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Editorial comment

Why we publish negative studies – and prescriptions on how to do clinical pain trials well

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In this issue of The Scandinavian Journal of Pain, Spreng et al. [1] publish a well written and well performed double-blind, placebo-controlled study of the effects of adding a small dose of ketamine to a multimodal pain-preventing regimen during haemorrhoidectomy. The other analgesic drugs made the patients more or less pain free, and (therefore?) they could not find any additional effect of ketamine. They were also interested in any prolonged effect of this NMDA-antagonist on persistent pain after haemorrhoidectomy. However, these secondary outcome measurements did not show any added effect of ketamine either.

So why do we still publish a study with only negative findings?

It is important that negative outcome findings of well designed studies with an interesting and important research question are published in order to prevent.

Publication bias of positive studies:

> If 20 studies are performed with the same aim of finding an effect of a drug, which in fact is an inactive drug, one of the 20 studies may find (false) positive results ($p < 0.05$) because of random variations of measurements. If all the negative studies are rejected by the editors of scientific journals, while studies with (false) positive findings are published, the scientific world is left with the impression that the new drug is effective, although it in fact this is not true (Type I – error).

And this may become even worse: the published studies will inspire more investigators to study the drug, and if the publication bias continues, more studies with false positive results become published, meta-analyses begin to appear, and the (false) truth is cemented. It changes practice of medical practitioners. It may take many years before real life experience shows that this was based on false positive findings. And eventually after many years of ineffective clinical use, maybe even at the cost of adverse effects of the inactive drug, renewed studies with negative, and true, findings become published. The clinicians realize that their clinical impressions were correct all along, and finally the drug, by now an old drug, is discarded.

The story about intra-articular morphine is an illustrative example of this phenomenon. A number of studies with (false) positive results, and also meta-analyses, had concluded that morphine administered into the knee-joint at the end of arthroscopic procedures, could prevent postoperative pain and markedly reduce the need for analgesics for 24 h, and longer. When Rosseland and coworkers did the right studies, including only patients with moderate to severe postoperative baseline pain before morphine in saline was injected into the newly operated knee-joint, they could demonstrate clearly that intra-articular saline with morphine does not have any effect on postoperative pain different from that of saline alone [2,3]. Some studies had more female patients in the placebo group than in the morphine group, and since women have more pain after surgery, the placebo group had more postoperative pain than the morphine group [4].

Will registration of studies abolish publication bias of false positive studies?

Spreng et al. [1] registered their study at http://www.clinicaltrials.gov.

This means that even if their manuscript was not accepted for publication in any scientific journal, it would still be possible for those interested in the effects of ketamine added to a multimodal analgesic regimen to track the study and its results. More and more scientific journals will consider for publishing studies only if they have been registered at an official trial register such as http://www.clinicaltrials.gov or http://www.clinicaltrials.govisrctn.org [5,6]. The World Health Organization has opened a web search portal for clinical trials from several primary registers (www.who.int/ictrp/en). When all clinical studies are registered and followed up with outcome data, the problem of publication bias, definitely becomes less.

Ethics of clinical studies on pain—unnecessary suffering?

One reason that clinical analgesic studies are performed with a "pre-emptive/preventive" design is the conviction that it is unethical to let patients suffer unnecessary, "just because we are studying pain". What *really is unethical* is to conduct a clinical pain trial where the results cannot be analysed properly. This is true if a large portion of the included patients would not have pain after

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surgery even without the placebo or test treatment. If trial patients have an effective rescue analgesic, freely available at any time the patient needs it, than the trial is ethically acceptable. Even a placebo treatment, initially gives some pain relief, but it is usually of short duration, at the most 1–2 h. At this time the patient will be able to get an effective rescue analgesic treatment. This does not invalidate the placebo controls, although it does lead to the various interpretations of LOCF (the last observation of pain intensity carried forward), or WOCF (the worst observation of pain intensity carried forward) [6].

What is the best pain scale in acute pain trials?

The Visual Analogue Scale (VAS) and the Numeric Rating Scales (NRS) are equally sensitive, an definitely more sensitive in detecting differences in pain intensity than a Verbal Rating Scale (VRS) [7]. However, the NRS is often more practical when the patient for various reasons cannot see the VAS scale clearly or cannot use a pen [8]. Using both a VAS and an NRS simultaneously is hardly useful.

Designing, conducting, and reporting clinical pain trials

Useful prescriptions on how to do clinical pain trials well and how to report them clearly are available [6,9–13]. Spreng and coworkers reported their study in an exemplary manner, using the checklist of the CONSORT-statement—see www.consort-statement.org.

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