



**Horace Roman, MD, PhD**

Department of Obstetrics and Gynecology, University Hospital Rouen, Rouen, France

### **Laparoscopic adhesiolysis do we have evidence? No**

The results of randomized controlled trials (RCTs) provide the most reliable information on any type of medical intervention (1). The strength of the evidence is such that RCT results are rarely contested by physicians; hence, research conclusions exert a considerable influence on clinical practice and thinking about treatments. RCTs can, however, conceal errors in design, conduct, or analysis (1-3). Strong evidence indicates that the quality of numerous RCTs is less than optimal. The aim of this presentation is to focus on the weakness of a RCT concerning laparoscopic adhesiolysis and to show that there is no available evidence suggesting the abandon of this surgical procedure.

The RCT was published in the Lancet 2003 by Swank et al and its aim was to compare laparoscopic adhesiolysis to diagnostic laparoscopy in the relief of chronic abdominal pain caused by adhesions (4). Although the study design did not demonstrate that the 2 procedures were equivalent, the conclusion clearly stated that they were and that consequently, the former should be abandoned.

The study, based on a sample of 100 randomized patients, reported a reduced pain in 57% of patients who underwent laparoscopic adhesiolysis and 42% who underwent diagnostic laparoscopy. The observed difference between groups (15%) was not statistically significant (4,5). Yet the study conclusion strongly recommended abandoning laparoscopic adhesiolysis as a treatment for chronic pain due to adhesions.

This conclusion appears to be an overstatement. The sample size was calculated on the assumption "that there was a 25% reduction in pain attributable to placebo and that 60% of patients would obtain pain relief 1 year after laparoscopic adhesiolysis." The analysis was able to "detect a 35% reduction in pain after adhesiolysis" compared with diagnostic laparoscopy, with a power of 80%. Ultimately, the authors of the RCT observed an increased rate of pain relief in controls (42%) that they attributed to a placebo effect. The high rate of pain relief following diagnostic laparoscopy reduced the observed difference between groups to only 15%; consequently, the sample size and the statistical power became insufficient to show that this difference between the 2 procedures was statistically significant.

The Two One-Sided Tests Procedure is an appropriate tool used to estimate whether a lack of statistical difference reported by a trial is due to the equivalence between treatments or to a lack of statistical power (6). First it is necessary to assess the precision with which the observed difference estimates the true difference between 2 treatments that would be found if the entire population of similar patients were investigated. A range of values is provided based on the observed data consistent with the true value, and the  $(1-2\alpha)$  CI of these values is estimated, where  $\alpha$  is the risk of making a type I error (0.05). The upper and lower limits of the  $(1-2\alpha)$  CI are calculated using both the number of patients and the rate of the outcome in the 2 groups. Equivalency can be concluded if the limits of the true difference 90% CI fall entirely within a predetermined equivalency interval, which is usually  $(-10\%; +10\%)$  (6).

As regards the RCT comparing laparoscopic adhesiolysis and diagnostic laparoscopy, we assessed the precision of the observed absolute difference between the 2 groups (15%) and calculated the 90% CI of the true difference  $(-1\%; +31\%)$ . We compared this interval with the predetermined equivalency interval  $(-10\%; 10\%)$  of the absolute difference. The upper limit (31%) of the 90% CI of the absolute difference estimated above was not found to fall within the equivalency interval (Figure), rendering inadequate any conclusion concerning the equivalency of the 2 procedures. In addition, the post hoc power to detect a difference of 15% between the 2 laparoscopic procedures was estimated. It was found that the sample size of 100 patients produces a probability of 25% of stating that the difference of 15% between laparoscopic adhesiolysis and diagnostic laparoscopy is statistically significant.

If the authors of the RCT had taken these facts into account, they would have been faced with a choice of whether to make no conclusion about the relationship between the 2 procedures or to continue the recruitment of patients after recalculating sample size to an extent adequate to prove the statistically significant difference. The latter is not recommended because it may lead to an inflation of the probability of type I error ( $\alpha$ ). Instead, the trial concluded that the surgical procedures were equivalent, most certainly an overstatement.

Five of the patients in the adhesiolysis group (9.6%) had major complications after undergoing the surgical procedure (4). In 9 other patients (17.3%), adhesiolysis was incomplete. As the aim was to

perform an intention-to-treat study, regardless of complications and incomplete adhesiolysis, these patients were not excluded from the study. However, both complications and incomplete adhesiolysis might decrease the rate of patients with improved pain; this fact should be clearly discussed in the Discussion section, with the mention that only 83% of patients in the treatment group benefited from a complete procedure. In addition, a full set analysis including only patients who underwent a complete procedure would have been useful to evaluate more accurately the effect of the laparoscopic adhesiolysis itself even though the comparability of the groups would have no longer been guaranteed.

As the difference observed between the surgical procedures compared in the RCT (15%) is consistently inferior to that of previously published studies (7,8), we recommend further investigation to ensure that the observed difference accurately estimated the true one. Although this difference appears to be small, the RCT reported that 6 of 10 patients experienced chronic pain relief 1 year after laparoscopic adhesiolysis. As the rate of pain relief was 42% in the diagnostic procedure group and 57% in the adhesiolysis group, an absolute difference of 15% means that performing adhesiolysis instead of diagnostic laparoscopy allows the relieving of chronic pain in 36% of supplementary patients.

A further point involves the way that the effectiveness of laparoscopic adhesiolysis can in theory be modified by the use of antiadhesion products. These products affect the reformation of adhesions after adhesiolysis, as demonstrated in randomized controlled trials (9). When antiadhesion products are used during adhesiolysis procedures, the decrease in adhesion reformation may lead to an increase in the rate of patients experiencing postoperative pain relief. An RCT comparing laparoscopic adhesiolysis using antiadhesion products to diagnostic laparoscopy only might provide a different answer to the question about the management of pain due to intraabdominal adhesions.

Although laparoscopic adhesiolysis has been performed throughout the world and numerous surgical teams have reported that use of this procedure has provided their patients with significant relief of chronic pain, many surgeons have probably chosen to abandon it on the basis of 1 RCT. This situation underlines the necessity of careful evaluation of RCTs in cases where the null hypothesis is not rejected.

Most epidemiologists believe that the authors of RCTs should not base their conclusions solely on the absence of statistical significance when the trials have not been specifically designed to prove an equivalency (6). However, data provided by an RCT that failed to show an expected difference might be used to estimate the number of subjects required by a new RCT, allowing the results of both RCTs to be combined in a systematic review. The RCT of Swank et al is valuable in its reporting of new information regarding the relationship between adhesions, chronic pain, placebo effect, and adhesiolysis. However, its conclusions concerning the use of laparoscopic adhesiolysis in the surgical management of chronic pain should not, in our opinion, be considered definitive.

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