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Pain measurement and critical review of analgesic trials
pain scores, functional pain measurements, limits and bias of clinical trials

Adrien Lemoine, Assistance Publique [a],
Valeria Martinez, Assistance Publique [b, c, d],
Francis Bonnet, Assistance Publique [a, *]

[a] Hôpitaux de Paris, Sorbonne Université, Faculté de Médecine Paris VI, Service d'Anesthésie-Réanimation Médecine Périopératoire, Hôpital Tenon, 4 rue de la Chine, 75020, Paris cedex, France
[b] Hôpitaux de Paris, Service d'anesthésie, Hôpital Raymond Poincaré, Garches, F-92380, France
[c] INSERM, U-987, Hôpital Ambroise Paré, Centre d'Evaluation et de Traitement de la Douleur, F-92100, France
[d] Université Versailles Saint-Quentin, F-78035, France

Randomized clinical trials designed to assess analgesic agents and/or techniques used for postoperative pain control have several limitations, which are addressed in this article. Efficacy of analgesics cannot be limited to the evaluation of pain intensity or the amount of opioid rescue medication, but it also means to evaluate parameters such as the delay and duration of the effect, the number of patients with satisfactory pain control, and side effects. Because combination of analgesics is the standard of care in clinical practice, its value also needs to be documented. Eventually, analgesic treatments have to be considered in the settings of postoperative supportive care and enhanced recovery programmes after surgery.

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Introduction

The European Medical Agency has made recommendation concerning the design of clinical studies aiming to evaluate new analgesic agents or techniques for the treatment of postoperative pain [1].

* Corresponding author.
    E-mail address: Francis.j.bonnet@gmail.com (F. Bonnet).

Clinical trials must be prospective randomized, with parallel groups. Three arms at least need to be considered: the placebo group, the group of patient receiving the standard of care, and the group receiving the new treatment. In addition, it is necessary to plan separately trials on visceral surgery, on the one hand, and orthopaedic surgery, on the other hand. Repeated administrations, corresponding to clinical practice, need to be evaluated and eventually the new treatments need to be assessed in specific cohort of patients (older patients, patients with co-morbidities, etc.). Evaluation of a new analgesic treatment also means not only quantifying the decrease in pain intensity but also the delay and the duration of its effect and the global satisfaction of the patient. Moreover, to determine the use of a new analgesic treatment, it is necessary to evaluate not only its efficacy but also its tolerance that depends on the occurrence of side effects more or less bothersome or even life threatening. In other words, the clinical profile of an analgesic treatment comprises directs effects on pain intensity, rescue medication consumption, side effects, and complications, and indirect effects such as accelerated recovery after surgery, decreased postoperative morbidity, and shortening of hospital stay.

Randomized prospective controlled trials (RCTs)

RCTs' are, in fact, commonly designed with two arms: a control group and a treatment group. In both groups, patients self-administer morphine or another opioid as a rescue, and pain intensity is measured at rest and on mobilisation with a visual analogue scale (VAS) or an equivalent method (simple numerical rating scale, verbal scale, etc.). The result of a study is considered positive when morphine consumption is significantly decreased in the treated group, and that is usually considered enough to draw conclusion provided satisfactory pain control is achieved (i.e. VAS scores $\leq$30). Indeed, comparable levels of analgesia should be theoretically achieved in the two groups but with different opioid consumptions (lower in the treatment group). Actually, side effects of opioids prevent from using high doses in the control groups, leading to a difference in pain scores between the control and the treated groups while the «true» difference in opioid consumption is underestimated. When a new analgesic treatment or technique is evaluated, small-size RCTs are usually designed initially so that positive results need to be confirmed in large-sized assays, and negative results are inconclusive because of the lack of statistical power.

The comparison of pain intensity scores is commonly based on the comparison of mean values at several pre-set time-points. Other measurements have been developed to quantify the effect of analgesic agents, such as pain intensity difference. This parameter can be measured at each time point, and the sum of pain intensity differences (SPID) can also be calculated [2]. Although the measurement of these parameters can be adapted to statistical evaluation, it is far from clinical relevance. It is also true for calculation and comparison of area under curves of pain intensity over time.

