Oral aspirin in postoperative pain: a quantitative systematic review

Jayne E. Edwards, Anna D. Oldman, Lesley A. Smith, Dawn Carroll, Philip J. Wiffen, Henry J. McQuay, R. Andrew Moore*


Received 17 July 1998; received in revised form 22 December 1998; accepted 8 January 1999

Abstract

Objectives: A systematic review of the analgesic efficacy and adverse effects of single-dose aspirin compared with placebo in postoperative pain. Design: Published studies were identified from systematic searching of bibliographic databases and reference lists of retrieved reports. Summed pain intensity and pain relief data were extracted and converted into dichotomous information to yield the number of patients with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat for one patient to achieve at least 50% pain relief. For adverse effects, relative risk and number-needed-to-harm were calculated. Sensitivity analyses were planned to test the impact of different pain models, pain measurements, sample sizes, quality of study design, and study duration on the results. Results: Seventy-two randomized single-dose trials met our inclusion criteria, with 3253 patients given aspirin, and 3297 placebo. Significant benefit of aspirin over placebo was shown for aspirin 600/650 mg, 1000 mg and 1200 mg, with numbers-needed-to-treat for at least 50% pain relief of 4.4 (4.0–4.9), 4.0 (3.2–5.4) and 2.4 (1.9–3.2) respectively. Single-dose aspirin 600/650 mg produced significantly more drowsiness and gastric irritation than placebo, with numbers-needed-to-harm of 28 (19–52) and 38 (22–174) respectively. Type of pain model, pain measurement, sample size, quality of study design, and study duration had no significant impact on the results. Conclusions: There was a clear dose–response for pain relief with aspirin, even though these were single dose studies. Adverse effects, drowsiness and gastric irritation were also evident in the single dose studies. The pain relief achieved with aspirin was very similar milligram for milligram to that seen with paracetamol. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Aspirin; Meta-analysis; Systematic review; Postoperative pain; Randomized controlled trial

1. Introduction

It is important for both prescribers and patients to have the best possible information about the efficacy and safety of analgesics. This need is reflected in patient surveys which show that postoperative pain is often poorly managed (Bruster et al., 1994). We also need to benchmark relative efficacy and safety of current analgesics so that we know how well new analgesics perform. The ideal would be to judge from direct comparisons of the various analgesics. Unfortunately there are few such trials of adequate size, and hence power, to allow credible conclusions. The alternative used here is to determine relative efficacy indirectly, using comparisons of different analgesics with placebo in similar clinical circumstances, with similar patients included, similar pain measurement and similar outcome measures, and deriving the number-needed-to-treat (Cook and Sackett, 1995) for at least 50% pain relief (McQuay and Moore, 1998). Using previously established methods for the conversion of pain outcome measures into dichotomous information (Moore et al., 1996, 1997ab), we have produced a quantitative systematic review of the analgesic efficacy of aspirin, to allow comparison with other analgesics. Meta-analyses in pain are based on a number of assumptions such as the comparability of different acute pain models, pain measurements, group sizes, the quality of study design, and study duration. Aspirin is widely used in clinical trials as a positive control, so these aspirin trials are likely to
be the largest data-set in acute pain. This gives the opportunity to test these various assumptions. The increased power of meta-analysis, increased relative to the individual component primary trials, also allowed us to test for factors that might bias interpretation of trial results (Khan et al., 1996), as well as the belief that non-steroidal anti-inflammatory drugs have a flat dose–response curve for analgesia (Brune and Lanz, 1984).

Safety is an important factor in choosing between drugs, and aspirin in multiple-dosing has a worse gastric safety record than some other non-steroidal anti-inflammatory drugs (Henry et al., 1996). The single-dose studies in postoperative pain which are widely used for assessing analgesic efficacy rarely generate sufficient safety data, and some adverse effects may only be detected in chronic use. The large set of single-dose aspirin studies allowed us to explore the idea that adverse effects, such as gastric irritation, may be evident in single-dose use, but only when the results from many trials are combined.

