Perspectives of Evidence-Based Surgery

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Key Words

Evidence-based medicine · Surgical research · Randomized controlled trials

Abstract

The assessment of the optimal treatment option based on best current knowledge is called evidence-based medicine (EBM). Considering the cost explosion in public health systems, EBM should also incorporate proper utilization of the restricted economical resources and should enforce quality assurance in medicine. It is imperative that surgeons realize that randomized controlled trials are applicable to the operative specialties in a large scale, and are necessary to provide evidence-based surgery. So far, only 3.4% of all publications in the leading surgical journals are randomized controlled trials. Furthermore, only 44.1% of the published surgical randomized controlled studies compared different surgical procedures, whereas 55.9% of the articles compared medical therapies in surgical patients. Evidence-based surgical therapy is essential for further development of a high-

quality surgical standard, which will also provide quality assurance in future surgical care. This article presents the definition of EBM and discusses specific problems involved in the introduction of its principles into the surgical discipline.

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Introduction

Over the last few decades, medicine has seen an information explosion with nearly uncontrollable quantities of information derived from scientific research. At the same time, medical practitioners faced the challenge of integrating this rapidly enlarging knowledge into a health care system with very limited financial resources. This process has led to an increasing recognition of the need for reliable evidence for treatment decisions, forcing the development of the Cochrane Collaboration. This international organization provides systematic reviews of trials of health care interventions. Evidence-based medicine (EBM) supplies different techniques to solve clinical questions and therefore transfers results out of clinical studies to numbers that can be used in surgical practice. Until now, only limited studies can be used for EBM purposes because of a lack in study design, analysis and presentation [1].

The following article is in part identical with the paper 'Chirurgisch-klinische Studien in der praktischen Durchführung', which was published in German in June 2000 by the same authors [1].

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Definition of EBM

Sackett et al. [2] have defined EBM as the integration of best research evidence with clinical expertise and patient values. Best research evidence is defined as clinically relevant data from basic sciences and especially quantitative clinical research. Together with the skills, past experience and knowledge of the surgeon and the unique preferences, concerns and expectations of each patient, an integrated clinical decision can be drawn for a specific problem [2].

Randomized controlled trials and their subsequent systematic reviews including meta-analyses represent the top of the hierarchy for finding evidence for medical routine and are therefore often defined as the 'reference standard' for clinical studies (table 1). Randomized controlled trials are the best method to compare the effectiveness of different therapeutic interventions and can have a direct impact on patient care. In order to provide all necessary information about external and internal validity and to reach the highest possible standard for reporting results of randomized controlled trials, the Consolidated Standards of Reporting Trials (CONSORT) criteria were established in 1996 and revised in 2001 [3, 4]. These CONSORT were created to improve the quality of research reports of randomized controlled trials and represent the most important standards of high-quality clinical research (table 2). The CONSORT statement found a rapid distribution into the scientific world and is now accepted as a general guideline for reporting of randomized controlled trials [5–7]. The wide support of the CONSORT checklist, encouraged by leading medical journals, has led to an improvement of reports of randomized controlled trials and thus to a facilitation of effective clinical decision making [8].

Introduction of EBM into Surgical Therapy

Randomized controlled trials are not appropriate for all surgical interventions, but should be seriously considered whenever a newly introduced intervention is being studied [9]. The first successful surgical randomized controlled studies were performed and presented in the 1960s, when Goligher et al. [10] randomized patients to different treatments for peptic ulcer disease (table 3).

Randomized controlled studies can provide valid results comparing treatment alternatives, and this available evidence should be considered for all therapeutic clinical decisions. Assessments of the integration of the principles

Table 1. Levels of evidence (from the web page of the NHS Research and Development – Center for Evidence-Based Medicine)

Level	Evidence obtained from
Ia	a systematic review of randomized controlled trials ¹
Ib	at least 1 individual randomized controlled trial
Ic	an all-or-none case series ²
IIa	a systematic review of cohort studies ¹
IIb	at least 1 individual cohort study ³
IIC	ecological studies or 'outcomes' research
IIIa	a systematic review of case-control studies
IIIb	an individual case-control study
IV	case series (and poor-quality cohort and case-control studies)
V	expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Produced by Phillips B., Ball C., Sackett D., Badenoch D., Straus S., Haynes B., Daves M. since November 1998. Obtained from the web page of the NHS Research and Development – Center for Evidence-Based Medicine (<http://cebm.jr2.ox.ac.uk/index.html>).

