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Validating speed of onset as a key component of good analgesic response in acute pain

R.A. Moore[1], S. Derry[1], S. Straube[2], J. Ireson-Paine[3], P.J. Wiffen[1]

1 Pain Research and Nuffield Division of Anaesthetics, Nuffield Department of Neurosciences, University of Oxford, UK
2 Institute of Occupational, Social and Environmental Medicine, University Medical Center Göttingen, Germany
3 Spreadsheet Factory, Oxford, UK

Correspondence
R. Andrew Moore
E-mail: andrew.moore@ndcn.ox.ac.uk

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Conflicts of interest
R.A.M. is the owner of Oxford Medical Knowledge (OMK), which received an unrestricted educational grant for the analysis. J.I.-P. acted as a paid consultant to OMK for this project. S.S. has previously received a lecture fee from and acted as a paid consultant to OMK, both unrelated to this project. S.D. and P.J.W. report no conflicts.

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Abstract

Background: Previous analysis of a single data set in acute pain following third molar extraction demonstrated a strong relationship between the speed of reduction of pain intensity and overall pain relief, as well as need for additional analgesia.
Methods: Individual patient data analysis of a single randomized, double-blind trial of placebo, paracetamol 1000 mg, ibuprofen sodium 400 mg and ibuprofen-poloxamer 400 mg following third molar extraction. Visual analogue scale pain intensity (VASPI) and other measurements were made at baseline, every 5–45 min, and at 60, 90, 120, 180, 240, 300 and 360 min.
Results: Most patients produced consistent VASPI results over time. For placebo and paracetamol, few patients achieved low VASPI scores and maintained them. For both ibuprofen formulations, VASPI scores fell rapidly during the first hour and were then typically maintained until later re-medication. Analysis of all patients showed that rapid VASPI reduction in the first hour was strongly correlated with good overall pain relief (high total pain relief over 0–6 h), and with lesser need for additional analgesia within 6 h. Results for this analysis were in very good agreement with a previous analysis, validating the relationship between fast initial pain intensity reduction and overall good pain relief in this setting.
Conclusions: In acute pain following third molar extraction, faster acting analgesic formulations provide earlier onset of pain relief, better overall pain relief and a less frequent need for additional analgesia, indicating longer lasting pain relief.

1. Introduction

Arguably, the most appropriate and patient-centred outcome for patients who have moderate or severe pain deriving from any painful condition, acute or chronic, is that of 'no worse than mild pain' (Moore et al., 2013). Rapid absorption and speed of onset in acute pain may represent one way of achieving this goal. With ibuprofen, plasma concentration and pain intensity are inversely correlated after 1 h (Laska et al., 1986). Fast-acting oral analgesic formulations typically involve rapidly dissolving salts such as ibuprofen sodium, lysine or arginine, or additional agents such as surfactants (polymeric surface active agent poloxamer 407 in this case) to increase tablet dissolution. Systemic administration of non-steroidal anti-inflammatory drugs is not necessarily better than the oral route (Tramèr et al., 1998).

Fast-acting oral formulations generally have lower (better) numbers needed to treat (NNTs) than standard formulations (Moore et al., 2011). Analysis of a single data set demonstrated a strong relationship between the speed of reduction of pain intensity and overall pain relief, and that early pain intensity reduction was asso-

What's already known about this topic?
- A single data set in acute pain has shown that rapid reduction of pain intensity in the first hour is associated with better overall pain relief and longer lasting analgesia with reduced need for re-medication.

What does this study add?
- Validation that rapid reduction in pain intensity is associated with good overall and longer lasting pain relief.

ciated with longer term outcomes of good overall pain relief and less need for additional analgesic (Moore et al., 2014). As has been pointed out, these results were derived from only one data set and should be validated by data from other trials in acute pain, and ideally in other pain conditions (Peloso, 2014).

Individual patient data analysis of a different clinical trial in third molar extraction comparing ibuprofen sodium, ibuprofen-poloxamer, paracetamol and placebo has therefore been used to verify the relationship between speed of onset of pain relief over the first hour with overall analgesic experience and duration of action. The published trial report demonstrated significant graded differences between placebo, paracetamol and fast-acting ibuprofen formulations. Relationships between speed of onset and overall analgesia can therefore be tested for particular interventions and for all patients together.

