Langenbecks Arch Surg (2006) 391: 301–303
DOI 10.1007/s00423-006-0062-4

EDITORIAL

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Randomized controlled clinical trials—support but not substitute of decision-making in surgery

Received: 16 May 2006
Accepted: 16 May 2006
Published online: 8 June 2006

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In the 21st century, the health care system is unquestionably in disarray worldwide. Each voter in state elections decides his position on the primacy of the health of his population. In the year 300 B.C., the Greek anatomist and surgeon Herophilus stated: "To lose once health renders science zero, art inglorious, strength unavailing, more wealth useless and eloquence powerless" [1].

After the turn of the century, concern about cost, accessibility and quality of health care has substantially raised in industrial countries. Impressive advances in molecular biology and a better understanding of disease pathophysiology along with progress in medical technology and pharmaceutical developments as well as surgical techniques of preservation and replacement of tissue and organs rendered treatment more effective and available for a broad spectrum of diseases. However, increasing treatment options continue to result in increased choices and demands of patients to take advantage of the new health care avenues.

Nowadays, many surgical procedures are well-established and safely practiced today. Among these techniques, hernia repair, minimal invasive surgery, cancer surgery, resection of pancreas and liver or cardiac valve replacement are selected examples only. Organ transplantation evolved on the basis of observation, surgical intuition, experimental data and personal experience. Hence, these techniques contributed effectively to the high level of health care, but the results rarely meet the new criteria set by the system of evidence-based medicine.

In their recent search for perfectionism, predictive factors, and evidence for decision-making, surgeons have accepted the perspectives of evidence-based medicine and the necessity for randomized clinical trials. But here surgery, in its effort to achieve accuracy and perfection, is at a true crossroad: "They are fine in theory but difficult to put into practise" [2]. While we all recognize the objectives of randomized clinical trial as a "gold standard" of evidence-based medicine to answer important questions in surgery, there is an increasing feeling of discomfort due to the difficulty to perform a randomized controlled trial (RCT) in the context of clinical practice. In surgery, a randomized controlled clinical trial is by no means the best way to demonstrate the highest degree of evidence for a new operative technique or a new multimodal therapy. The mathematically and statistically verified statements from a study are only valid with regard to its own study population, and each extrapolation of the results to other populations is by analogy, which does not necessarily correspond to biological reality.

Randomized controlled trials in surgery are profoundly different from medical RCTs. While standardizing

medical trials in clinical practice is usually only a problem of founding, it is hard to standardize a surgical trial. In medical trials, patients receive standardized treatment by application of drugs at defined dosages and application time, to determine differences with placebo or with different dosages. Medical trials are independent of the skill of the physician. By contrast, in surgical trials, the quality of the treatment varies with the skill and experience of the surgeon performing the procedure. In performing a "standard" operation, the surgeon often encounters unexpected situations, which require variations of the standard techniques. Even in the presence of considerable experience, the operative performance between surgeons still varies considerably. Although we think that surgical practice is evidence-based, the proportion of surgical treatments supported by RCTs is much smaller than that found in general medicine. The surgical patient is an open adaptive system turning away from the homeostatic study state by the metabolic and immunological impact of the intervention or the effects of trauma.

First-degree evidence from a study is no more true than a second-degree evidence, just possibly more probable. Reducing medicine to statistical mathematics skips humanity and may lead to a loss of health care benefits for both the control and the treatment groups. Informed consent before randomization usually causes a double selection bias, as the patient must be informed about both procedures, the doctor in charge of information about the treatment protocol always has a preference for one of them. A double-blinded study to evaluate an operative technique is either not practicable at all or at least extremely demanding on patients and subsequently clinical researchers. It is impossible to remain unaware of an operative technique used when long-term results are the issue. In addition, a controlled clinical study in surgery imposes an ethical deficit, as the surgeon has to convince half of the study patients to accept the second best surgical procedure, which at least in comparison will be the worse of the two. Randomization is associated with weaknesses and faults. There are, of course, differences in the methodologies of data collection and especially in the heterogeneity of the populations.

In commenting a report on the discrepancy between meta-analysis and subsequent RCTs [3], Carson provided a critique in an editorial entitled: "Meta analysis or meta deception?" [4]. The report by Le Lorier [3] and associated by the University of Montreal showed that the outcomes of 12 large RCTs were not predicting accurately. According to this study, if there had been no subsequent RCTs, the meta-analysis would have led to an ineffective treatment in 32% and to the rejection of the useful treatment in 33% of the cases [3]. Randomized controlled surgical trials including outcome data in surgical oncology are time-consuming, long-lasting, and expensive. After finishing the RCT, the results have to be contrasted with the numbers of patients who finally did not enter or refuse to be included in the trial. The aging of the results of randomized clinical trials reduces the degree of evidence [5]. The legislation and governing administrations impose additional bureaucratic barriers to perform multi-institutional RCTs. The budget of the hospitals and of the health care providers are not in charge of the high financial requirements of multi-institutional controlled clinical trials and for outcome research. To catch up with the approval of the ethic committees of the institutions participating on the multi-institutional trial appears to be the most time-consuming step before starting a trial [6].

Surgical competence and intellectual honesty are absolute fundamental prerequisites for research in human beings. The success of operative therapy is only little determined by surgical talent. Today, it is unquestionable that success of a surgical procedure depends on 75% cognitive performance and only on 25% on surgical skills [7]. Surgical competence includes a mental attitude in making decisions before, during, and after operation. In an evaluation of a surgical practice and evidence-based surgery, Salomon concluded from his evaluation in 1995 that only 39% of surgical treatments could be subject to randomized controlled trials [8].

Today, we recognize that the world is not deterministic and stable but rather of evolving structure and function, full of reversible reactions. Instability and randomizations are rules, much beyond our capacity for prediction by the classical laws [9]. The human organism at the top of the evolutionary process is a most complex structure. By means of RCTs and outcomes research, medicine seeks the certainties of statistical data and the objectivity for better clinical practice. However, medicine and surgical practice continues to be a fundamental human endeavor. In contrast to applications from outcomes in industry dealing with inanimate objects, we deal with adaptive and dissipative complex organism of highly unpredictable behavior in medicine. RCTS, meta-analysis, and the outcome research provide very valuable information that should aid and support, but not substitute for clinical knowledge rationing sense and intuition in surgical decision-making confronting the uncertainty of individual circumstances. Surgeons should, without doubt, be stimulated towards performing RCT, as written in the new section named "Evidence-based Surgery" of the Journal of the American College of Surgeons: "These trials, if they are designed by surgeons, supported by competitive funds and obtained by peer review, provide evidence of safety and efficiency that is credible, useful, and not influenced by competing interests. Before adapting new techniques, surgeons need evidence that the techniques work, are safe for the patients, and are cost effective" [10]. Evidence-based medicine requires the integration of the best research evidence, with our clinical expertise and our patients' unique values and preferences [11].

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