 8.5 mm lower (95% CI 1.8, 15.2) and patients were less likely to experience moderate to severe pain on postoperative day 2 (RR 0.58, 95% CI 0.35, 0.95), comparing verum to placebo groups.

Conclusion: Pre-operative supplementation with a fruit and vegetable supplement rich in AM may improve postoperative QoL and reduce surgical morbidity and post-operative complications after surgery.

Trial registration: ClinicalTrials.gov Identifier: NCT01145820; Registered June 16, 2010.

1. Introduction

Surgical removal of lower third molars (wisdom teeth) is one of the most common surgical procedures. It is associated with marked postoperative morbidity as a consequence of surgical trauma, including pain, swelling and reduced mouth opening (trismus) [1,2]. Whilst it is recognised that there is significant inter-individual variability in postoperative morbidity, patient-level determinants remain poorly understood.

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Abbreviations

[a] AM	Antioxidant Micronutrients
[b] ROS	Reactive Oxygen Species
[c] QoL	Quality of Life
[d] GSH	Tripeptide Reduced Glutathione
[e] GSSG	non-radical form of Glutathione
[f] Nrf2	Nuclear Factor E2 (Erythroid 2)-Related Factor 2
[g] F&V	Fruit and Vegetable = active group
[h] VAS	Visual Analogue Scale
[i] PoSSe	Postoperative Symptom Severity
[j] BMI	Body Mass Index
[k] SMAC	Small Molecule Antioxidant Capacity
[l] AE	Adverse Event
[m] SD	Standard Deviation
[n] IQR	Interquartile range
[o] ITT	Intention To Treat
[p] CI	Confidence Interval
[q] GI	Gastrointestinal

Reactive Oxygen Species (ROS)[b] released by inflammatory cells, in particular neutrophils, play a key role in wound healing, with normal ROS levels facilitating healing, and excess ROS creating oxidative stress. Oxidative stress activates major redox-regulated pro-inflammatory signalling cascades via the redox-sensitive gene transcription factor Nuclear Factor kappa-B (NFkB), and thus the redox status of healing tissues and their constituent cells impacts upon wound healing dynamics [3,4]. A wide variety of antioxidant micronutrients (AM)[a] are implicated in regulating the redox environment during wound healing. Excess ROS are removed by various antioxidant systems working in concert via redox cycling reactions, such as vitamins E, C and the non-radical tripeptide, Reduced Glutathione (GSH)[d], the terminal stage of which results in the oxidation of GSH to its oxidized counterpart GSSG[e] [5]. GSH however, must be synthesised by cells, a process that requires the activation of the redox-regulated gene transcription factor Nuclear Factor E2 (Erythroid 2)-Related Factor 2 (Nrf2)[f] [6,7]. Whole food nutrition rather than individual vitamin supplementation is therefore generally recommended in order to maintain AM in homoeostatic balance and preserve GSH, which is a powerful regulator of cellular redox state and thus of key transcriptional events. In acute models of rodent wound healing, tissue levels of GSH, ascorbate and vitamin E show a sustained decrease of 60–70% after wounding [8]. Furthermore, tissue levels of AM are considerably reduced in the wounds of aged rats relative to young rats [9], and in immunosuppressed rats compared with immunocompetent animals [10]. Thus, impaired healing appears to be associated with reduced AM tissue levels known to affect key redox-regulated signalling pathways, such as Nrf2 and NFkB.

Given the role of ROS in wound healing and control of infection, there is a surprising paucity of data on the effect of AM intake and wound healing, including the incidence of post-surgical complications/morbidity. Therefore, here we report a double-blind, placebo-controlled, randomised clinical trial to ascertain the efficacy of pre-operative supplementation with encapsulated fruit and vegetable juice powder concentrate to reduce post-operative morbidity and improve QoL following lower third molar surgery.

2. Materials and methods

2.1. Study design and participants

The FAVOURITE study was a randomised, double-blind, placebo-controlled two-arm parallel clinical trial conducted at the School of Dentistry, University of Birmingham and Birmingham Dental Hospital, Birmingham, UK. The study protocol was approved by the South Staffordshire Local Research Ethics Committee (Reference 09/H1203/82). All enrolled patients provided written informed consent.

The objective of this study was to evaluate whether encapsulated fruit and vegetable powder concentrate (JuicePlus+®, The Juice Plus+ Company, LLC, Collierville, Tennessee, USA) supplementation, beginning 10 weeks before surgery, improved postoperative QoL and reduced postoperative morbidity and complications following lower third molar surgery compared to placebo.

Patients aged between 18 and 65 years who required the surgical removal of one mandibular third molar were considered eligible to participate. Patients on long term antimicrobial or anti-inflammatory drugs or taking any vitamin or mineral supplements, patients requiring pre-operative antibiotic prophylaxis, patients with allergies to any of the ingredients contained in the active or placebo capsules, patients with a self-reported inability to swallow the supplied capsules, an inability or unwillingness to give informed consent, patients requiring additional concomitant tooth extractions at the time of surgery, pregnant or lactating women, and patients with any clinically significant or unstable physical or mental condition or disability were excluded from the trial.