2. Methods

The data for the analyses were at the individual patient level, supplied as 38 PDF files of data listings for study NL0406, a published clinical trial using standard methods in third molar extraction (Daniels et al., 2009). Briefly, eligible patients were 16–40 years of age with a primary diagnosis of at least one mandibular third molar (with full bony impaction and an impaction score of ≥4 on a 5-point scale) indicated for removal, or two ipsilateral third molars with a combined total impaction score no greater than 6. After extraction, and for entry into the trial, patients had to have moderate or severe baseline pain intensity as assessed using a 4-point categorical pain intensity scale and confirmed with a visual analogue scale (VAS) score of ≥50 mm but ≤85 mm (where 0 = no pain and 100 mm = worst pain).

There were four treatment arms in this randomized and double-blind trial, which was designed to test the efficacy of two fast-acting formulations of ibuprofen against paracetamol and placebo. Sodium ibuprofen delivers maximum plasma drug concentrations at about 30–40 min, compared with around 90–120 min for standard ibuprofen acid formulations (Moore et al., 2014). The second investigational ibuprofen formulation contained ibuprofen acid plus the surfactant poloxamer 407 from the poloxamer family of polymeric non-ionic surface-active agents to increase the rate of dissolution of the tablet and enable more rapid absorption relative to standard ibuprofen formulations. There is inadequate evidence that ibuprofen-poloxamer delivers very much faster peak plasma concentrations than standard ibuprofen acid (Moore et al., 2014). The four treatment arms included 80–82 patients receiving:
- placebo: two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen-poloxamer tablets plus two matched placebo for 500 mg paracetamol caplets;
- paracetamol 1000 mg: 2 × 500 mg paracetamol (Tylenol Extra Strength) caplets plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for ibuprofen-poloxamer tablets;
- ibuprofen sodium 400 mg: 2 × 256 mg ibuprofen sodium dihydrate tablets (each tablet equivalent to 200 mg ibuprofen acid) plus two matched placebo for ibuprofen-poloxamer tablets plus two matched placebo for 500 mg paracetamol caplets;
- ibuprofen-poloxamer 400 mg: 2 × 200 mg ibuprofen acid tablets, each tablet incorporating 60 mg of the surfactant poloxamer 407, plus two matched placebo for sodium ibuprofen tablets plus two matched placebo for 500 mg paracetamol caplets.

Among other measurements, visual analogue scale pain intensity (VASPI) and categorical pain relief scores were measured at baseline, and every 5–45 min, and then at 60, 90, 120, 180, 240, 300 and 360 min. Information was also available on the time after dosing when any re-medication occurred. Analgesic results were calculated for each individual patient.

The slope (mm/min) of the regression line of VASPI against time over the period of 0–60 min was calculated for each patient using least-squares regression. The mean value of VASPI was computed for the periods 0–6 and 2–6 h. For the calculation of total pain relief (TOTPAR), data from a 5-point categorical pain relief scale (none = 0, slight = 1, moderate = 2, good = 3 and complete pain relief = 4) were used to calculate the sum of pain relief scores over 6 h. If a patient had complete pain relief immediately after taking an analgesic and maintained that level of pain relief for 6 h, he/she would have a 6-h maximum TOTPAR of 24 (4 × 6). For each patient, TOTPAR was converted to percentage of maximum TOTPAR (%maxTOTPAR) by division into the calculated maximum value (Cooper, 1991). Missing values between measurements were linearly interpolated. For any patient who re-medicated, pain intensity returned to its initial level and pain relief to zero for all subsequent time points (baseline observation carried forward, BOCF). The NNT with 95% confidence intervals was calculated by the method of Cook and Sackett (1995). Statistical differences between NNTs were examined using the *z*-test (Tramèr et al., 1997).