2. Methods

Single dose, randomized controlled trials of aspirin in postoperative pain (post dental extraction, postsurgical or postpartum pain) were sought. Different search strategies were used to identify eligible reports from MEDLINE (1966–March 1998), EMBASE (1980–Jan 1998), the Cochrane Library (Issue 1, 1998), and the Oxford Pain Relief Database (1950–1994) (Jadad et al., 1996a). A free text search was undertaken using the terms `aspirin’, `acetylsalicylic acid’, `clinical trial’, `trial’, `study’, `random*’, `double blind’, `analges*’, `pain*’, `post-operat*’, `surg*’, `dental’, `molar’, `extraction’, `operat*’, `postsurgical’. Variants of the individual terms were also used, for example `post-surgical’ and `postsurgical’. No restrictions to language were made. Additional reports were identified from the reference lists of retrieved reports. Neither pharmaceutical companies nor authors of papers were contacted for unpublished reports. Abstracts and review articles were not sought. The inclusion criteria used were: randomized allocation to treatment groups which included aspirin and placebo, full journal publication, postoperative oral administration, adult patients, baseline pain of moderate to severe intensity (which for visual analogue scales (VAS) equates to >30 mm (Collins et al., 1997)), double blind design and an established measure of postoperative pain. Acceptable pain measurements were: (i) a five-point pain relief scale with standard wording (none, slight, moderate, good, complete); or (ii) a four-point pain intensity scale (none, mild, moderate or severe); or (iii) a VAS for pain relief or pain intensity; or (iv) total pain relief (TOTPAR) or summed pain intensity difference (SPID) or their visual analogue equivalents (VASTOTPAR or VASSPID) at 4, 5, or 6 h (or sufficient data provided to allow their calculation).

We excluded reports of aspirin for the relief of other pain conditions, aspirin in combination with other drugs, trials which reported data from a cross-over design as a single data set, trials where the number of patients per treatment group was less than ten (L’Abbe et al., 1987), and trials which included pain relief data collected after additional analgesic was given. Trials using enteric-coated, sustained release or suspension formulations were excluded; tablet formulation was assumed when formulation was not stated (Table 1).

Each report which could possibly be described as a randomized controlled trial was read independently by at least three authors (JE, AO, LS) and scored using a commonly-used three item, 1–5 score, quality scale (Jadad et al., 1996b). Consensus was then achieved. The maximum score of an included study was five and the minimum score was two.

2.1. Statistical analyses

From each report we took: the numbers of patients treated, the mean TOTPAR, SPID, VASTOTPAR or VASSPID, study duration and the dose given. Information on adverse effects was also extracted. For each report, the mean TOTPAR, SPID, VASTOTPAR or VASSPID values

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study characteristics</td>
</tr>
<tr>
<td>Number of comparisons</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>300/325</td>
</tr>
<tr>
<td>500</td>
</tr>
<tr>
<td>600/650</td>
</tr>
<tr>
<td>900</td>
</tr>
<tr>
<td>1000</td>
</tr>
<tr>
<td>1200</td>
</tr>
<tr>
<td>Number of comparisons</td>
</tr>
<tr>
<td>Pain model</td>
</tr>
<tr>
<td>Dental</td>
</tr>
<tr>
<td>Episiotomy</td>
</tr>
<tr>
<td>Post surgical</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Table/capsule</td>
</tr>
<tr>
<td>Buffered</td>
</tr>
<tr>
<td>Soluble</td>
</tr>
<tr>
<td>Did not state</td>
</tr>
<tr>
<td>Duration (h)</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>Quality score</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Language</td>
</tr>
<tr>
<td>English</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
for active and placebo were converted to the percentage of the maximum possible TOTPAR or SPID, %maxTOTPAR or %maxSPID, by division by the calculated maximum value (Cooper, 1991). The proportion of patients in each treatment group who achieved at least 50% of the maximum TOTPAR was calculated using verified equations (Moore et al., 1996; Moore et al., 1997a; Moore et al., 1997b). These proportions were then converted into the number of patients achieving at least 50% of the maximum TOTPAR by multiplying by the total number of patients in the treatment group. Information on the number of patients with at least 50% of the maximum TOTPAR for active and placebo was then used to calculate relative benefit (RB) and number-needed-to-treat (NNT).

