

PAIN

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

S. Fenlon<sup>1\*</sup>, J. Collyer<sup>2</sup>, J. Giles<sup>1</sup>, H. Bidd<sup>1</sup>, M. Lees<sup>3</sup>, J. Nicholson<sup>3</sup>, R. Dulai<sup>4</sup>, M Hankins<sup>5</sup> and N. Edelman<sup>6</sup>

<sup>1</sup> Department of Anaesthesia and <sup>2</sup> Department of Maxillofacial Surgery, Queen Victoria Hospital, East Grinstead, West Sussex RH19 3DZ, UK

<sup>3</sup> Department of Anaesthesia, Eastbourne District General Hospital, King's Drive, Eastbourne, East Sussex BN21 2UD, UK

<sup>4</sup> Department of Anaesthesia, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3NG, UK

<sup>5</sup> Centre for Innovation and Leadership in Health Sciences, Faculty of Health Sciences, University of Southampton, Southampton SO17 1BJ, UK

<sup>6</sup> Centre for Health Research, Room 262, Mayfield House, University of Brighton, Falmer, Brighton BN1 9PH, UK

\* Corresponding author. E-mail: stephen.fenlon@qvh.nhs.uk

### 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 (acetaminophen). *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<sup>1</sup> and other surgical procedures,<sup>2</sup> 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.<sup>3</sup> I.V. administration has been described as the route of choice for rapid analgesia after surgery,<sup>4</sup> with evidence it can replace or reduce consumption of other analgesic preparations.<sup>5 6</sup> I.V.

administration achieves a rapid, reliable serum paracetamol level within the therapeutic antipyretic range,<sup>7,8</sup> although analgesic effect may not directly equate to antipyretic effect.<sup>9</sup> Oral paracetamol also has a good clinical pedigree. Its effect depends on absorption which itself depends on the circumstances of administration.<sup>10</sup> 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.<sup>11</sup> 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  $\pm 20$  mm.<sup>12</sup> 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](http://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,

were packed in their original containers. To maintain concealment, these preparations, placebo or paracetamol, were revealed in a separate, locked area by an anaesthetist not involved in the study, run into identical burettes, and the containers discarded. Each burette was labelled with the pack code and patient identifier and passed to the anaesthetist responsible for that patient. Each participant received either oral paracetamol and i.v. placebo (100 ml 0.9% saline) or oral placebo and i.v. paracetamol according to pack contents. The patient and team caring for them were blinded to allocation. Before going home, patients were asked whether they knew which preparation they had received.

### Treatment protocol

All the participants of the trial received a standardized treatment protocol. They received **1 g oral paracetamol** or oral placebo **at least 45 min before surgery**. Anaesthesia was induced with fentanyl  $3 \mu\text{g kg}^{-1}$  and propofol  $2\text{--}3 \text{ mg kg}^{-1}$ . All patients had a flexible laryngeal mask airway and

anaesthesia maintained by spontaneous ventilation of 1–2% isoflurane and nitrous oxide 60% in oxygen. The i.v. solution (1 g paracetamol or placebo, 0.9% saline) was administered to the patient immediately after induction of anaesthesia. The surgeon infiltrated a solution of 1:100 000 epinephrine to minimize bleeding. All surgery was carried out by the same consultant surgeon (J.C.), who recorded the difficulty of each extraction with a three-point grading scale. After arrival in the recovery area, patients were asked by the recovery nurse to complete a VAS score of their pain at 1 h after surgery. Adverse events were recorded. If at any time patients judged their pain to be inadequately controlled, they were asked to complete a VAS score at that time and rescue analgesia (i.v. diclofenac 50 mg) was given.