2.2. Randomisation and allocation concealment

At the baseline visit, following written informed consent and verification of eligibility criteria, eligible patients were assigned the next available randomisation number and then provided with the corresponding supplements. Randomisation was carried out using block randomisation with variable block size in a 1:1 ratio using a computer algorithm [www.randomization.com]. Test and placebo capsules were provided to the study centre in consecutively numbered, identical tubs. Both patients and clinicians were blinded to group assignment. The randomisation list was not kept at the study centre and was not accessible by investigators during the study.

2.3. Intervention

The verum test capsules were based on commercially available formulations of Juice Plus+® (active, F&V[g]) and contained a fine, granular powder, encapsulated in a size 00 gelatine capsule. The capsule contained a blended fruit and vegetable pulp and juice powder concentrate derived from Acerola cherry, apple, beet, beetroot, broccoli, cabbage, carrot, cranberry, dates, garlic, kale, orange, peach, papaya, parsley, pineapple, prune, spinach, sugar beet, tomato, with Spirulina pacifica, *Lactobacillus acidophilus*, rice bran, oat bran and *Dunaliella salina*. These active ingredients were supplemented to provide declared totals (daily dose) of β-Carotene (7.5 mg), vitamin E (46 mg), vitamin C (200 mg) and folic acid (400 μg). The amount of polyphenolic AM contained within the phytonutrient capsules varies according to growing and harvest conditions, and absolute levels were not analysed. The placebo (control) capsules were of identical appearance and contained microcrystalline cellulose.

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Patients were asked to take two capsules, twice daily with food (= four supplements per day) for 10 weeks prior to their surgical intervention. Following wisdom tooth surgery, participants were asked to continue taking the study medication for the first post-operative week.

Capsule counts were performed on the day of surgery and at the final study visit, when all remaining capsules were returned to the study centre.

2.4. Surgery and follow-up

Patients had standard outpatient third molar surgery ten weeks following randomisation (see online supplement for details on surgical procedure). Patients received a postoperative diary after the surgical intervention to record analgesic consumption and pain intensity on a 10 cm Visual Analogue Scale (VAS)[h] once daily for 1 week. Additionally, patients were clinically examined 2 days and 1 week (final study visit) following surgery (see Study Flow Chart, Fig. 1).

2.5. Outcome measures

Postoperative QoL was the primary outcome and was determined at the 1-week follow-up visit using the Postoperative Symptom and Severity (PoSSe)[i] scale; a self-administered, validated instrument specifically designed to evaluate QoL over the first postoperative week following third molar surgery. The instrument measures QoL in seven domains (subscales), including eating, speech, sensation, appearance, pain, sickness and interference with daily activities. The overall score is a weighted sum of the subscale scores, ranging from 0 to 100 with higher scores indicating worse QoL [2].

Secondary outcomes of morbidity and post-operative complications included (i) trismus, which represents the reduction in a patient's mouth opening postoperatively compared to baseline, (ii) pain intensity during the first postoperative week, and (iii) analgesic consumption.

Mouth opening was measured by the clinician as the inter-incisal distance in mm before surgery and on postoperative day 2 and day 7 using a ruler. Pain intensity and analgesic consumption were recorded by the patient in the patient diary.

2.6. Other data and laboratory analyses

Recorded demographic and anthropometric data included age, gender, race/ethnicity, smoking status, weight, height and Body Mass Index (BMI)[j]. We assessed a number of tooth- and surgery-related measures on the day of surgery (see online supplement for details). Venous blood samples were taken, processed and stored at all visits for the analysis of a range of micronutrients at the end of the study. Details regarding blood sampling and laboratory procedures are described in the online supplement. We estimated small molecule antioxidant capacity (SMAC)[k] in serum from serum