Relative benefit and relative risk (RR) estimates were calculated with 95% confidence intervals (CI) using a fixed effects model (Gardner and Altman, 1986). NNT or number-needed-to-harm (NNH) with 95% confidence intervals were calculated by the method of Cook and Sackett (1995) when the relative benefit or relative risk estimates were statistically significant. The confidence interval of the NNT indicates no benefit of one treatment over the other when the upper limit includes infinity. A statistically significant difference from control was assumed when the 95% confidence interval of the relative benefit did not include one.

Calculations were performed using Excel v. 5.0 and StatView v. 4.5 on a Power Macintosh 8500/150.

Efficacy analysis was carried out for all dose groups with sufficient sample size (a minimum of three trials). Sensitivity analyses were performed using the largest data set (aspirin 600 mg combined with aspirin 650 mg). Graphical analysis and analysis of variance were used for the sensitivity analyses.

3. Results

One hundred and seventy-five publications were identified. Of these, six could not be obtained from the British Library (Gallardo et al., 1982, 1984; Cordero, 1985; Mandujano; Or and Bozkurt, 1985; Carstens et al., 1987). Of the remaining studies 31 were not placebo controlled, 16 failed to meet our inclusion criteria for baseline pain, 16 had no extractable data, 13 used an inappropriate study design, eight were not randomized, seven used both postoperative and trauma pain, five were duplicate publications (De Vroey, 1978; Honig, 1978; Rye and Siegel, 1978; Cooper, 1980; Cooper et al., 1986), two used excluded formulations of aspirin, and two were not double-blind. The references to these excluded trials are available at http://www.jr2.ox.ac.uk/Bandolier/painres/aspac/aspac.html.

Sixty-nine publications, reporting on 72 trials, met our inclusion criteria. These trials generated a total of 88 aspirin versus placebo comparisons, providing data on 6550 patients (3253 received aspirin, and 3297 placebo). The median quality score for the trials was four. Dental surgery was the setting for 68% of the comparisons, 66% stated that they used tablets or capsules, 56% were 6-h studies and 98% were published in English. Further study characteristics are listed in Table 1, and full details of the included trials are available at http://www.jr2.ox.ac.uk/ Bandolier/painres/aspac/aspac.html.

3.1. Efficacy analysis

Insufficient data were available for analysis of aspirin 300/325 mg and 900 mg.

3.1.1. Aspirin 500 mg (256 patients)

The proportion of patients with at least 50% pain relief varied between 26% and 46% (mean 34%) for aspirin 500 mg, and 20–32% (mean 28%) for placebo. The relative benefit of aspirin 500 mg versus placebo was 1.2 (0.8–1.8), indicating no statistically significant benefit of this dose of aspirin over placebo in these trials (Table 2).

3.1.2. Aspirin 600/650 mg (5069 patients)

Fig. 1 (top panel) shows the proportion of patients with at least 50% pain relief on aspirin 600/650 mg (11–90%, mean 40%) compared with placebo (0–50%, mean 17%), relative benefit 2.0 (1.8–2.2). For a single dose of aspirin 600/650 mg compared with placebo, the number-needed-to-treat for at least 50% pain relief was 4.4 (4.0–4.9) over 4–6 h (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Aspirin dose (mg)</th>
<th>Number of comparisons</th>
<th>Patients with at least 50% pain relief with aspirin</th>
<th>Patients with at least 50% pain relief with placebo</th>
<th>Relative benefit (98% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>3</td>
<td>45/135</td>
<td>32/115</td>
<td>1.2 (0.8–1.8)</td>
<td>nc</td>
</tr>
<tr>
<td>600/650</td>
<td>68</td>
<td>960/2499</td>
<td>404/2562</td>
<td>2.0 (1.8–2.2)</td>
<td>4.4 (4.0–4.9)</td>
</tr>
<tr>
<td>1000</td>
<td>5</td>
<td>153/357</td>
<td>64/359</td>
<td>2.2 (1.4–3.4)</td>
<td>4.0 (3.2–5.4)</td>
</tr>
<tr>
<td>1200</td>
<td>5</td>
<td>85/140</td>
<td>27/139</td>
<td>3.3 (1.8–6.3)</td>
<td>2.4 (1.9–3.2)</td>
</tr>
</tbody>
</table>

nc, Not calculated because relative risk not statistically significant.
3.1.3. Aspirin 1000 mg (716 patients)

