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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.

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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 homeostatic 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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