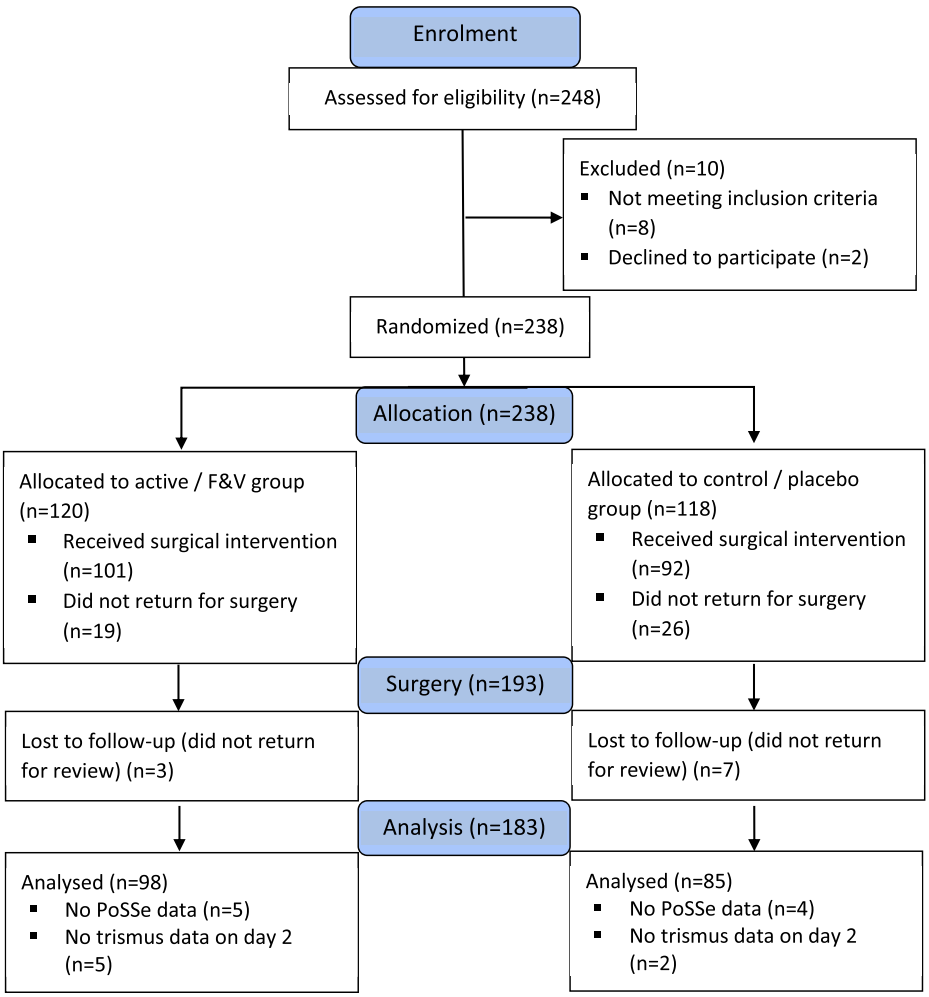

Fig. 1. CONSORT flow diagram.

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concentrations of uric acid and vitamins A, C and E for baseline and day of surgery as previously described [11].

2.7. Statistical analyses

2.7.1. Primary endpoint and sample size

The primary endpoint was the between-group difference in oral health-related QoL over the first postoperative week assessed with the PoSSe scale. The study required a minimum of 170 patients (n = 85 per group) in order to achieve 90% power to detect a standardised effect size of 0.5 at a significance level of $\alpha = 0.05$, which would generally be considered a clinically meaningful difference in QoL between groups [12]. Subjects lost to follow-up were replaced until the target sample size for the primary endpoint was reached.

2.7.2. Secondary endpoints

Assessment of the following secondary endpoints was performed:

- Specific QoL domains (PoSSe subscales),
- Trismus on postoperative day 2 and day 7, i.e., the difference between the pre-operative interincisal distance on the day of surgery and the interincisal distance 2 days and 7 days following surgery, respectively,
- Mean pain score from postoperative days 1 to 6,
- The proportion of patients that reported pain of 50 mm or higher on day 2 and day 6,
- The proportion of patients experiencing an absolute increase of 20 mm in pain score on any day between postoperative day 4 and day 6, compared to the previous day (a surrogate for alveolar osteitis/wound infection),
- The between-group difference in total consumption of analgesics during the first postoperative week,
- Adverse Events (AEs)[l].

2.7.3. Pre-specified analysis plan

Statistical analysis was performed according to a pre-specified analysis plan (see online supplement for details). Briefly, analyses were done according to the Intention-To-Treat (ITT)[o] principle, which included all randomised patients who received the supplements and returned for at least one follow-up appointment. Summary statistics were calculated as appropriate. For comparisons between groups for primary and secondary endpoints, we calculated effect estimates, 95% confidence intervals and p-values for using appropriate multiple regression models. In addition to unadjusted estimates, we calculated estimates adjusting for important baseline characteristics only and estimates adjusting for important baseline as well as surgical characteristics. Further details, including the handling of missing data, are described in the online supplement.

2.7.4. Compliance

Compliance was calculated for patients for whom follow-up capsule counts were available as the proportion of capsules taken relative to the expected number of capsules taken with 100% compliance. 'Good compliance' was defined as at least 80% of capsules taken [13,14].

3. Results

3.1. Baseline characteristics

3.1.1. Randomised patients

Patients were enrolled between June 2010 and October 2013. A total of 248 patients were assessed for eligibility. Eight patients did not meet the inclusion criteria and two patients withdrew consent. Therefore, 238 participants were randomised out of which 120 belonged to the active and 118 to the placebo group (Fig. 1). Baseline characteristics of all randomised patients were overall well balanced between the two treatment arms (Table 1).

3.1.2. ITT population

Of the 238 randomized patients, 19 patients allocated to F&V and 26 patients allocated to placebo did not return for surgery. Therefore, surgery was performed in 193 participants. A further ten patients (active n = 3, placebo n = 7) did not return for any follow-up appointments. Hence, 183 patients had data available for at least one endpoint (ITT population) (Fig. 1). Detailed descriptions of patients lost to follow-up and missing data can be found in the Online Supplemental Material. Briefly, current smokers were less likely to attend for surgery, and patients with poor oral hygiene and less extensive surgery were less likely to attend for follow-up after surgery (Supplemental Table 1). Due to some patients not recording all required details in their postoperative diary, not returning their diary, or some participants not attending one of their follow-up appointments, some endpoint analyses contained less than 183 patient data (Fig. 1). Further details on missing data are presented in Supplemental Table 2.