### Results

Participants were enrolled and analysed as shown in Figure 1. One hundred and thirty-nine patients were identified at initial consultation by the surgeon and informed about the study, verbally and in writing. On the day of surgery, four

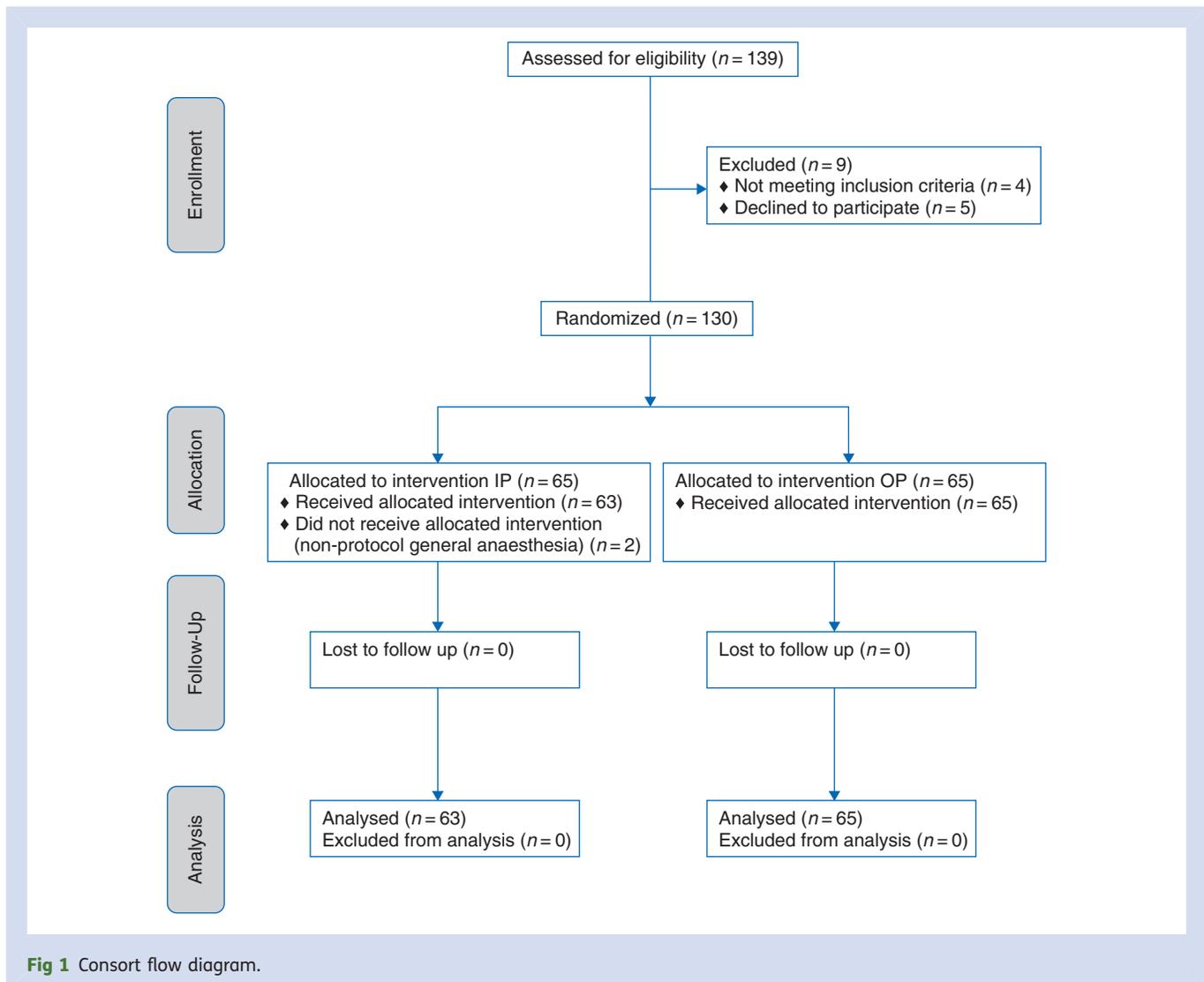


Fig 1 Consort flow diagram.

decided not to take part in the study, and five patients were found to have failed the inclusion criteria; hence, 130 were allocated. Both allocated groups were compared on a number of baseline and intraoperative variables to ensure adequate randomization; the comparisons are shown in Table 1. The primary outcome measure was the proportion in each group IP or OP reporting satisfactory pain relief, defined as VAS scores of  $\leq 30$  mm at the 1 h postoperative time. The secondary outcome measure compared the means of all 1 h postoperative VAS scores across both groups. The primary and secondary outcome analysis is shown in Table 2. For both measures, 90% confidence intervals of the difference between Groups IP and OP lie within the pre-defined 20% tolerable clinical difference in pain relief. By these criteria, both measures show non-inferiority of oral paracetamol compared with i.v. paracetamol for the method and measures chosen. Adverse events amounted

to only two patients, one experiencing dizziness after surgery resolving after 1 h, the other sustaining a burn to the lip from the surgical drill. The latter was dealt with through the Trust's incident-reporting process. All patients went home the same day with no delay to discharge.