¹ Systematic reviews with homogeneity, i.e. free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.

² Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

³ Including low quality randomized controlled trials, e.g. with less than 80% follow-up rate.

of EBM into clinical practice were first performed in the field of general medicine. Ellis et al. [11] studied the treatment in a university-affiliated general medicine team and grouped the treatments in three categories: (1) evidence from randomized controlled trials; (2) convincing nonexperimental evidence, based on nonrandomized prospective trials and large retrospective studies, and (3) interventions without substantial evidence, based on case reports or small clinical studies.

Eighty-two percent of all medical treatments in this study were evidence based (53% group I, 29% group II). In a similar study about the efficacy of surgical practice, it was shown that general surgical practice is evidence based (95% group I and II), but only 25% of the patients received treatment based on randomized controlled trials and thereby presumed to be of the best available quality [12]. In a study about evidence-based general thoracic surgical practice, comparing 50 different types of thoracic surgical treatments, 14% were supported by group I, and 64% by group II level of evidence [13]. Therefore, these studies demonstrate that the majority of commonly per-

Table 2. Checklist for reporting a randomized trial – CONSORT (from Moher et al. [4])

Section and topic	Item	Descriptor
Title and abstract	1	how participants were allocated to interventions (e.g. ‘random allocation’, ‘randomized’, ‘randomly assigned’)
Introduction		
Background	2	scientific background and explanation of rationale
Methods		
Participants	3	eligibility criteria for participants and the settings and locations where the data were collected
Interventions	4	precise details of the interventions intended for each group and how and when they were actually administered
Objectives	5	specific objectives and hypotheses
Outcomes	6	clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors)
Sample size	7	how sample size was determined and, when applicable, explanation of any interim analyses and stopping rules
Randomization		
Sequence generation	8	method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification)
Allocation concealment	9	method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	10	who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
Blinding (masking)	11	whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment; if done, how the success of blinding was evaluated
Statistical methods	12	statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow	13	flow of participants through each stage (a diagram is strongly recommended); specifically, for each group report, the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe protocol deviations from study as planned, together with reasons
Recruitment	14	dates defining the periods of recruitment and follow-up
Baseline data	15	baseline demographic and clinical characteristics for each group
Numbers analyzed	16	number of participants (denominator) in each group included in each analysis and whether the analysis was by ‘intention-to-treat’; state the results in absolute numbers when feasible (e.g. 10/20, not 50%)
Outcomes and estimation	17	for each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence interval)
Ancillary analyses	18	address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory
Adverse events	19	all important adverse events or side effects in each intervention group
Comment		
Interpretation	20	interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes
Generalizability	21	generalizability (external validity) of the trial findings
Overall evidence	22	general interpretation of the results in the context of current evidence

formed surgical procedures and treatments are evidence based, but the fraction of evidence from randomized controlled trials is still smaller than in general medicine.

A recent analysis of the MEDLINE database (01/1966–12/2000) confirmed these numbers, as previously

Table 3. Introduction of the randomized controlled trial (RCT) into surgery (from Solomon and McLeod [15])

Decade	Progress
1900s	decades of intensive basic research not easily translated into clinically valid applications
1940s	first <i>medical</i> RCT
1960s	early successful <i>surgical</i> RCTs hospital ethics committees and the ethical debate about RCTs
1970s	reaffirmation of the scientific rigor of the RCT US Food and Drug Administration introduces mandate title 21, requiring RCTs before any drug can be released for sale
1980s	linear improvement in quality of <i>medical</i> RCTs little change in quality or quantity of <i>surgical</i> RCTs
1990s	reassessment of generalizability and reporting of <i>medical</i> RCTs
>2000	EBM

reported [1]. Of the 134,689 published randomized controlled trials, only 20,376 (15.1%) dealt with surgical contents (table 4). In a detailed analysis of all articles (n = 45,342) out of 5 leading surgical journals (*Annals of Surgery*, *Archives of Surgery*, *British Journal of Surgery*, *World Journal of Surgery*, *Surgery*), only 3.4% (n = 1,530) of all papers were randomized controlled trials (table 5). In further analysis, all randomized controlled trials out of these 5 surgical journals from the last decade (01/1991–12/2000) were categorized according to their main subject. This analysis revealed that 10.8% (n = 78) of the articles defined as randomized controlled trials (n = 728) did not fulfill the criteria or were mislabeled. To improve the quality of publishing randomized controlled trials, all journals should accept the conditions of the CONSORT guidelines [14].