Baseline and surgical characteristics of the ITT population were overall well balanced (Table 2). However, the proportion of current smokers (29.6% vs 15.3%) and plasma vitamin C concentrations at baseline (61.4 μmol/L vs 52.9 μmol/L) were higher, and bone removal was lower (minor bone removal in 28.2% vs. 43.9%) in the active compared to the placebo group, respectively.

3.1.3. Compliance

On average, patients took more than 80% of the assigned capsules. There were no statistically significant differences between

Table 1
Baseline patient characteristics and micronutrient levels by treatment group.

	Placebo (n = 118)	F&V (n = 120)
Age, years	26 [24, 32]	28 [24, 34]
Male, n (%)	40 (33.9)	49 (40.8)
Smoking status, n (%)		
Never	63 (53.4)	63 (52.5)
Ex-smoker	27 (22.9)	23 (19.2)
Current smoker	28 (23.7)	34 (28.3)
Index of multiple deprivation	34.7 (18.2)	33.6 (18.1)
Systolic Blood Pressure (mmHg)	127.3 (13.0)	128.1 (14.8)
Diastolic Blood Pressure (mmHg)	79.0 (12.4)	79.6 (10.8)
Weight (kg)	75.2 (18.9)	76.4 (16.8)
Height (m)	1.69 (0.11)	1.70 (0.10)
BMI	25.1 [21.8, 28.9]	25.4 [22.2, 30.1]
Race, n (%)		
White	72 (61.0)	79 (65.8)
Asian	30 (25.4)	22 (18.3)
Black	9 (7.6)	12 (10.0)
Other	7 (5.9)	7 (5.8)
Micronutrients[a]		
Vitamin C (μmol/L)	55.2 (25.0)	60.1 (26.4)
Lutein (μmol/L)	0.19 [0.14, 0.25]	0.20 [0.15, 0.26]
Zeaxanthin (μmol/L)	0.05 [0.04, 0.07]	0.05 [0.04, 0.07]
Cryptoxanthin (μmol/L)	0.10 [0.07, 0.17]	0.10 [0.08, 0.15]
Lycopene (μmol/L)	0.87 [0.55, 1.19]	0.76 [0.55, 1.10]
α-Carotene (μmol/L)	0.08 [0.04, 0.12]	0.08 [0.05, 0.11]
β-Carotene (μmol/L)	0.29 [0.18, 0.46]	0.32 [0.23, 0.52]
α-Tocopherol (μmol/L)	20.2 (4.6)	20.9 (5.8)
Retinol (μmol/L)	1.33 (0.33)	1.28 (0.34)
SMAC (μmol/L Teq)	381 [330, 441]	385 [346, 457]

Continuous variables are presented as mean (SD) or median [IQR].
[a] There is missing baseline data for all micronutrients for 13 patients assigned to placebo and 13 patients assigned to F&V.

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Table 2
Baseline patient characteristics, surgical characteristics, and micronutrient levels by treatment group for those that received surgery and returned for at least one follow-up appointment.

	Placebo (n = 85)	F&V (n = 98)
Age, years	28 [24, 33]	28.5 [23, 34]
Male, n (%)	32 (37.7)	39 (40.0)
Smoking status, n (%)		
Never	54 (63.5)	56 (57.1)
Ex-smoker	18 (21.2)	13 (13.3)
Current smoker	13 (15.3)	29 (29.6)
Index of multiple deprivation	35.5 (18.1)	33.6 (17.2)
Systolic Blood Pressure (mmHg)	128.0 (13.5)	127.2 (14.3)
Diastolic Blood Pressure (mmHg)	80.4 (12.5)	79.2 (10.3)
Weight (kg)	76.0 (18.9)	75.9 (17.0)
Height (m)	1.70 (0.11)	1.71 (0.09)
BMI	25.1 [22.2, 29.0]	24.7 [22.0, 29.5]
Race, n (%)		
White	51 (60.0)	66 (67.4)
Asian	23 (27.1)	19 (19.4)
Black	7 (8.2)	7 (7.1)
Other	4 (4.7)	6 (6.1)
Baseline micronutrients[a]		
Vitamin C (μmol/L)	52.9 (24.3)	61.4 (27.1)
Lutein (μmol/L)	0.19 [0.14, 0.25]	0.20 [0.15, 0.26]
Zeaxanthin (μmol/L)	0.05 [0.04, 0.07]	0.05 [0.04, 0.07]
Cryptoxanthin (μmol/L)	0.09 [0.07, 0.17]	0.11 [0.08, 0.16]
Lycopene (μmol/L)	0.91 [0.55, 1.18]	0.77 [0.57, 1.10]
α-Carotene (μmol/L)	0.08 [0.04, 0.13]	0.08 [0.06, 0.11]
β-Carotene (μmol/L)	0.31 [0.18, 0.52]	0.32 [0.25, 0.52]
α-Tocopherol (μmol/L)	19.0 [16.4, 23.1]	20.0 [17.0, 23.4]
Retinol (μmol/L)	1.23 [1.06, 1.49]	1.25 [1.01, 1.48]
SMAC (μmol/L Teq)	382 [325, 447]	383 [346, 441]
Surgical measures		
Bone removal, n (%)		
Minor	24 (28.2)	43 (43.9)
Moderate	49 (57.7)	47 (48.0)
Severe	12 (14.1)	8 (8.2)
Oral hygiene		
Good/very good	70 (82.4)	85 (86.7)
Fair/poor/very poor	13 (15.3)	10 (10.2)
Missing	2 (2.3)	3 (3.1)
Length of surgery (minutes)	13 [9, 20]	12 [8, 17]
Tooth sectioning, n (%)	57 (67.1)	54 (55.1)
Pre-operative CHX rinse, n (%)	42 (49.4)	45 (45.9)
Lingual flap, n (%)	22 (25.9)	18 (18.4)
Envelope flap, n (%)	50 (58.8)	61 (62.2)

