British Journal of Anaesthesia **110** (3): 432–7 (2013)
Advance Access publication 6 December 2012 · doi:10.1093/bja/aes387

BJA

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Oral *vs* intravenous paracetamol for lower third molar extractions under general anaesthesia: is oral administration inferior?

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Editor's key points

- Paracetamol can be a useful component of perioperative analgesia.
- It is unclear how i.v. compares with oral paracetamol in terms of efficacy.
- Pain levels 1 h after surgery were used to study equivalence of oral and i.v. paracetamol.
- No clinical benefit of i.v. compared with oral paracetamol was found with correct timing of administration.

Background. Paracetamol formulations provide effective analgesia after surgery [Duggan ST, Scott LJ. Intravenous paracetamol (acetominophen). *Drugs* 2009; **69**: 101–13; Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008: CD004602]. I.V. paracetamol is superior to oral for pain rescue (Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. *Clin Drug Invest* 1997; **14**: 474–81). By randomized, double-blinded trial, we aimed to determine whether preoperative oral paracetamol provides inferior postoperative analgesia to preoperative i.v. paracetamol.

Methods. One hundred and thirty participants received either oral paracetamol and i.v. placebo (Group OP), or oral placebo and i.v. paracetamol (Perfalgan™) (Group IP). Oral preparations were given at least 45 min before surgery; i.v. preparations after induction of anaesthesia. Pain was assessed by a 100 mm visual analogue scale (VAS) 1 h from the end of surgery. Rescue analgesia was given on request.

Results. A total of 128 patients completed the study. There were no significant differences in baseline characteristics or intraoperative variables between the groups. The study was designed to reveal whether OP is inferior to IP, with an inferiority margin of 20%. The number of patients reporting satisfactory analgesia at 1 h with VAS $\leq$30 mm were 15 (OP) and 17 (IP), respectively. The secondary outcome measure of the mean (standard deviation) VAS (mm) for the whole of each group was 52 (22) for OP and 47 (22) for IP. Analysis of confidence intervals indicates that oral paracetamol is not inferior to i.v. paracetamol. The median survival (90% CI) to rescue analgesia request was 54.3 (51.2–57.4) min in Group OP and 57.3 (55.4–59.2) min in Group IP; there was no significant difference in this measure.

Conclusions. In this study of lower third molar extraction, oral paracetamol is not inferior to i.v. for postoperative analgesia.

ISRCTN Registration. http://www.controlled-trials.com/ISRCTN77607163.

Keywords: acetaminophen; analgesia; analgesics, non-narcotic; molar, third

Accepted for publication: 31 August 2012

Paracetamol is an effective, safe analgesic for the management of mild to moderate pain. It is of proven benefit for the management of pain after extraction of third molar teeth[1] and other surgical procedures,[2] and available in oral, rectal, and i.v. formulation. Since 2003, a stable i.v. solution of paracetamol supplanted propacetamol, easing complexity of administration with no loss of effectiveness.[3] I.V. administration has been described as the route of choice for rapid analgesia after surgery,[4] with evidence it can replace or reduce consumption of other analgesic preparations.[5 6] I.V.

administration achieves a rapid, reliable serum paracetamol level within the therapeutic antipyretic range,[7 8] although analgesic effect may not directly equate to antipyretic effect.[9] Oral paracetamol also has a good clinical pedigree. Its effect depends on absorption which itself depends on the circumstances of administration.[10] Although overall bioavailability is quoted as 69–84% of administered dose, the area under the absorption/time curve in healthy subjects is equivalent to i.v. paracetamol.[11] Whether rapid attainment of peak plasma concentration *per se* confers a lasting analgesic advantage to i.v. paracetamol is unknown; administering oral paracetamol earlier allows a logical comparison.

I.V. paracetamol has enjoyed a sharp increase in popularity, particularly in the perioperative setting. We felt it useful to investigate with a consistent pain model whether oral paracetamol is inferior in clinical effect to i.v. paracetamol and enable clinicians to make informed prescribing decisions.