Fig. 1 (middle panel) shows the proportion of patients with at least 50% pain relief on aspirin 1000 mg (24–65%, mean 44%) compared with placebo (0–32%, mean 20%), relative benefit 2.2 (1.4–3.4). For a single dose of aspirin 1000 mg compared with placebo, the number-needed-to-treat for at least 50% pain relief was 4.0 (3.2–5.4) over 4–6 h (Table 2).

3.1.4. Aspirin 1200 mg (279 patients)

Fig. 1 (bottom panel) shows the proportion of patients with at least 50% pain relief on aspirin 1200 mg (50–75%, mean 62%) compared with placebo (7–36%, mean 19%), relative benefit 3.3 (1.8–6.3). For a single dose of aspirin 1200 mg compared with placebo, the number-needed-to-treat for at least 50% pain relief was 2.4 (1.9–3.2) over 4–6 h (Table 2).

The efficacy dose–response for aspirin is shown in Fig. 2 together with the dose–response for paracetamol (Moore et al., 1997c).

3.2. Sensitivity analyses

Trials of aspirin 600/650 mg versus placebo were used for the sensitivity analyses. Numbers-needed-to-treat for analgesic efficacy, at least 50% pain relief single-dose postoperative pain for 4–6 h, compared with placebo, were calculated by group size, quality score, pain model, type of pain measurement, and study duration.

3.2.1. Group size

The median aspirin group size for all comparisons was 38 patients. For group sizes below the median the number-needed-to-treat for at least 50% pain relief was 4.1 (3.5–5.0) compared with 4.6 (4.1–5.3) for group sizes greater than or equal to 38. There was no significant difference between the numbers-needed-to-treat of the larger and smaller group sizes ($P = 0.8$).

3.2.2. Quality score

Trials with quality scores of three and above were com-
pared with those with a quality score of two. Little difference was evident between the NNTs for studies with different quality scores (Fig. 3).

### 3.2.3. Pain model

Trials in dental pain were compared with all the other pain models (episiotomy, post-surgical and trauma plus post-surgical models) (Fig. 3). There was no statistically significant difference between the number-needed-to-treat of 4.7 in dental pain (95% CI, 4.2–5.4) and the number-needed-to-treat of 3.9 for the other pain models (3.3–4.7) (Fig. 3).

### 3.2.4. Pain measurement and study duration

There was no significant difference between the numbers-needed-to-treat for the different pain measurements or for the different study durations (Fig. 4).

### 3.3. Adverse effects

#### 3.3.1. Total adverse effects

Sixty of the 72 trials reported adverse effect information for the various doses of aspirin and placebo. Six trials reported no adverse effects with either aspirin or placebo. A total of 313/2619 (12%) of the patients on aspirin (all doses) and 261/2660 (10%) of the patients on placebo reported at least one adverse effect (Table 3), relative risk 1.3 (0.9–1.5). The most frequently reported effects were dizziness, drowsiness, gastric irritation, nausea and vomiting. All effects were of mild or moderate severity and no patients withdrew as a result.

#### 3.3.2. Analysis by dose of aspirin

Among the various doses tested in the trials, there was sufficient information for the analysis of individual adverse effects only for aspirin 600/650 mg compared with placebo. A total of 257/1976 (13%) of the patients on aspirin 600/650 mg and 229/2088 (11%) of the patients on placebo reported an adverse effect, relative risk 1.2 (1.03–1.4). The number-needed-to-harm was 44 (23–345) for aspirin 600/650 mg compared with placebo.