Continuous variables are presented as mean (SD) or median [IQR].
[a] There is missing baseline data for all micronutrients for 2 patients assigned to placebo and 4 patients assigned to F&V.

active and placebo groups in terms of compliance (Supplemental Table 3). Thirteen patients stopped taking the capsules because of AEs (placebo = 7, F&V = 6).

3.2. Main results

3.2.1. Primary endpoint

PoSSe scale data was available for 172 patients (Table 3) and showed that, on average, patients in the active intervention group (mean 33.8, SD 15.5) reported less postoperative morbidity during the first postoperative week than patients in the placebo group (mean 38.4, SD 16.4, unadjusted mean difference in PoSSe score: −4.59, 95% CI[P]: −9.37 to 0.18, p = 0.059). When the treatment effect estimate was adjusted for baseline age, BMI, gender, race, and smoking status, the mean difference between PoSSe scores was −5.57 points (95% CI: −10.48 to −0.66, p = 0.027).

Additional adjustment for surgical characteristics, i.e. amount of bone removal, length of surgery, tooth sectioning, and pre-operative chlorhexidine rinse, rendered a mean difference between PoSSe scores of −3.97 for active compared to placebo group (95% CI: −8.79 to 0.84, p = 0.105).

3.2.2. Secondary endpoints

Comparing active to placebo groups, the analysis of separate PoSSe domains shows significantly lower impact for pain in unadjusted analyses, and significantly lower impacts for pain, eating and sickness in analyses adjusted for baseline characteristics. Following adjustments for surgical characteristics, none of the differences between subscale impacts were statistically significant (Table 3). Trismus (limitation of mouth opening) on postoperative day 2 was lower in the active intervention compared to placebo group by −3.1 mm (95% CI: −6.1 to −0.1, p = 0.042). Adjustment for baseline characteristics resulted in −3.7 mm (95% CI: −6.6 to 0.7, p = 0.016). However, additional adjustment for surgical factors resulted in an attenuated difference in trismus between groups (−2.7 mm, 95% CI: −5.6 to 0.2, p = 0.069) (Table 3). One week following surgery, the estimate of a difference in trismus between active and placebo decreased to less than 1.5 mm and showed no statistical significance for any analysis.

The mean pain score for postoperative days 1–6 also revealed a statistically significant difference between groups in all analyses, with a higher mean pain score by a mean of 8.5 mm for the control group compared to the active group when adjusting for both baseline and surgical factors (95% CI: −15.5 to −1.6, p = 0.017). The conclusion was the same after imputation.

There was a 46% lower risk of VAS score over 50% on follow-up day 2 in the active group after adjusting for baseline and surgical covariates with a 95% CI: 0.32 to 0.89, which was statistically significant at the 5% significance level (p = 0.015).

Other secondary outcomes were not statistically significantly different at the 5% significance level between treatment groups (Table 3).

3.2.3. Micronutrient levels

The levels of vitamin C, α-Tocopherol, α-Carotene, and β-Carotene were statistically significantly higher in the F&V group compared to placebo, following 10 weeks of supplementation and having adjusted for their respective baseline levels (Table 4). For active compared to placebo between baseline and surgery, the mean difference in vitamin C was 23.6 μmol/L (95% CI: 17.1 to 30.1, p < 0.001), the mean difference for β-Carotene was 1.13 μmol/L (95% CI: 0.88 to 1.38, p < 0.001), the mean difference for α-Tocopherol was 2.86 μmol/L (95% CI: 1.69 to 4.05, p < 0.001), and the mean difference in α-Carotene was 0.02 μmol/L (95% CI: 0.00 to 0.03, p = 0.045). For these AMs, the treatment effect estimates were also statistically significant at day 2 and day 7 for active compared to placebo after adjusting for the baseline levels. There were no statistically significant differences between treatment groups for the other micronutrients. Estimated serum SMAC was significantly higher in the active compared to the placebo group at the time of surgery.