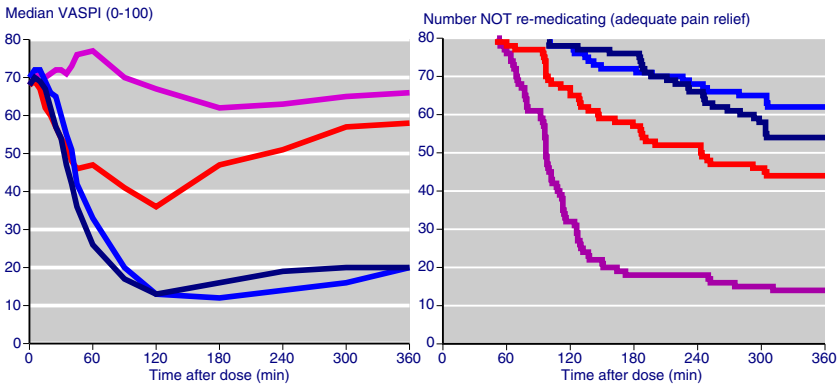

Figure 1 Evolution of median visual analogue scale pain intensity (VASPI) and patients remaining in the study without re-medicating. Placebo = purple; paracetamol 1000 mg = red; ibuprofen sodium 400 mg = light blue; ibuprofen-poloxamer 400 mg = dark blue.

Computations were performed by a commercial spreadsheet calculating and programming service (www.spreadsheet-factory.com). Analyses were performed according to treatment, comparing average results with those for individuals for changes in VASPI over time, and for patients from all four treatment groups combined to repeat the assessments of association of speed of pain intensity reduction and overall pain relief as well as need for re-medication.

3. Results

Trial data were available for all 322 patients; 62% were women and the mean age was 21 years. The mean baseline VASPI was 68/100 mm, with a range of 50–89 mm.

3.1 Analysis by treatment

Patients given the fast-acting ibuprofen formulations had more rapid and profound median reductions in pain intensity using VASPI than did those given paracetamol or placebo (Fig. 1). This was reflected in lower rates of re-medication (Fig. 1). Using categorical pain relief scores, for the outcome of ≥50%maxTOTPAR, both ibuprofen formulations were significantly better than paracetamol 1000 mg (Table 1). NNTs compared with placebo were 1.6 and 1.7 for ibuprofen 400 mg rapid formulations for achievement of ≥50%maxTOTPAR over 6 h, and 4.1 for paracetamol 1000 mg.

Table 1 Numbers needed to treat (NNTs) for the outcome of ≥50%maxTOTPAR compared with placebo calculated from individual patient data for different treatments.

		≥50%maxTOTPAR 0–6 h		
Treatment	Dose (mg)	Active	Placebo	NNT 95% CI
Paracetamol	1000	36	11	4.1 (2.7–8.2)
Ibuprofen sodium	400	69	11	1.7 (1.4–2.2)
Ibuprofen-poloxamer	400	74	11	1.6 (1.3–2.0)

Each ibuprofen formulation significantly better than paracetamol, $p < 0.001$, z-test.
CI, confidence interval.

3.2 Individual patient response by treatment

Individual patient responses to treatment are shown in Fig. 2, where BOCF imputation used initial pain intensity from the time of use of additional medication, and early re-medication is seen as a series of parallel horizontal lines in consequence. Most patients reported consistent results over time whether VASPI was high or low. For placebo and paracetamol, few patients achieved low VASPI scores and maintained them. For both ibuprofen formulations, VASPI scores fell rapidly during the first hour and were then typically maintained until later re-medication.

3.3 All patients – speed of onset and overall analgesic response

The relationship between speed of onset of pain relief and overall pain experience was investigated by seeking an association between the slope of change in pain intensity over 0–60 min and %maxTOTPAR over 0–6 h. In these analyses, all patient data were examined together, irrespective of treatment. Figure 3 shows the relationship, in individual patients, between the overall pain relief over 0–6 h measured as the percentage of maximum TOTPAR obtained, and the speed of pain intensity reduction over the first hour, measured as the slope of the regression line fitted to VASPI data, compared with the previous analysis (Moore et al., 2014). The degree of consistency in these two relationships is remarkable with equations to the regression line of:

$$\text{NL0406 (this analysis): } Y = -39X + 24 \left(r^2 = 0.52\right)$$

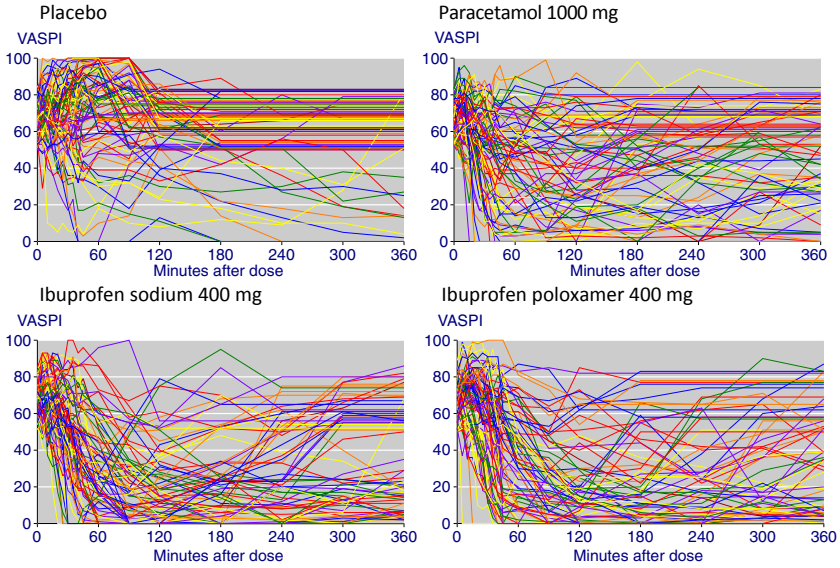

Figure 2 Evolution of individual patient visual analogue scale pain intensity (VASPI) scores over 6 h for all four treatments. Individual colours represent individual patients, with 80–82 patients in each treatment arm.

Previous analysis: $Y = -39X + 26\ (r^2 = 0.43)$

Rapid initial fall in pain intensity in individuals (higher negative values) corresponded to high overall levels of pain relief (%maxTOTPAR) over 6 h. As with the previous analysis, slopes of VASPI reductions of −0.5 mm/min or more negative (roughly equivalent to a VASPI reduction of about 30 mm or more in the first hour) over the first hour resulted in a high proportion of patients with ≥50%maxTOTPAR (Fig. 4).

3.4 All patients – speed of onset and additional analgesia

Of the 322 patients in the study, 147 required additional analgesia within 6 h. For these, the mean initial rate of pain intensity reduction was 0.22 ± 0.56 (SD) mm/min. For the 175 patients who did *not* require additional analgesia within 6 h, the mean initial rate of pain intensity reduction was 0.72 ± 0.50 mm/min. This statistically significant difference ($p < 0.001$, Student's *t*-test) was similar to that of the previous analysis (Moore et al., 2014).

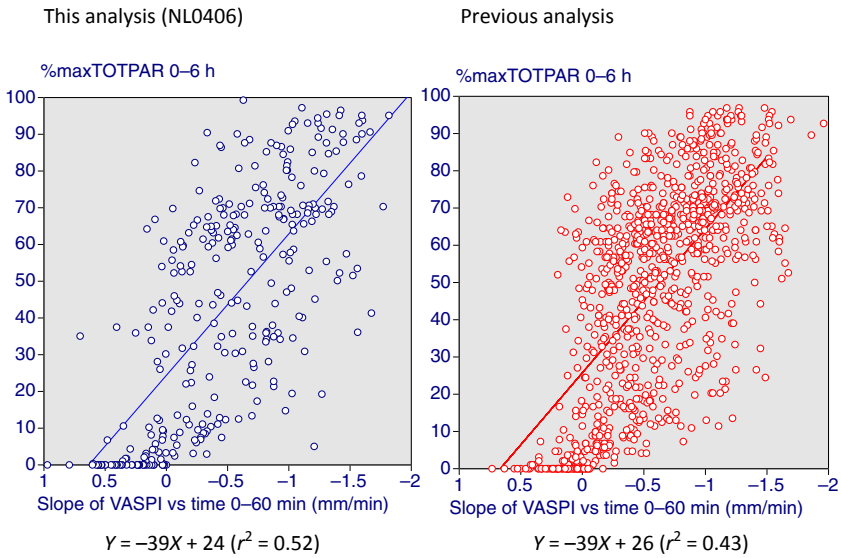

Figure 3 Relationship between speed of reduction of visual analogue scale pain intensity (VASPI) over 0–60 min and overall pain experience measured as %maxTOTPAR over 0–6 h in individual patients, for the analysis in this paper (NL0406) and a previous analysis (Moore et al., 2014).