Significantly higher incidences of drowsiness and gastric irritation were reported with aspirin 600/650 mg than with placebo, numbers-needed-to-harm 28 (19–52) and 38 (22–174) respectively (Table 3). No significant difference between aspirin 600/650 mg and placebo was shown for nausea, vomiting, dizziness or headache (Table 3).

### 4. Discussion

Aspirin has been known to be an effective analgesic for many years. Rheumatism has affected man since the great river cultures of the Middle East. Clay tablets from the Sumerian period described the use of willow leaves to treat it. The Egyptians were also aware of the pain-relieving effects of potions made from myrtle or willow leaves. Edward Stone, a vicar from Chipping Norton in Oxfordshire, is generally recognized as the man who gave the first scientific description of the effects of willow bark. In 1763 he wrote a letter to the Earl of Macclesfield, then President of the Royal Society in London, in which he described treating patients suffering from ague (fever) with 20 grains (approximately a gram) of powdered willow bark in a dram of water every 4 h.

The results of the present systematic review confirm aspirin’s efficacy as a single dose postoperative analgesic. The analgesic dose–response tells us that bigger doses give more analgesia, and comparing aspirin with paracetamol the analgesia produced by the two drugs is very similar. One gram of aspirin gives the same analgesia as one gram of paracetamol (Fig. 2). This mg for mg equivalence is the same conclusion reached by Houde and Wallenstein after their randomized comparison of 600 mg of aspirin and 600 mg paracetamol, cited in (Houde et al., 1965).

Houde and Wallenstein also quite correctly emphasized that with NSAIDs (unlike opioids) it was often very difficult to show an analgesic dose–response for outcomes such as peak relief. When differences were apparent in single trials, they were seen using total pain relief. This meta-analysis shows that there is indeed an underlying dose–response, and we used total pain relief (area-under-the-curve for pain relief against time). As Fig. 2 shows, the slope of the
dose–response is very similar for aspirin and paracetamol. The area-under-the-curve for pain relief against time may conceal differences between formulations of a particular drug, and indeed difference between drugs. Fast-onset fast-offset medications may theoretically underperform compared with slower-onset longer-offset alternatives. That question could not be addressed adequately from this data. Whether it is clinically relevant is also unclear. Within the aspirin trials we saw little indication of substantial differences in time-effect curves between formulation, or between drug. Extreme differences in time-effect curves would clearly require us to investigate with a finer tool than the area-under-the-curve, for pain relief against time. For the present we believe that the NNT derived from that area is a robust and clinically useful comparator.

The importance of this aspirin dose–response, and that found with similar analytic methods for ibuprofen but not diclofenac (Collins et al., 1998), is that it suggests that potentially safer NSAIDs, such as COX-2 drugs, might allow us to exploit the analgesic potential of higher NSAID doses. We do not know whether higher doses of NSAIDs alone could replicate the analgesia which high doses of opioid alone can achieve. Injecting 20 mg of morphine has a NNT of less than two, better than the NNT of 10 mg of morphine (2.9; 2.6–3.6) (McQuay et al., 1999; Norholt et al., 1996). If higher doses of COX-2 NSAIDs can emulate this feat, this opens up the prospect of NSAID replacing opioid for certain indications.

A second intriguing feature of this review is the information about adverse effects. Single-dose trials of analgesics are usually too small to give us credible incidence data for more common adverse effects. A third problem is that we are sceptical of the predictive value of single dose gastric irritation for the chronic problem, but we do know that we can detect single dose gastric irritation by pooling data from multiple small trials. The significant drowsiness seen with aspirin 600/650 mg, NNT 28 (19–52), has been seen with a similar analysis for ibuprofen (Edwards et al., 1999), with higher incidence after dental surgery than after other procedures.

Imagine a meta-analysis of an analgesic, in which we pooled data from different postoperative pain states, such as dental or orthopaedic surgery, or pooled data from trials which used different pain measurements. Any conclusions

Another view of the same problem is that about one elderly person will be admitted to hospital with ulcer bleeding per 3000 NSAID prescriptions (Hawkey et al., 1997). We do not know the predictive value of single dose gastric irritation for the chronic problem, but we do know that we can detect single dose gastric irritation by pooling data from multiple small trials. The significant drowsiness seen with aspirin 600/650 mg, NNT 28 (19–52), has been seen with a similar analysis for ibuprofen (Edwards et al., 1999), with higher incidence after dental surgery than after other procedures.