Methods

The study was carried out at Queen Victoria Hospital NHS Foundation Trust in East Grinstead, West Sussex, UK. Approval was gained from the local Research and Development Committee, The Brighton West Research Ethics Committee, and the trial registered (EudraCT ref:2008-000427-26).

Patients undergoing third molar tooth extraction gave written informed consent and were then randomized to one of the two groups. One group received active paracetamol as the oral formulation and the other group received active paracetamol as the i.v. formulation. Both groups received appropriate placebo preparations. Assessors were blinded as to treatment allocation and postoperative visual analogue scores (VAS) were recorded in patients undergoing third molar extractions.

Inclusion and exclusion criteria

Patients aged 18–65 booked to undergo at least one lower third molar extraction under general anaesthesia as a day case were screened by the consultant maxillofacial surgeon at the Maxillofacial outpatient clinic 2 weeks before surgery. Patients were not recruited to the trial if they were unwilling to give consent, had taken analgesic medication in the preceding 24 h or caffeine in the preceding 6 h, could not swallow tablets, had allergy to any of the trial medications, previous liver or renal dysfunction, were pregnant or breast feeding, or had a history of drug or alcohol abuse. Baseline data were collected from each patient including, their age, sex, BMI, ASA status, and pain score before surgery.

Sample size calculation

The non-inferiority sample size calculation was based on self-reported 100 mm VAS for pain measurement. Studies on similar patient groups using the same pain model report a standard deviation of ± 20 mm.[12] A tolerable difference of 20% reporting satisfactory pain relief was then set as demonstrable of equivalence. These criteria were used to compute an equivalence sample size calculation. This indicated 61 patients per arm would be required with $\alpha=0.05$ and a power of 80% to identify if oral paracetamol is equivalent or inferior to i.v. paracetamol in providing satisfactory pain relief at 1 h after surgery on self-reported pain VAS with an inferiority margin of 20%.

Recruiting and consent

Patients attending the Maxillofacial outpatient clinic 2–3 weeks before surgery were first approached by the consultant surgeon. A participant information leaflet was given to the patient and the trial explained to them. The patient was then interviewed on the morning of surgery by a member of the research team whose task was to explain the trial, review the participant information sheet, ensure suitability and willingness to enter the trial, and take informed written consent. Individual data sheets were created for each patient and completed by relevant responsible staff according to the study protocol. After consent, patients were allocated drug packs on a sequential basis, the contents having been randomized by the supplier. Each pack carried a unique reference number used in all future identification of the patient and their study record. All adverse incidents were recorded and where necessary dealt with through local incident reporting. There was no incident requiring the study code to be broken. On completion of the list for the day, all result sheets were collected and data entered by a member of the research team into a dedicated password-protected database. Paper copies were filed in a locked cabinet.

Outcome data collected

The primary outcome measure was the VAS score at 1 h after surgery. Further outcome measures included: the number and type of tooth extracted (always included at least one lower third molar); length and difficulty of surgery; time to request for rescue analgesia if applicable; VAS at the time of rescue analgesia (carried forward as last pain observation); adverse incidents and patient perception of which preparation they had received.

Randomization and blinding

Study packs were prepared by Nova Laboratories Ltd (Martin House, Gloucester Crescent, Wigston, Leicester, UK, MHRA Site Number 4097). They manufactured and packaged all placebo preparations in house. Pack contents were randomized to OP or IP in 12 blocks using a web-based randomization service (www.randomization.com); all packs were identical in appearance. A qualified pharmacist at Nova Laboratories approved coding concealment, database randomization, and pack contents. At QVH, study packs with the unique randomization code number were dispensed by the study pharmacist to each named consented patient. All oral preparations, active and placebo, were encapsulated identically, prescribed by the research team and administered by nursing staff according to the prescription and pack code label. I.V. preparations, due to stability concerns,