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COMMENTARY

Predicting postoperative analgesia outcomes: NNT league tables or procedure-specific evidence?†

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Number needed to treat (NNT) values have been recommended and used to assess efficacy of analgesics for acute pain management. However, the data analysed come from a variety of procedures, which may potentially hinder the interpretation of the NNT value for specific procedures. We reanalysed available NNT data with acetaminophen in relation to the magnitude of surgical injury. Acetaminophen was less effective for pain relief after orthopaedic procedures than after dental procedures. The relative risk ratio for more than 50% pain relief, compared with placebo, was only 1.87 compared with 3.77 ($P<0.05$). Although NNT can give a valuable overview of efficacy, this concept is not necessarily applicable to all types of surgery. We suggest that estimates of NNT should be related to specific surgical procedures.

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A prerequisite for the successful management of postoperative pain, and for optimal patient recovery, is the use of dynamic analgesic protocols that aim to maximize benefit whilst minimizing adverse events.[1] The need for accessible information on analgesics has led to the construction of analgesic league tables, whereby the efficacy and adverse events of analgesics are ranked.[2] Relative benefit is expressed as the number needed to treat (NNT): the number of patients that must receive an analgesic to observe an effect in one more patient than in a placebo comparator group. Adverse events are expressed as the number needed to harm (NNH): the number of patients that must receive a treatment to observe a side-effect or a complication in one more patient than in the placebo group. The data to calculate these values are derived by pooling the results of multiple studies examining the efficacy and safety profiles of analgesic interventions in different surgical procedures, and are based on the proportion of patients with at least a 50% maximal pain response (≥50%maxTOTPAR) over 4–6 h after surgery.

League tables have been constructed to provide clinicians with an overview of comparative analgesic efficacy and harm, assisting in the planning of postoperative pain management protocols. However, they have a significant limitation: available NNT data have not identified statistically significant differences between analgesics with efficacies as disparate as those of acetaminophen and morphine,[2] which is not clinically intuitive. This raises the fundamental question of whether pooling data of analgesic effects from different procedures and in different patient groups limits their interpretability, by creating an average value with a wide margin of error that lacks applicability to particular clinical scenarios.

Are NNT values for analgesics applicable to specific surgical procedures?

An assumption in the construction of analgesic league tables is that different pain models are comparable, and that benefit and harm can be extrapolated from one model to another.

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Table 1 Percentage maximum pain relief of aspirin and placebo in different pain models. Figures are mean (standard error). After Cooper, 1991[3]

Drug/dose	Placebo	Aspirin 650 mg	Margin of benefit
Postoperative	24.8 (2.0)%	46.4 (9.1)%	21.6%
Postpartum	41.9 (2.6)%	52.9 (3.5)%	11.0%
Dental impaction	16.7 (2.4)%	27.1 (2.2)%	10.4%

Although such extrapolation is not unusual in clinical practice, it was not until comparatively recently that this approach was scrutinized. One of the first publications to examine this issue reviewed the effects of aspirin *vs* placebo in the postoperative, postpartum and dental impaction settings (Table 1).[3]

A number of important observations can be made from this analysis. Firstly, the placebo response differs substantially between the pain models: for example, the response in the postpartum setting is over twice as large as that in dental pain. Secondly, the response to aspirin and the margin of efficacy over placebo differ between pain models. From a clinical perspective, it is interesting to note that aspirin is more effective in postpartum women than in the other two pain models, with the highest proportion of maximum relief obtained. However, the high placebo response means that the margin of efficacy over placebo is around half of that seen in the postoperative setting. A final observation is that the standard error for the aspirin response is larger in the postoperative setting than in the two remaining pain models. This suggests that the pooling of data from a number of different surgical procedures creates a more heterogeneous outcome compared with analysing data from single settings, such as dental impaction. In his publication of these data, Cooper indicated that there were 'some clinically relevant differences among the models'.[3]

