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Randomized controlled trial of vagal modulation by sham feeding in elective non-gastrointestinal (orthopaedic) surgery

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Abstract

Background: Enhanced recovery, in part, aims to reduce postoperative gastrointestinal dysfunction (PGID). Acquired – or established – vagal dysfunction may contribute to PGID, even for surgery not involving the gastrointestinal tract. However, direct evidence for this is lacking. We hypothesized that chewing gum reduces morbidity (including PGID) by preserving efferent vagal neural activity postoperatively after elective orthopaedic surgery.

Methods: In a two-centre randomized controlled trial ($n=106$), we explored whether patients randomized to prescribed chewing gum for five days postoperatively sustained less morbidity (primary outcome, defined by the Postoperative Morbidity Survey), PGID and faster time to become morbidity free (secondary outcomes). In a subset of patients ($n=38$), cardiac parasympathetic activity was measured by serial Holter monitoring and assessed using time and frequency domain analyses.

Results: Between September 2011 and April 2014, 106 patients were randomized to chewing gum or control. The primary clinical outcome did not differ between groups, with similar morbidity occurring between patients randomized to control (26/30) and chewing gum (21/28; absolute risk reduction (ARR): 13% (95% CI: –6–32); $P=0.26$). However, chewing gum reduced PGID (ARR: 20% (95% CI: 1–38); $P=0.049$). Chewing gum reduced time to become morbidity-free (relative risk (RR): 1.62 (95% CI: 1.02–2.58); $P=0.04$) and was associated with a higher proportion of parasympathetic activity contributing to heart rate variability (11% (95% CI: 1–20); $P=0.03$).

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Conclusions: Chewing gum did not alter overall morbidity, but reduced PGID. These data show for the first time that prescription of sham feeding preserves vagal activity in surgery not directly involving the gastrointestinal tract.

Clinical trial registration: ISRCTN20301599.

Key words: gastrointestinal motility; general surgery; parasympathetic nervous system; postoperative complications; vagus nerve

Editor's key points

- Impaired vagal neural activity may produce postoperative gastrointestinal dysfunction, and chewing gum, which would preserve efferent vagal neural activity, may reduce postoperative morbidity.
- Although chewing gum for 5 days postoperatively did not affect the incidence of postoperative morbidity, it reduced the incidence of postoperative gastrointestinal dysfunction and time to become morbidity-free.
- Postoperative chewing gum may be useful for enhanced recovery.

The mechanisms underlying the potential benefit of specific components of enhanced recovery remain unclear.¹ Enhanced recovery programs, in part, have focused on preventing/reducing postoperative gastrointestinal dysfunction (PGID), particularly after colorectal surgery.^{2–3} However, PGID is common after surgery not directly involving the gastrointestinal tract,^{4–5} and implicated in fuelling distant organ dysfunction.^{6–7} Furthermore, sham feeding appears to be beneficial even at colorectal anatomical sites where vagal innervation is absent.⁸

A ubiquitous feature of major surgery is the relative loss of parasympathetic neural activity.⁹ Reduced vagal tone may impair neural cardioprotective mechanisms,¹⁰ augment systemic inflammation^{11–12} and retard restoration of normal gastrointestinal function.¹³ The parasympathetic motor supply to the gastrointestinal tract originates from brainstem neurons located in the dorsal motor vagal nucleus and nucleus ambiguus.¹⁴ Circulating inflammatory mediators (e.g. TNF α) inhibit vagal motoneuron activity.¹⁵ Commonly administered perioperative drugs including propofol,¹⁶ inhalation and neuromuscular blocking agents¹⁷ also inhibit parasympathetic activity at the level of the central nervous system. Morphine blocks central vagal neuronal activity, suppressing insulin- and meal-induced release of gastrointestinal hormones, critical for normal feeding.^{18–20} PGID may therefore be caused by vagal dysfunction, even in surgeries where the bowel is not handled or traumatized. If parasympathetic dysfunction leading to PGID is common in operations not involving the bowel, clinical interventions such as sham feeding (chewing gum) that reduce postoperative ileus^{21–29} may also be applicable to non-gastrointestinal surgery where vagal activity is reduced perioperatively.

We therefore hypothesized that sham feeding through chewing gum reduces morbidity (including PGID) by preserving efferent vagal neural activity postoperatively, in a randomized controlled trial of patients undergoing elective (non-gastrointestinal) orthopaedic surgery.

Methods

A dual-centre, randomized, single-blinded controlled trial (POM-X: postoperative Morbidity-X) was conducted in two hospitals

(University College Hospital, London; Robert Jones and Agnes Hunt Orthopaedic Hospital Oswestry) in the UK. The trial was approved by the NRES Committee London (Camden & Islington; MREC: 11/H0722/3) and registered with Controlled Trials (ISRCTN20301599). The Medicines and Healthcare Products Regulatory Agency designated this as a non-medicinal trial. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed. Written informed consent was obtained from all patients before surgery. The trial protocol has been available online at www.ucl.ac.uk/anaesthesia/trials. Adult patients undergoing elective joint replacement surgery were eligible for recruitment provided they satisfied the following criteria: a. ASA grade II–IV; age >50 yr; undergoing general anaesthetic or sedation with/without neuraxial/ peripheral nerve block. Exclusion criteria included refusal of consent, established nasogastric/gastrostomy feeding, or unsafe swallow. For patients declining, or with contraindications for neuraxial blockade, local anaesthetic infiltration was performed by the surgical team. Scheduled i.v. (or oral) acetaminophen and morphine (either i.v. patient controlled analgesia or oral, as required) analgesia was prescribed for all patients postoperatively. At Robert Jones and Agnes Hospital, the postoperative analgesic regimen did not routinely use morphine, as all patients were prescribed oxycodone twice per day and oxycodone as required for up to 72 h or patient-controlled analgesia (morphine), plus pregabalin up to 72 h postoperatively. All postoperative management decisions were taken by senior clinicians who retained the discretion to alter any aspect of patient care. Preceding audit showed that both hospitals had similar median lengths of stay. Postoperative management was conducted according to local clinical guidelines. Surgical antibiotic use at the time of the operation at all centres was undertaken according to local microbiology policies, on a prophylactic basis (i.e. preoperative and two subsequent doses). Thus, antibiotic use 48 h postoperatively was seen as a deviation from normal postoperative care.

Randomization and procedures to minimize bias

A randomization list was produced using a computer program (NCSS/PASS, Kaysville, UT, USA) and then concealed using envelopes. Participants were centrally allocated to treatment groups. To minimize the possibility of bias, investigators did not reveal study group allocation to attending surgical and/or physician teams. Patients were randomized to chew a single stick of sugar-free chewing gum four times per day for 30 min, for five days postoperatively [or until discharge]. Chewing gum was prescribed on each patient's drug chart, and was continued when patients resumed oral food intake. Although we had originally planned patients to commence chewing gum preoperatively, this was impractical for logistic and local practice reasons (and hence never undertaken). Patients randomized to chew gum first did so in the post-anaesthetic care unit, as soon as they were able to chew. Surgical and nursing personnel were not informed directly of the arm into which each patient had been randomized. Compliance was

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