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Heterogeneity in meta-analyses of treatment of acute postoperative pain: a review

F. Espitalier[1,2,3,6]*, E. Tavernier[1,2,4,8], F. Remérand[3,6], M. Laffon[3,5,7], J. Fusciardi[3,5,6] and B. Giraudeau[1,2,4,5,8]

[1] INSERM, U738, Paris, France
[2] INSERM, CIC 202, Tours, France
[3] Département d'Anesthésie Réanimation, CHRU de Tours, Tours, France
[4] CHRU de Tours, Tours, France
[5] Université François Rabelais, Tours, France
[6] SAR II, Hôpital Trousseau, CHRU de Tours, 37044 Tours, France
[7] SAR I, Hôpital Bretonneau, CHRU de Tours, 37044 Tours, France
[8] CIC, Hôpital Bretonneau, CHRU de Tours, 37044 Tours, France

* Corresponding author: SAR II, Hôpital Trousseau, CHRU de Tours, 37044 Tours, France. E-mail: fabien.espitalier@univ-tours.fr; f.espitalier@chu-tours.fr

Editor's key points

- Acute postoperative pain is intrinsically heterogenous.
- This review examined the type of surgery as one of the sources of heterogeneity in meta-analyses of treatment of acute postoperative pain.
- Not all meta-analyses addressed heterogeneity resulting from the type of surgery adequately.
- For better clinical implications, any meta-analysis of acute postoperative pain should address heterogeneity resulting from the type of surgery.

Background. Heterogeneity and its causes must be assessed using meta-analyses (meta-analysis). Especially in meta-analysis dealing with treatment of acute postoperative pain, the type of surgery is a source of heterogeneity. We aimed to assess whether the type of surgery is considered a source of heterogeneity in meta-analysis and how it is taken into account in meta-analysis evaluating the efficacy of treatment of acute postoperative pain. We further compared meta-analysis that pooled trials of surgeries with highly heterogeneous postoperative pain levels, the *heterogeneous group*, with meta-analysis that pooled trials involving surgeries with homogeneous pain levels, the *homogenous group*.

Methods. The meta-analysis reports available in Issue 3, 2011 of the electronic database of the Cochrane library and pooling results of randomized or quasi-randomized controlled trials that assessed the efficacy of treatment of acute postoperative pain alone were considered. A survey of experts established a rating of the postoperative pain levels for the type of surgery. For each meta-analysis, the different pain level ratings associated with the trials included in the meta-analysis were considered and the standard deviation (SD) of these ratings calculated. From the distribution of SD values, we defined the *heterogeneous* and *homogeneous groups*.

Results. Sixty-one meta-analyses were included; all assessed heterogeneity. Twenty-six meta-analyses considered the type of surgery as a subgroup (50% *vs* 38% in the *homogeneous group vs heterogeneous group*). Forty-four reports discussed the type of surgery as a source of clinical heterogeneity (85% *vs* 62% for the *homogeneous vs heterogeneous group*). Twenty-nine meta-analyses compared 'postoperative pain from dental surgery' to 'other type of surgery'.

Conclusions. Meta-analyses evaluating treatment of postoperative pain should explore clinical heterogeneity associated with the type of surgery for better implications for practice.

Keywords: acute pain; pain; analgesics; pain, postoperative

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Understanding the causes of heterogeneity in a meta-analysis increases its scientific value and clinical relevance.[1 2] Heterogeneity, and especially its sources, must be assessed.[3] Concerning analgesia, a narrow panel of drugs is used in a wide range of situations. Thus, a common dose of aspirin used in different pain models leads to various pain relief.[4] Acute postoperative pain is influenced by surgical variables, patient variables, and anaesthetic procedure.[5] Finally, the type of surgery is the main factor determining the intensity of postoperative pain.[5]

The meta-analyses of treatment of acute postoperative pain are intrinsically subject to clinical heterogeneity. For example, in a meta-analysis of the effect of paracetamol for postoperative pain in adults,[6] the risk ratio (RR) of the global treatment effect was 2.7 [95% confidence interval (CI) 2.4–3.0], but sensitivity analyses revealed a difference in treatment efficacy when comparing dental pain models [RR 4.1 (95% CI 3.3–5.2)] *vs* other surgical models [RR 1.7 (95% CI, 1.5–2.0)]. This observation raises concerns about the interpretation and implications of results of such meta-analysis.