3.2.4. Adverse events

In total 14 AEs, which were classified as having a “possible” or “probable” relationship with the intervention, were recorded. The vast majority of these (n = 11) were gastrointestinal (GI)[q] upset; mainly nausea and bloating. Other possible AEs were “itchiness” (n = 2) and “tiredness” (n = 1). All of the patients with GI upset stopped taking the supplements, as did one patient with itchiness (50%) and the one patient with reported tiredness. Overall, 57% of AEs were reported in the placebo group (GI upset n = 5 (45%), itchiness n = 2 (100%), tiredness n = 1 (100%)).

4. Discussion

Clinical research on the effect of perioperative nutritional supplementation on wound healing has focussed mainly on critically ill patients and/or patients with chronic wounds, such as pressure

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Table 3
Comparison of standardised PoSSe score at 7 days post-surgery, PoSSe subscale scores and other secondary outcomes between treatment groups.

	Unadjusted treatment effect estimate (95% CI), p-value	Adjusted treatment effect estimate (95% CI), p-value[a]	Adjusted treatment effect estimate (95% CI), p-value[b]
PoSSe score at 7 days post-surgery[c]	−4.6 (−9.4 to 0.2), 0.059	−5.6 (−10.5 to −0.7), 0.027	−4.0 (−8.8 to 0.8), 0.105
PoSSe subscales:[c]			
Eating	−0.25 (−0.55 to 0.05), 0.098	−0.32 (−0.63 to −0.02), 0.04	−0.23 (−0.53 to 0.07), 0.128
Speech	−0.10 (−0.40 to 0.20), 0.526	−0.10 (−0.40 to 0.20), 0.517	−0.08 (−0.39 to 0.23), 0.609
Sensation	−0.17 (−0.32 to 0.28), 0.910	−0.03 (−0.32 to 0.27), 0.867	0.01 (−0.30 to 0.31), 0.953
Appearance	−0.16 (−0.46 to 0.14), 0.286	−0.22 (−0.54 to 0.09), 0.158	−0.14 (−0.45 to 0.18), 0.395
Pain	−0.31 (−0.61 to −0.01), 0.041	−0.33 (−0.64 to −0.02), 0.038	−0.26 (−0.58 to 0.33), 0.110
Sickness	−0.22 (−0.52 to 0.08), 0.151	−0.31 (−0.61 to −0.16), 0.039	−0.26 (−0.56 to 0.05), 0.099
Interaction	−0.21 (−0.51 to 0.08), 0.159	−0.24 (−0.55 to 0.08), 0.137	−0.15 (−0.46 to 0.15), 0.322
Trismus at day 2 (mm)[c]	−3.11 (−6.11 to −0.11), 0.042	−3.66 (−6.63 to −0.68), 0.016	−2.70 (−5.61 to 0.21), 0.069
Trismus at day 7 (mm)[c]	−1.43 (−4.50 to 1.64), 0.360	−1.85 (−5.01 to 1.30), 0.247	−0.50 (−3.57 to 2.57), 0.749
Mean pain score for days 1–6[c]	−8.49 (−15.2 to −1.81), 0.013	−9.31 (−16.2 to −2.43), 0.008	−8.51 (−15.5 to −1.55), 0.017
Total consumption of analgesics (day 1–6)[c]	−2.27 (−5.85 to 1.31), 0.212	−3.02 (−6.64 to 0.60), 0.101	−2.38 (−6.11 to 1.36), 0.211
Proportion patients pain score>50% VAS on day 2[d]	0.58 (0.35 to 0.95), 0.030	0.54 (0.33 to 0.90), 0.017	0.54 (0.32 to 0.89), 0.015
Proportion patients pain score >50% VAS on day 6[d]	0.72 (0.40 to 1.28), 0.259	0.65 (0.37 to 1.14), 0.133	0.71 (0.40 to 1.24), 0.227
Proportion of patients with absolute increase of 20% on VAS on any day from day 4 to day 6, compared to the previous day[d]	0.55 (0.29 to 1.06), 0.073	0.56 (0.28 to 1.10), 0.092	0.60 (0.30 to 1.20), 0.149

PoSSe subscales are standardised to have SD = 1.
[a] Treatment effect estimate is adjusted for smoking, age, gender, ethnicity and BMI.
[b] Treatment effect estimate is adjusted for smoking, age, gender, ethnicity and BMI, and amount of bone removal, length of surgery, tooth sectioning, and pre-operative chlorhexidine rinse.
[c] Linear regression model.
[d] Poisson regression model so treatment effect estimate is a risk ratio.

Table 4
Effect of treatment on micronutrient levels.