A systematic review of the efficacy of acetaminophen, NSAIDs and their combination in postoperative pain was also able to examine relative effects in different pain models.[4] Although the reviewers were unable to draw firm conclusions because of methodological problems in some of the individual studies examined, they found evidence that acetaminophen and NSAIDs had equivalent efficacy in major surgery, but that in dental pain NSAIDs had an advantage over acetaminophen for pain scores. This issue has been re-examined recently using data for aspirin, acetaminophen and ibuprofen, with pooled data from two groups of studies: dental extraction and postoperative pain.[5] Using ⩾50%maxTOTPAR to calculate NNT values, the authors observed that the relative benefit of these agents did not differ significantly between the two pain models examined. However, in common with the observations of Cooper, the efficacy of placebo and active agents differed, albeit not to the point of statistical significance, between the postoperative and dental pain settings. The relative benefits of aspirin, acetaminophen and ibuprofen were consistently lower in the postoperative than in the dental pain setting (Table 2). Furthermore, as with the analysis of Cooper, the range of benefits within the postoperative group was wider than in the dental group, a finding that again suggests differences between the procedures pooled in the postoperative group.

Table 2 Comparison of analgesic treatment outcomes following dental procedures or surgery. A comparison of the percentage of patients who achieved ⩾50% pain relief with aspirin, acetaminophen or ibuprofen compared with placebo. This shows the relative efficacy of the active compared with the placebo treatment. Note that the efficacy of all the agents relative to placebo is greater in dental procedures than in the postsurgical setting. Data from the analysis of Barden *et al*.[5]

Drug and dose	Pain model	Proportion of patients benefiting from		
		Active drug	Placebo	Relative benefit
Aspirin 600/650 mg	Dental pain	35%	14%	2.5 (2.2–2.8)
	Postsurgical pain	47%	20%	2.3 (1.9–2.7)
Acetaminophen 600/650 mg	Dental pain	36%	12%	2.9 (2.3–3.7)
	Postsurgical pain	41%	23%	1.9 (1.5–2.4)
Acetaminophen 975/1000 mg	Dental pain	37%	9%	3.7 (2.7–5.1)
Acetaminophen 1000 mg	Postsurgical pain	51%	26%	2.2 (1.9–2.5)
Ibuprofen 400 mg	Dental pain	56%	12%	5.2 (4.1–6.6)
	Postsurgical pain	55%	21%	3.7 (2.6–5.1)

From these data, it can be hypothesized that the effects of analgesics differ significantly between pain models. In order to examine this hypothesis further, we analysed a large database for the effects of acetaminophen on postprocedure pain (Fig. 1).[6] The first clue from these data, which pooled results from studies of postoperative, postpartum, dental extraction and oral surgery pain, is that the data are highly significantly heterogeneous ($P<0.00001$), a sign that they lack comparability. Although it has been argued that conventional heterogeneity tests may be unhelpful,[7] these data are also highly heterogeneous according to the updated criteria of Higgins and colleagues ($I^2=75.4\%$).[8] When the effects of acetaminophen are analysed on a procedure-specific basis, with a single study from the 23 originally included removed as it contained data from mixed procedures, the reason for this heterogeneity becomes clear: the effect of acetaminophen in the postoperative setting, derived from orthopaedic procedures, differs significantly from that in the dental extraction model (Fig. 2). These data strongly support what many clinicians know to be intuitive: what works in one procedure may have a different effect or no significant effect at all in another. They also demonstrate that, in averaging effects from different procedures, the strength of evidence from one particular model (for example, dental pain, a commonly used model to examine efficacy) can falsely weight the average in a particular direction.

Are NNT values for analgesics interpretable for clinical practice?

In seeking measures of analgesic outcome that have validity for clinical trials and are also suitable for combining in