Other issues need to be addressed such as the difference between statistical and clinical differences in pain intensity. A clinical difference implies that the patient perceives that pain intensity has decreased. It has been evaluated that this feeling corresponds to at least a 10–18 mm change in the VAS score (0–100) corresponding to about 20% change in pain intensity [3,4]. The threshold value that documents statistically significant difference, depends on the sample size, implying that in large-sized clinical trials there are more chances to achieve a threshold of significance, with a small absolute difference in pain intensity, below the threshold of clinical perception of the difference in pain scores. The rational is the same when one considers the decrease in opioid consumption. For example, paracetamol obtains most of the time a less than 10 mg decrease in morphine consumption over 24 h and hundred of patients are required to make this difference significant [5]. On the other hand, due to a 30–50% decrease in morphine consumption, NSAIDs are easily demonstrated to be effective [6]. However, from a clinical point of view, a decrease in morphine consumption makes sense only if it is associated with a decrease in the incidence of side effects such as nausea, vomiting, urinary retention, pruritus, or prolongation of postoperative ileus.

Another point is the absolute value of pain score corresponding to a pain-free patient. It is commonly considered as close to 30 mm (and not zero!) [4]. However, patients may experience satisfactory pain control at rest while remaining in pain with high VAS scores on mobilization.

The last point refers to the treatment applied in the control group. To make the difference in pain scores more dramatic, the authors of clinical trials tend to minimize the analgesic treatment in the

control group that is sometimes limited exclusively to rescue medication (morphine Patient-Controlled Analgesia). However, in real life, patients are treated even if these treatments are considered less than ideal justifying other investigations to improve pain control. It is therefore important to consider that the patients need to benefit to the standard of care for a given surgical procedure to make a valuable comparison with a new treatment susceptible to be given to patient to improve their comfort.

When considering unmet needs in postoperative pain treatment, RCTs suffer from several flaws and limitations. Most of them are small-size clinical trials as mentioned before. In addition, studies concerning the same agent or technique are heterogeneous because of different type of surgical procedures, different cohorts of patients, and different doses, routes and timing of administration. This is especially true for academic research that presents a scattering approach of the evaluation of analgesic agents related to different clinical practices. This matter of fact commonly precludes from definite conclusion. There are consequently important difficulties to characterize the value and the clinical use of drugs, for example, alpha-2 adrenergic agents, ketamine, gabapentinoids and dexamethasone. The problem is even more complex when the combination of analgesic agents is considered because no one uses the same combination, at the same dose, and at the same time, for the same categories of patients. For example, when considering the use of ketamine, some clinicians give a single dose after anaesthetic induction, while others give a continuous infusion or repeated doses and still others use PCA devices [7]. For gabapentin, doses range from 300 mg given once to 1200–1600 mg during several days after surgery! [8].

Systematic reviews and meta-analysis: value and limitation

The multiplication of post-operative trials evaluating the same analgesic molecule has increased so much that an overview of the literature has become increasingly difficult to achieve, even for an expert in the field. Systematic reviews are based on a comprehensive, systematic search for scientific evidence at a given time. They make it possible to bring together a very large amount of information and give the most objective possible analysis of the literature. Once there is a critical mass of comparable studies designed to address a common research question, a meta-analysis can be done. Meta-analyses are based on two main principles. The first is that the data is aggregated to achieve a combined effect. The second is that the included studies are weighted, i.e., meta-analyses give more weight to the more accurate studies with a higher number of patients. They are based on a rigorous, reproducible methodology. The value of a meta-analysis is that it quantifies treatment effects and their uncertainty, increases power, increases precision, explores differences between studies, settles controversies from conflicting studies, and generates new hypotheses. Systematic review provides a quantitative summary through a meta-analysis.

Although meta-analyses are considered as providing the highest level of evidence, it is important wondering how confident we can be in the estimate of the observed effect. Confidence in a meta-analysis result is an important consideration that can be evaluated [9]. The GRADE methodology is a systematic approach rating the certainty of evidence in systematic reviews at four levels (high, moderate, low, very low). However, five factors can reduce the confidence in the estimated effect.