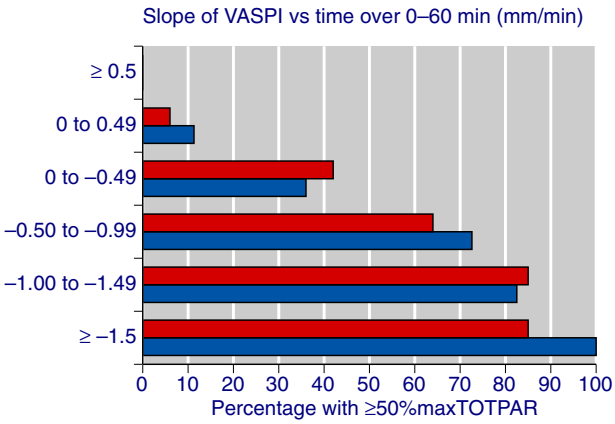

Figure 4 Relationship between speed of reduction of visual analogue scale pain intensity (VASPI) over 0–60 min and proportion of patients achieving the standard individual pain relief outcome of ≥50%maxTOTPAR over 0–6 h, for the analysis in this paper (NL0406; red) and a previous analysis (Moore et al., 2014 blue).

Faster onset of pain relief was associated with a lesser chance of requiring additional analgesia within 6 h. Where the slope was −0.5 or more negative, the chance of a patient needing additional analgesia was 3 in 10. Where the slope was more positive than this, the chance was above 6 in 10.

4. Discussion

These analyses have validated a previous finding using patient level data from acute pain trials that the rate of pain intensity reduction over the first hour after dosing is strongly related to overall pain relief over 6 h, and that fast initial pain reduction is strongly associated with better overall pain relief and lesser need for additional analgesia. The level of agreement was remarkably high, and it is probably therefore safe to conclude that, for acute pain following third molar extraction, faster acting analgesic formulations provide earlier onset of pain relief, better overall pain relief, and a lesser need for additional analgesia, indicating longer lasting pain relief. Systematic reviews confirm this (Moore et al., 2011).

The presentation of longitudinal pain intensity scores from individual patients, as performed here, is novel and supports the consistency of the results. They demonstrate that, irrespective of treatment, patients either do consistently well and have low pain intensity scores, or do badly and have high pain intensity scores. What we do not see is any of the variability predicted for responders or non-responders (Dworkin et al., 2014).

Confidence about this result for third molar extraction should not be extrapolated to all acute pain conditions. It needs replication in other acute pain settings, such as other post-surgical pain, in acute pain from other causes, and independently in conditions like tension headache or migraine. Post hoc analysis of trials in these setting requires the availability of individual patient data in trials that have recorded pain intensity and pain relief frequently in the first hour as well as overall. Alternatively, direct comparison of fast-acting and standard formulations of analgesics at the same dose might serve to demonstrate superiority of fast-acting formulation. The active participation of the pharmaceutical industry is needed to drive knowledge in this area, as well as to investigate the impact of formulation in chronic pain (Peloso, 2014).

The implication that equivalent analgesic effect can be delivered at a lower dose of drug (Moore et al., 2014) has important safety as well as efficacy implications for individuals and populations because the effect of a fast-acting formulation can be equivalent to doubling the dose (McQuay and Moore, 2007; Moore et al., 2014).

5. Conclusion

In acute pain following third molar extraction, faster acting analgesic formulations provide earlier onset of pain relief, better overall pain relief and a lesser need for additional analgesia, indicating longer lasting pain relief.

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Author contributions

R.A.M. developed the original concept for the study. All authors were involved in defining the broad aims and objectives. J.I.P. and S.S. performed the data analyses. R.A.M. wrote the original draft, and all authors contributed to the development of interim and final drafts.

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