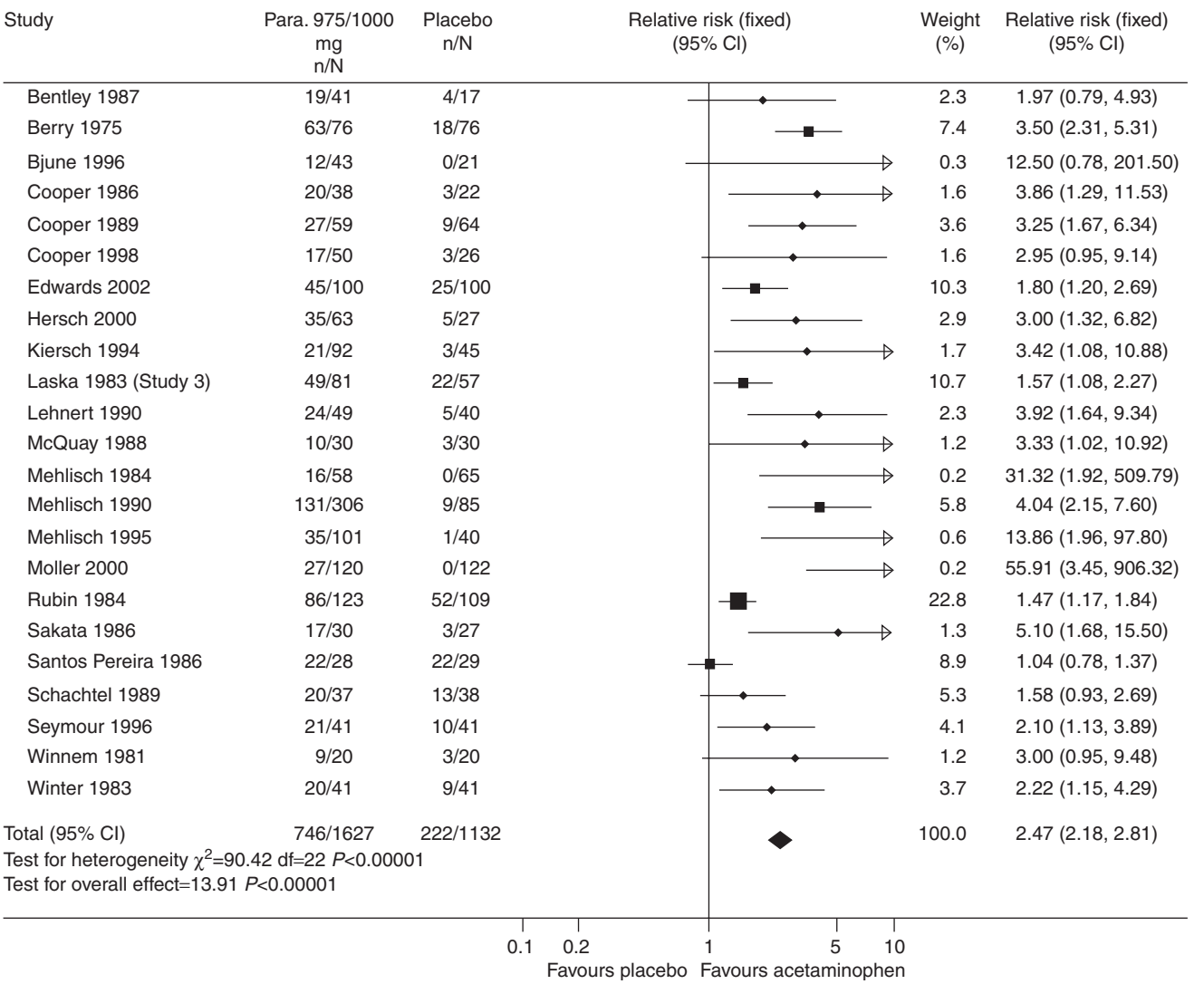

Fig 1 Single-dose acetaminophen for postprocedure pain (postoperative, postpartum, dental extraction and oral surgery pain studies). Number of patients with ⩾50% pain relief.[15–37]