The first is the risk of bias due to the inclusion of poor-quality studies in the meta-analysis, which includes the limitations of study design and execution of randomized control trials. For example, the difficulties of blinding a regional analgesic treatment, or a significant loss of follow-up, in studies evaluating the risk of chronic pain after surgery, are a common source of bias.

The second is inconsistency of results across studies, when they produce widely different estimates of the effect. It is important to look for the causes of the heterogeneity, which could be differences in populations, interventions, or outcomes. For example, the surgical procedures, the doses of drugs, or even the definition of pain are frequent factors of heterogeneity in postoperative trials. The examination of heterogeneity is an important question in the development of new hypotheses.

The third point is indirectness - that is, confidence that the results expressed relate to the heath care question that was posed at the beginning. This question was expressed in the PICO format (Population, Intervention, Control, Outcomes) present in the paragraph method of systematic review. The PICO format helps evaluating whether the evidence is sufficiently direct to provide reasonable confidence that it can be used to answer the health care question. Direct evidence comes from trials that measure

the outcomes of interest. For example, in RCTs evaluating the benefit of strong opioids in chronic pain, it is common practice to exclude patients who have psychological vulnerability or addiction problems. This situation is far from real life and can downgrade the quality of evidence in such meta-analyses [10].

The fourth factor is imprecision of the results. It depends from some criteria such as sample size: the larger the sample size, the greater is the precision. The optimal information size depends on the incidence of events in the control group and on the level of difference that is considered clinically significant. It is important to address this point in a meta-analysis that combines rare events such as adverse events and/or when it includes outcomes considered as secondary outcomes in the primary study - such as chronic pain after surgery [11].

The fifth factor is publication bias. Publication bias leads to a false assessment of the effect due to selective publication of studies. It is known that positive trials are more likely to be published than negative trials in all fields. Studies funded by pharmaceutical companies are more likely to have positive outcomes. A funnel plot has to be used to check to document publication bias. However, a simple and effective way to check that the literature search is exhaustive is to ensure that in the method section of the systematic review, at least three databases have been explored and that the search for unpublished trials is performed in the registration site such as ClinicalTrials.gov and WHO ICTRP. Unpublished data account for more than 70% of the evidence for some analgesics [12].

While conventional meta-analyses can evaluate whether a particular analgesic is effective, they do not answer the clinician's question: what is the best treatment among the various existing treatments? Controlled analgesic trials rarely compare treatment with each other. The lack of direct comparison makes it difficult to determine a comparative efficacy or even tolerance of different analgesics treatments. Recently, a new form of overview has emerged to provide a solution to this issue: the network meta-analysis [13]. Network meta-analysis makes it possible to estimate the relative effectiveness of the different treatments available to treat the same condition. The "network" refers to available treatments and existing direct comparisons between these treatments (randomized controlled trials). A network meta-analysis, then, consists of a comprehensive quantitative overview using existing direct comparisons and credible indirect comparisons. In the indirect comparison, the efficacy of the two treatments A and B is compared via their respective efficacy against a common comparator. This method allows classifying treatments in terms of efficacy and tolerance. Furthermore, bringing together evidences of efficacy and/or tolerance of available treatments in the form of a network analysis, makes it possible to quickly visualize missing studies, and guides future research. In the field of pain management, several "datasets" in the scientific literature, could greatly benefit from such an approach. Not only do they make it possible to compare pharmacological treatments with each other [14–16] but also pharmacological treatments with non-pharmacological treatments [12].

What are the unmet needs?