Request for and timing of rescue analgesia is often used as a measure of analgesic efficacy and was compared between both groups. Within the first hour after surgery, nine patients in Group IP and 18 patients in Group OP received rescue analgesia of 50 mg diclofenac i.v., effective in all cases. The Kaplan–Meier survival analysis (Fig. 2) revealed no significant difference between study arms in the requirement for rescue analgesia (log-rank test  $P=0.066$ ). The median time to rescue when required was 54.3 min (95% CI: 51.2, 57.4) for OP and 57.2 min (95% CI: 55.4, 59.2) for IP.

**Table 1** Patient characteristics

Variable	Oral (n=65)	I.V. (n=63)
Age (range) (yr)	18.1–57.7	18.7–54.4
Mean BMI (SD)	24.4 (4.3)	24.5 (5.0)
Gender (n)		
Male	14	20
Female	51	43
ASA (n)		
I	57	57
II	8	6
Mean preop VAS (SD)	0.35 (0.99)	0.22 (0.71)
Mean length of surgery (min) (SD)	17.8 (8.9)	18.1 (11.5)
Surgical difficulty (n)		
1	24	24
2	26	16
3	15	23
Extraction codes (n)		
1 lower wisdom+others	8	15
2 lower wisdom+others	28	23
1 lower wisdom	9	10
2 lower wisdom	20	15
Patient aware of route of administration	8	8
Correct perception of route of administration	5	0

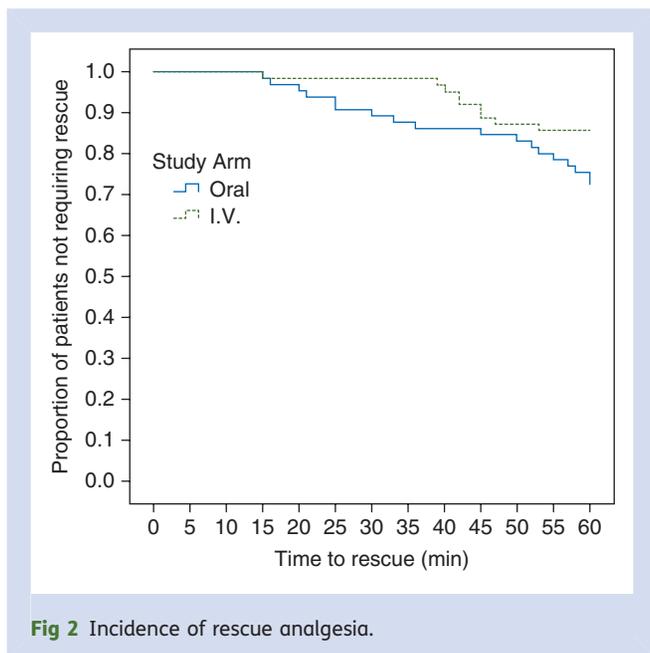
## Discussion

The analysis of results across groups by primary outcome measure of VAS  $\leq 30$  mm, mean VAS score, and time to rescue does not show clinically or statistically significant inferiority of oral paracetamol compared with i.v. paracetamol for the relief of pain after third molar extraction. From this, we conclude that in such clinical practice, **both routes** are **equivalent**.

Previous study shows that i.v. paracetamol or its equivalent pro-drug propacetamol are useful for the treatment of **mild to moderate** pain after many surgical procedures, and compare favourably with other analgesia such as morphine.<sup>5</sup> Studies also support the use of oral paracetamol in many equivalent situations, again with low side-effects and good response compared with other analgesic drugs.<sup>1</sup> With some evidence of **higher** and **more reliable** serum levels attained by **i.v.** paracetamol, it is a reasonable deduction that i.v. paracetamol will provide **better** analgesic effect. However, oral paracetamol, in healthy fasted individuals with **normal** gastric **emptying**, having elective day-case surgery **should** also achieve **adequate** serum levels for analgesia and this study would appear to support this. I.V. paracetamol is widely used by anaesthetists in the UK and elsewhere,<sup>13</sup> we propose that for some operations, with some planning, oral premedication could be used to equivalent effect. This conclusion cannot be readily extrapolated to other groups of patients, for instance, those in whom gastric emptying is delayed.