In this review, we aimed to assess how heterogeneity (and especially heterogeneity associated with the type of surgery) was assessed and taken into account in meta-analysis of randomized or quasi-randomized controlled trials evaluating the efficacy of treatment of acute postoperative pain. We further aimed to compare meta-analyses that pooled trials involving surgeries with highly heterogeneous postoperative pain levels to meta-analyses that pooled trials involving surgeries with homogeneous pain levels.

Methods

The definitions of the concepts of interest (heterogeneity and clinical heterogeneity) and statistical and graphical tools (Cochran *Q* test, I^2, and L'Abbé, Galbraith, Baujat, and Forest plot graphical representations) are from the Cochrane Handbook or original literature and are described in the Supplementary material, Appendix S1.

Data sources and searches

We searched for reports of meta-analyses in Issue 3, 2011 of the electronic database of the Cochrane Library Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE). Meta-analyses had to pool results of randomized or quasi-randomized controlled trials, assess the efficacy of drug or non-drug treatment for acute postoperative pain alone, and be written in English or French. For the CDSR, we first searched for meta-analyses included in Cochrane reviews grouping *anaesthesia, or pain, palliative, and supportive care*, then meta-analyses under the topic 'Anesthesia and Pain Control' and with the keywords 'anesthesia', 'acute pain', or 'pain control'. For the DARE, we used the keywords 'acute pain', 'pain control', or 'anesthesia'. For 'pain control', we used the limits 'no chronic pain, no low back pain, no cancer-related pain'.

One reviewer (F.E.) manually screened all titles and abstracts, and obtained the full text for reports of potentially relevant meta-analyses, which were selected after reading the title, the abstract and, if necessary, the full text.

Data extraction and quality assessment

A pre-tested standard data extraction form was used to collect relevant information. Meta-analysis was assessed in a random order, and data were extracted by one of us (F.E.) from the full text and from appendices or any other materials available online.

Data extraction

We collected data on the general characteristics of each meta-analysis: date of publication, Cochrane or non-Cochrane review, and types of trials included (randomized or quasi-randomized). The methodological quality of meta-analysis was assessed by the AMSTAR tool.[7]

Data on the types of evaluated interventions (drug or non-drug treatment), number of included trials, number of included subjects, number and types of endpoints used (patient-reported outcomes, physician-assessed outcome, or other), description of endpoints, and types of surgeries (names of the surgical procedures) were collected.

The following data on heterogeneity were collected: whether heterogeneity was assessed for the primary endpoints and which tools were used; whether a random-effects or fixed-effects statistical model was used; whether clinical heterogeneity was discussed, which type of clinical heterogeneity was discussed (patient, intervention, co-intervention, outcome, or other related clinical heterogeneity) and in which section it was discussed; whether the type of surgery was discussed as a patient-related clinical heterogeneity; whether subgroup analyses were performed and, if so, whether the type of surgery was used to define subgroups; whether a subgroup analysis was performed by drug dose, independent of the type of surgery; whether subgroup analyses were pre-specified or not; whether a sensitivity analysis was pre-specified, whether this sensitivity analysis was performed; whether a 'subgroup' type or a 'leave-one-out' type of analysis was conducted and whether a meta-regression analysis was performed and whether it was pre-specified.

Heterogeneity of surgical-procedure pain level, as assessed by experts

To our knowledge, international consensus is lacking on rating surgical-procedure pain level. Therefore, we asked an expert panel to rate the pain level for all surgical procedures identified for this review. We then distinguished two groups of meta-analyses: (i) those that pooled trials with heterogeneous surgical-procedure pain levels (*heterogeneous group*); and (ii) those that pooled trials with homogeneous surgical-procedure pain levels (*homogeneous group*). The detailed method is discussed subsequently.

Surgical-procedure pain level rating

We listed the different types of surgeries from the selected meta-analyses. Then five postoperative analgesia experts were asked to independently rate the postoperative pain level for each procedure. The experts were experienced anaesthesiologists (with 3, 16, 20, 30, and 37 yr, respectively, of experience). They used a continuous scale from 0 (no pain) to 10 (maximal pain). If they did not have any knowledge about the postoperative pain level for a surgery, their response was 'x'. If they were not able to evaluate a surgery (i.e. the type of surgery was not sufficiently specified), the response was 'not applicable'. The responses were averaged with at least three responses among the five experts and if no more than one expert gave a response of 'not applicable'. Thus a pain level rating for surgical procedures was obtained.

Meta-analyses heterogeneity in surgical-procedure pain level

Heterogeneity in surgical-procedure pain level was quantified as a standard deviation (SD). For each selected meta-analysis, the SD of the surgical-procedure pain level rating was calculated, discarding trials without a rating for surgical-procedure pain level. If >10% of the trials included in a meta-analysis