From a clinical point of view, a few millimetres decrease in VAS score or a few milligrams decrease in morphine consumption does not make sense and is not demonstrative enough to induce significant changes in clinical practice except in passionate believers. When one wants to change its clinical practice for the better, a series of steps need to be followed. First, it is necessary to determine whether patients are treated according to evidence-based medicine provided by systematic review of the clinical trials with reasonable methodological quality (see above). Once the analgesic protocol is determined and used in routine practice, it needs to be evaluated. There are several instances corresponding to an unsatisfactory pain control. Patients may remain permanently in pain during the postoperative period, but this is usually not the case; otherwise, a complete revision of the protocol needs to be performed. More frequently pain at rest is controlled, but mobilization remains painful. It is as much worrisome that patients are included in programs requiring active participation. Persistent pain on movement may preclude the compliance of patients to rehabilitation process. Such an issue may require changing continuous administration for intermittent boluses or providing rescue medication to be taken before mobilisation. Last but not least, the analgesic protocol could be satisfactory in most of the patients, while some of them remain in pain. The issue is consequently not to lower the mean level of pain intensity in the whole population but better to reduce the percentage of patients

who are still in pain despite adequate compliance to the current treatment. Sometimes, these patients can be identified preoperatively and benefit from a special adaptation of the current treatment (for example, patients with chronic pain already treated with analgesics) In most of the case, it is not possible to clearly identify preoperatively these patients. Thus, a clinical trial comparing the standard of care to a new therapeutic approach may consequently focus on reducing this percentage that could be considered as the main goal of the trial or the main criterion for comparison of the two groups of patients.

A comparison of the number-needed-to-treat (NNT) (how many patients do I have to treat before one of them benefit from the treatment) and the number needed to harm (NNH) (how many patients are exposed to a treatment before occurrence of a side effect) in the same population of patients may help to determine the value of introducing a new drug or treatment in the setting of postoperative pain. Thus, the NNT to achieve 50% pain relief is commonly compared to the NNH to induce nausea or urinary retention … However, because the occurrence of pain is common postoperatively, NNT values of analgesic agents are low regardless of their efficacy (ranging between 3 and 5). Although comparisons of NNT may also account for efficacy, comparison of NNH is especially valuable in the setting of postoperative pain treatment in patients scheduled for rehabilitation process.

The pathway for a new drug to become a routine treatment

Beside development of new drugs by pharmaceutical companies that follow predetermined rules, academic research may promote the use of pre-existing drugs or describe new (regional analgesic) technique to improve pain management. Such a development is usually based on preliminary cohort studies that describe the technique and suggest its efficacy. In case of regional analgesia, this approach is completed by anatomical studies that describe the diffusion of the solution and the nerve structures involved. Then, a few randomised controlled studies are published with encouraging results compared to the standard of care and key opinion leaders promote the technique. Later, other studies are published documenting controversial results or including more important cohorts of patients confirming or not preliminary results and documenting the incidence of side effects. At this stage, results of all the studies published with adequate methodology are included in systematic review and meta-analysis eventually confirming the efficacy of the new promoted treatment. However, the conclusions of meta-analysis do not close the debate for two reasons: first, systematic review commonly reveal the heterogeneity of studied protocols and surgical procedures. Second, meta-analyses usually do not address the issue of doses, duration and mode of administration. There is consequently a need for a confrontation of the literature and the clinical needs and to evaluate the balance between advantages and drawback of a new treatment. At least, the literature needs to be analysed considering two points: only articles referring specifically to the surgical procedure that is considered, need to be analysed to determine the value of a given analgesic treatment for controlling pain in this setting and eventually evidences must be found in the recent literature considering that the surgical techniques are continuously changing (laparoscopic instead of laparotomy, robotic surgery, etc.) as well as the global management of the patients (shortening of hospital stay, early mobilization, etc.) [17,18].

Practice points

- A surgical procedure-specific, evidence-based, evaluation of postoperative pain treatments is better than a global approach.
- In addition to the effect on pain intensity and opioid consumption, the efficacy of pain treatments should be assessed on other parameters such as the number of patients with satisfactory analgesia.
- A clinical approach of analgesic treatments should also consider the balance between efficacy and side effects
- Postoperative analgesic protocols should be designed and applied, in the setting of enhanced recovery after surgery.

Research agenda

- New analgesic treatments should be compared to the standard of care for the surgical procedure considered.
- Combination of analgesics and single agents should be evaluated.
- The impact of postoperative pain treatment on the occurrence of chronic pain after surgery should be more commonly evaluated

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