	Placebo, Median [IQR]	Active, Median [IQR]	Mean difference (95% CI), p-value
Vitamin C, μmol/L			
Surgery	54.0 [31.4, 70.5]	80.7 [62.5, 98.6]	23.6 (17.1 to 30.1), <0.001
2-day post-op review	49.1 [26.1, 68.4]	74.8 [61.9, 92.5]	23.1 (16.2 to 30.0), <0.001
7-day post-op review	46.8 [26.9, 66.3]	76.1 [59.6, 93.0]	24.1 (17.5 to 30.8), <0.001
α-Tocopherol, μmol/L			
Surgery	19.7 [16.7, 22.9]	22.8 [19.6, 28.1]	2.86 (1.69 to 4.05), <0.001
2-day post-op review	18.7 [16.4, 21.6]	21.9 [19.1, 27.2]	2.57 (1.53 to 3.62), <0.001
7-day post-op review	19.7 [16.3, 22.1]	23.2 [20.0, 28.0]	3.14 (2.10 to 4.17), <0.001
β-Carotene, μmol/L			
Surgery	0.31 [0.18, 0.44]	1.11 [0.55, 1.95]	1.13 (0.88 to 1.38), <0.001
2-day post-op review	0.28 [0.17, 0.44]	1.08 [0.58, 1.82]	1.04 (0.82 to 1.27), <0.001
7-day post-op review	0.27 [0.18, 0.44]	1.15 [0.51, 1.74]	1.04 (0.81 to 1.27), <0.001
α-Carotene, μmol/L			
Surgery	0.08 [0.05, 0.11]	0.08 [0.06, 0.12]	0.02 (0.00 to 0.03), 0.045
2-day post-op review	0.07 [0.04, 0.11]	0.08 [0.06, 0.12]	0.02 (0.00 to 0.03), 0.024
7-day post-op review	0.07 [0.04, 0.11]	0.08 [0.06, 0.12]	0.02 (0.00 to 0.03), 0.037
Retinol, μmol/L			
Surgery	1.28 [1.01, 1.48]	1.26 [1.05, 1.49]	0.05 (−0.01 to 0.10), 0.102
2-day post-op review	1.07 [0.86, 1.30]	1.08 [0.92, 1.32]	0.05 (−0.01 to 0.11), 0.080
7-day post-op review	1.20 [0.99, 1.38]	1.25 [1.01, 1.49]	0.06 (−0.00 to 0.13), 0.061
Lutein, μmol/L			
Surgery	0.19 [0.15, 0.26]	0.20 [0.14, 0.26]	−0.02 (−0.03 to 0.00), 0.061
2-day post-op review	0.18 [0.14, 0.24]	0.19 [0.13, 0.24]	−0.01 (−0.03 to 0.00), 0.130
7-day post-op review	0.18 [0.14, 0.24]	0.19 [0.14, 0.24]	−0.01 (−0.02 to 0.01), 0.374
Lycopene, μmol/L			
Surgery	0.80 [0.54, 1.17]	0.74 [0.52, 1.01]	0.02 (−0.07 to 0.11), 0.670
2-day post-op review	0.78 [0.56, 1.13]	0.72 [0.49, 0.97]	0.00 (−0.10 to 0.10), 0.980
7-day post-op review	0.73 [0.50, 1.13]	0.65 [0.49, 1.04]	−0.03 (−0.14 to 0.07), 0.534
Cryptoxanthin, μmol/L			
Surgery	0.11 [0.07, 0.17]	0.11 [0.07, 0.19]	0.02 (−0.01 to 0.05), 0.180
2-day post-op review	0.10 [0.06, 0.16]	0.11 [0.07, 0.19]	0.02 (−0.00 to 0.05), 0.111
7-day post-op review	0.10 [0.06, 0.15]	0.10 [0.08, 0.19]	0.03 (0.00 to 0.05), 0.020
Zeaxanthin, μmol/L			
Surgery	0.06 [0.04, 0.07]	0.05 [0.04, 0.07]	−0.00 (−0.01 to 0.01), 0.874
2-day post-op review	0.05 [0.04, 0.07]	0.05 [0.04, 0.06]	0.00 (−0.01 to 0.01), 0.955
7-day post-op review	0.05 [0.04, 0.07]	0.05 [0.04, 0.06]	0.00 (−0.00 to 0.01), 0.489
SMAC, μmol/L Teq			
Surgery	364 [317, 422]	388 [338, 451]	18.4 (4.2 to 32.6), 0.012

Day of surgery n = 82 for placebo and n = 93 for active; day 2 n = 79 for placebo and n = 92 for active; day 7 n = 78 for placebo and n = 82 for active.
Treatment effect is adjusted for baseline measurements of micronutrient levels.
SMAC – Small molecule antioxidant capacity, micromoles of Trolox equivalents/litre (μmol/L Teq).
SMAC not available for postoperative day 2 and day 7.

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ulcers [15]. Although the role of AMs in wound healing is widely recognised [16], there is a paucity of data on the potential effect of micronutrient supplementation on the healing of surgical wounds. Lower third molar surgery is a very common surgical procedure associated with significant postoperative morbidity and is also an attractive surgical model for clinical research [17–20]. Postoperative sequelae include pain, swelling, trismus (reduced mouth opening) for several days and occur as a result of the inflammatory response to the surgical trauma to bone and soft tissues as well as the microbial challenge to the intraoral wound. These sequelae lead to functional incapacity affecting QoL. This randomised, double-blind, placebo-controlled clinical trial examined whether the pre- and perioperative intake of a commercially available fruit and vegetable pulp and juice powder concentrate (Juice Plus+®) was associated with improved QoL and reduced morbidity postoperatively. The results suggest that the intervention may have a modest benefit in terms of overall QoL, trismus and postoperative pain.