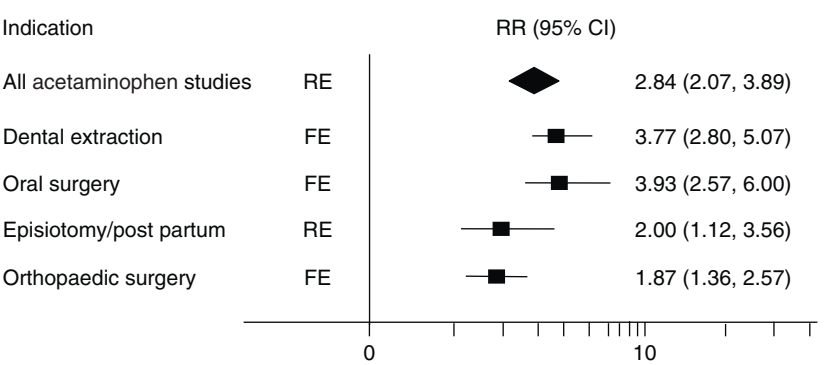

Fig 2 Relative risk (RR) of achieving ⩾50% maximal pain relief for acetaminophen *vs* placebo in different pain models. FE, fixed effects meta-analysis model; RE, random effects meta-analysis model. Data derived from the meta-analysis of Barden *et al*.[6]

meta-analyses, a number of methods have been used. The calculation of the potential maximum analgesic benefit in a given trial and the proportion of this maximum achieved by individual patients [the area under the pain curve (AUC), %maxTOTPAR] provides a useful measure of analgesic benefit over a period of time.[9,10] These are also used to calculate NNT values.[9,10] A mathematical model can be used to calculate the proportion of patients achieving a

≥50%maxTOTPAR without the need for individual patient data.[9 10] This measure not only gives an impression of analgesic benefit during the postoperative period, but also takes into account the lack of a normal distribution in pain response.[11]

However, the shape of the analgesic benefit curve, not merely the area beneath it, can provide clinically important information. For example, similar AUCs may be achieved with agents with different times of onset, peak analgesic efficacy and duration of action. However, these specific details have significant implications for clinical practice. Furthermore, a 50% maximal pain response may not provide clinically relevant information. Guidelines suggest that a visual analogue scale (VAS) score of <30/100 mm is an appropriate target for analgesia, and a minimum clinically relevant drop in pain intensity has been considered to be 13 mm.[12] It is also likely that, in order to achieve a clinically relevant drop in pain intensity, a larger decrease is required in patients with an initially higher pain intensity than in those with a lower pain intensity.[13]

NNT values based on a 50% response do not therefore provide information on whether the change was from high- or low-intensity pain (for example, from a VAS score of 90 to 45 or from 40 to 20). Additionally, they provide no information on reduction in time or overall need for supplementary analgesia. An analgesic intervention may provide little additional benefit in VAS scores, but may decrease supplementary opioid use; this is an important finding that cannot be contained within an NNT value. Thus, NNT values derived using this method may eliminate the details of analgesic benefits that are important for clinicians in making prescribing decisions.

How can we optimize postoperative analgesia prescribing decisions?

The use of NNT values can therefore be criticized on a number of counts. Firstly, a credible NNT value needs to be derived from at least 500 patients,[14] which has demanded the pooling of data from heterogeneous studies. Despite this recommendation, of the 50 NNT values quoted, most (32/50) are based on fewer than 500 patients, with eight based on fewer than 100.[2] By pooling the data, an average effect of a given analgesic is created, with a wide margin of error, which ignores the specific effects of analgesics in different procedures. This creates a league table with many overlapping values, with the propensity to confuse clinicians and lead to extrapolations of efficacy that are inappropriate for all procedures. Secondly, the calculation of NNT values, which are derived through mathematical modelling and not from individual patient data, removes specific information concerning the pattern of effect of interventions, depriving clinicians of valuable information. Lastly, although these values may provide an accessible method of comparing different agents, they are not clinically intuitive for many physicians, as they provide little indication of what change in pain the patient is likely to experience with a given analgesic, and they give no information concerning the placebo responses in specific procedures, which are markedly different.

In conclusion, using calculated outcome measures may not provide the most useful or reliable information on analgesic efficacy for clinical practice. It may be that the impact of analgesics *vs* placebo on pain intensity scores at multiple time points—one of the most basic measures of efficacy—still provides the most useful marker for clinicians. This needs to be supplemented by data on the effects on reducing supplementary analgesic consumption, an important endpoint that has utility in aiding clinicians to reduce postoperative opioid consumption. However efficacy information are presented, it is clear that average values derived by pooling data from different procedures can provide misleading information to clinicians. This reinforces the need to examine procedure-specific outcomes wherever possible, to ensure that postoperative pain management protocols are optimized, although further work is needed to define the boundaries of procedure-specificity.

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