**Table 2** Comparison of pain relief by VAS

Measure	Oral	I.V.	Difference in proportions	90% CI	Inferiority margin
Proportion of study arm achieving meaningful analgesic effect at 1 h	15/65, 23.1%, 95% CI: 14, 35	17/63, 27.0%, 95% CI: 17, 40	–0.039	–0.17, 0.09	Lower bound of CI within tolerable difference of 0.2 (ns)
Mean (SD) VAS by study arm	5.2 (2.2)	4.7 (2.2)	Mean diff. 0.5	–0.11, 1.2	Lower bound of CI within tolerable difference of 0.2 (ns)



There are limitations to the study. There is **no perfect pain model**, although the **third molar extraction model** is widely **accepted**,<sup>14</sup> and used to compare analgesia for both prevention<sup>15</sup> and treatment<sup>16</sup> of postoperative pain. The use of a VAS grades the patient's perception of their pain and is subject to inter-rater variability, in the region of  $\pm 20$  on a 0–100 scale.<sup>12</sup> Determining a clinically significant difference in pain score depends on the level of pain measured, the variability, the expected treatment effect size, and a view on the clinical difference likely to be significant to that patient population studied. Taking these facts in mind, and drawing from previous work,<sup>17</sup> we chose to accept 20% as a measurable, significant, between-group 'tolerable difference'.

Grouping postoperative VAS scores can improve their validity,<sup>18</sup> our chosen primary outcome measure grouped patients into those considered to have no pain or satisfactory pain control by VAS of 0–30 mm. Only one-fifth of the patients fell into this group, indicating that most patients had significant pain and neither form of paracetamol provided adequate analgesia in this setting. Conversely, four-fifths of the patients did not request or seemingly require rescue analgesia. By this variable, the majority of the patients may have indicated higher pain scores but felt they did not require further treatment. While a higher upper limit of VAS for satisfactory analgesia could have been chosen at the end of the study, it was felt better to hold to the original proposal of VAS 0–30 mm and not subject data to multiple *post hoc* analyses.

Recruitment of patients and completion by study protocol was good with few refusing consent or failing to meet recruitment criteria and only two patients removed after consent due to violations of the anaesthetic protocol. Comparing both groups' baseline variables reveals no significant differences, but there is a tendency for the more difficult dental extractions to appear in Group IP. The study may

have some bias on this point, although the difference does not reach statistical significance, and can only be attributed to chance.

Opportunities exist for further scrutiny of paracetamol and its place in postoperative pain. There is a multitude of surgical procedures to study, together with changes in the dose and formulation of paracetamol given. The benefits of **pre-operative oral loading** doses of **2 g** paracetamol, **as shown** with **i.v.** paracetamol,<sup>19</sup> remain to be **explored** and seem an intuitive step to take.<sup>20</sup> Support for this approach comes from the study of selected groups in which **supra-therapeutic** doses of **oral** paracetamol appear **safe**,<sup>21</sup> although against this is set **on-going concern** around **safety** of even **standard** doses when applied to a very **large population** base.<sup>22</sup>

Ultimately, does this study provide new information and will that benefit patients and assist the practicing clinician? We believe that with facilities to give oral medication some time before surgery, the perceived benefits of i.v. paracetamol over oral are less than may be imagined and unlikely to significantly alter the patient's perception of pain after surgery. With this information, clinicians may choose to avoid the additional costs and risks attached to the i.v. preparation.

## Acknowledgements

Beyond the authors, many gave their time to assist in the project. We would also like to thank Mr James Rust of Nova Laboratories for his helpful advice and support throughout the study and the involved members of the NIHR Research Design Service—South East for their support with methodology and funding application.

## Declaration of interest

None declared.

## Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0408-16304). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Handling editor: L. Colvin