These results need to be cautiously interpreted in light of the limitations of this study. Firstly, the supplements evaluated in the present study are made from a wide variety of different fruit and vegetables and are enriched with carotenoids and vitamins. It is therefore unclear which specific constituents or combination of constituents would be responsible for any observed effect. However, evidence suggests that the beneficial effects of higher fruit and vegetable consumption on inflammatory diseases are attributable to the additive and synergistic interactions of the plethora of phytochemicals present in whole foods by targeting multiple signal transduction pathways [21], and these mechanisms could be underpinning the effects observed in the present study. The supplements evaluated here have been shown to contain a substantial amount of different (poly)phenolic compounds, demonstrating that the capsules preserve these compounds as they occur in the large variety of source plants used in their manufacture [22]. Alternatively, the observed effect may be attributable to a few or a single specific constituent. Serum concentrations of α-tocopherol, β-carotene and vitamin C increased significantly over 10 weeks of supplement intake in the active group, and marked differences between groups in the plasma concentrations of these micronutrients were evident at the time of surgery, resulting in higher estimated small molecule antioxidant capacity in serum (Table 4). However, whether or not the observed effects are a result of increased antioxidant capacity is uncertain, and future research would ideally assess markers of oxidative stress in the local wound environment. Vitamin C plays a crucial role in various wound healing processes [16,23], and emerging evidence suggests that vitamin C, possibly in concert with vitamin E, may have antinociceptive effects, as demonstrated in different pain models [24–27]. Recent clinical studies suggest that administration of vitamin C can alleviate inflammatory pain, including postoperative pain [28–30]. In the present study, the strongest effects were observed for the secondary pain endpoints, with patients in the verum group being almost half as likely to experience moderate to severe pain 2 days after surgery than patients in the placebo group, and reduced pain levels could directly or indirectly explain the effects on other endpoints.

Secondly, the observed p-values for the primary endpoint, as well as several secondary endpoints hover around the 5% significance level, depending on if and what baseline and surgical characteristics are included in the statistical models. In the absence of anchor-based estimates of a minimally important difference in QoL following third molar surgery, the sample size was set to achieve 90% power to detect a standardised effect size of 0.5 [12]. However, research on other patient reported outcomes suggests that standardised effect sizes of 0.2–0.3 would represent small but important, i.e., clinically significant differences [31]. The effect sizes observed in this trial for QoL (including the eating, sickness and pain subscales) and the secondary endpoints of pain and trismus were in that range or slightly larger. However, our study lacked power to detect differences smaller than 0.5 and the possibility that the observed differences are due to chance must be acknowledged.

Loss to follow-up before surgery was relatively high at 19%, but was unlikely to be related to the intervention and cannot have been related to the study outcomes as these patients did not receive surgery. Current smoking was the only baseline characteristic that was significantly associated with patients not attending for surgery, possibly a marker of lower compliance, which has also been reported in the context of observational research [32–34]. Our secondary analyses adjusted for surgical factors deemed important for surgical morbidity, including markers of surgical complexity/severity of trauma (bone removal, tooth sectioning, duration of surgery) and pre-operative chlorhexidine rinse [35]. While these are variables collected after randomisation, the difficulty of surgery/surgical trauma or decision to use pre-operative chlorhexidine rinse cannot have reasonably been affected by group assignment in this double-blind trial, and these statistical adjustments allow appreciation of the effect of chance differences between groups. As can be expected for a moderately sized trial, some imbalances were observed at baseline, including a moderately higher vitamin C concentration in the active group. In a post-hoc sensitivity analysis, adjustment for baseline vitamin C concentrations yielded similar estimates (results not shown).

Finally, patients in the present study received supplements for a relatively long period of 10 weeks preoperatively. Nutritional supplement formulations such as the one evaluated in this study are usually taken long-term, and in the absence of short-term pharmacokinetic data we were confident that steady state would be achieved by 10 weeks [36]. However, such preoperative supplementation for 10 weeks would be difficult or impossible to implement in many clinical scenarios, and short-term supplementation should therefore be evaluated in future studies. Notwithstanding these uncertainties and limitations, our results should encourage further research into the possible effects of nutritional supplements and their constituents on postsurgical pain, morbidity and wound healing. In conclusion, perioperative supplementation with a commercially available fruit and vegetable pulp and juice powder concentrate (Juice Plus+®) may reduce postoperative morbidity and improve QoL during recovery after lower third molar surgery.

Conflict of interest statement and funding

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Statement of authorship

TD and ILC designed research. TD, DS, DP, WS and RL conducted research. PG, DB, KH and TD analysed data and performed statistical analyses. PG, DB and TD wrote the paper. TD had primary responsibility for final content.

All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.08.004.

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