Table 3

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of trials</th>
<th>Patients with adverse effects with aspirin</th>
<th>Patients with adverse effects with placebo</th>
<th>Relative risk (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>Total adverse effects</td>
<td>60</td>
<td>313/2619</td>
<td>261/2660</td>
<td>1.3 (0.0–1.5)</td>
</tr>
<tr>
<td>Aspirin 600/650 mg</td>
<td>Total adverse effects</td>
<td>53</td>
<td>257/1976</td>
<td>229/2088</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30</td>
<td>41/1429</td>
<td>27/1557</td>
<td>1.6 (0.9–2.6)</td>
<td>nc</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>33</td>
<td>103/1542</td>
<td>56/1672</td>
<td>1.9 (1.4–2.5)</td>
<td>28 (19–52)</td>
</tr>
<tr>
<td>Gastric irritation</td>
<td>11</td>
<td>20/546</td>
<td>65/652</td>
<td>2.5 (1.2–5.1)</td>
<td>38 (22–174)</td>
</tr>
<tr>
<td>Headache</td>
<td>29</td>
<td>34/1237</td>
<td>56/1363</td>
<td>0.7 (0.4–1.02)</td>
<td>nc</td>
</tr>
<tr>
<td>Nausea</td>
<td>34</td>
<td>54/1563</td>
<td>68/1683</td>
<td>0.8 (0.6–1.2)</td>
<td>nc</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>12/835</td>
<td>18/927</td>
<td>0.7 (0.4–1.6)</td>
<td>nc</td>
</tr>
</tbody>
</table>

nc. Not calculated because relative risk not statistically significant.
might be said to be faulty because apples were pooled with oranges, rather than pooling either apples alone or oranges alone. This review provides empirical evidence from aspirin that results will be the same for different acute pain states, different pain measurements, different group sizes, different quality of study design, and different study durations. This should help future reviewers who wish to study interventions in postoperative pain. It is important empirical support for the 'lumpers', who wish pragmatically to pool all admissible data, against a 'splitter' contention that pain is different at different sites and responds differently to analgesics. Common sense should operate. This is not a proposal to replace injected opioid on the day of major surgery with oral aspirin. Rather the evidence suggests that trials that tested oral aspirin in different clinical settings came up with very similar efficacy, despite the difference in clinical setting. A second cautionary note is that although this review identified a very large number of papers and hence patients compared with similar reviews of other analgesics, we had to discard two-thirds of the papers we found because they did not meet the inclusion criteria. The confidence intervals around answers to important questions of efficacy and safety remain wide, despite a unique wealth of information.

Acknowledgements

This study was supported by grants from NHS R and D Health Technology Evaluation programmes (#93/31/4 and #94/11/4), European Union Biomed 2 BMH4 CT95 0172, SmithKline Beecham Consumer Healthcare, the Biotechnology and Biological Sciences Research Council, and Pain Research Funds. David Gavaghan and Martin Tramer provided very helpful comments.

Appendix A. Included reports


[44] London, R., Sundaram, G.S., Feldman, S. and Goldstein, P., Epi-


[55] Okun, R., Green, J.W. and Shackleford, R.W., An analgesic com-


References


McQuay, H.J., Carroll, D. and Moore, R.A., Injected morphine in post-
operative pain: a quantitative systematic review, J. Pain Symptom Man-


Moore, A., McQuay, H. and Gavaghan, D., Deriving dichotomous out-

Moore, A., McQuay, H. and Gavaghan, D., Deriving dichotomous out-
come measures from continuous data in randomized controlled trials of analgesics: verification from independent data, Pain, 69 (1997a) 120–130.

Moore, A., McQuay, H. and Gavaghan, D., Deriving dichotomous out-
come measures from continuous data in randomized controlled trials of analgesics: use of pain intensity and visual analogue scales, Pain, 69 (1997b) 311–315.