In addition, 55.9% (n = 363) of all randomized controlled studies (n = 650) in the analyzed surgical journals dealt with medical therapies in surgical patients, such as analgesic, antibiotic or neo-/adjuvant cancer treatment concepts. Only the remaining 44.1% (n = 287) of the articles compared different surgical procedures or operative and conservative treatments (table 6).

Remarkably, over 80% of all published surgical studies are still case reports or single institutional small series

Table 4. Literature analysis (MEDLINE) 1966–2000¹

Clinical trials (total) ²	n = 289,807	100.0%		
RCT ³	n = 134,689	46.5%		100.0%
RCT, surgical ⁴	n = 20,376	–		15.1%
	RCT ³	RCT surgical ⁴	RCT surgical double-blind ⁵	RCT surgical multicentric ⁶
1966–1970	1,008	265	14	0
1971–1975	2,389	243	14	0
1976–1980	6,526	878	176	0
1981–1985	12,508	1,847	381	0
1986–1990	23,506	3,514	715	185
1991–1995	41,835	6,242	1,451	796
1996–2000	46,917	7,576	1,924	936
1966–2000	134,689	20,376	4,675	1,861

RCT = Randomized controlled trials.
¹ MEDLINE analysis at <http://www.ncbi.nlm.nih.gov> (01-30-2001).
² ‘Clinical trial’.
³ ‘Randomized controlled trial’.
⁴ ‘Randomized controlled trial’ + all fields = ‘surgery’.
⁵ ‘Randomized controlled trial’ + all fields = ‘surgery’ + ‘double-blind OR double-blinded’.
⁶ ‘Randomized controlled trial AND multicenter study’ + all fields = ‘surgery’.

Table 5. Randomized controlled trials in leading scientific surgical journals (MEDLINE 1966–2000)

Journal	RCT								1966–2000	
	1966–1970	1971–1975	1976–1980	1981–1985	1986–1990	1991–1995	1996–2000	1966–2000	articles	RCT, %
Ann Surg	5	20	38	33	60	75	89	320	8,070	4.0
Arch Surg	8	16	20	28	46	61	53	232	9,914	2.3
Br J Surg	18	45	89	106	110	162	126	656	13,475	4.8
World J Surg ¹	–	–	5	18	20	40	39	122	3,566	3.4
Surgery	2	4	22	50	39	45	38	200	10,317	1.9
Total	33	85	174	235	275	383	345	1,530	45,342	3.4

¹ First issue 1977.

[15]. Despite the fact that they are cheap and easy to perform, they generate only a low level of evidence about the efficacy of different treatment options.

Specific Problems of Randomized Controlled Studies in Surgery

The small number of randomized controlled trials in surgery has been criticized for years. At the same time, the implementation of EBM into the field of surgery faces some specific problems. Compared with randomized controlled studies in internal medicine, which were originally developed to compare two different drug protocols, there are some unique pitfalls and sources of bias in surgical randomized trials.

First, randomized, double-blinded and placebo-controlled trials are the only way to not only control the biased investigator but also the placebo effects. Sham operations have been performed, i.e. internal mammary artery ligation was reported as providing relief for pain in angina pectoris, but the trials were discontinued when, in comparison, a sham operation showed a similar success rate [16, 17]. In recent years, the use of placebo operations and the substantial ethical concerns about sham surgery in particular have been discussed anew. In this presently ongoing discussion, two recently published studies using placebo surgery should be used as prime examples. Freeman et al. [18] used placebo surgery for a cellular-based therapy of Parkinson's disease and provided a basis for a new discussion about ethical aspects of sham operations [18–20]. Moseley et al. [21] could prove that there is no difference in pain relief after arthroscopic or placebo surgery for osteoarthritis of the knee. This led to a first version of ethical guidelines on the use of surgical placebo

Table 6. Detailed analysis of surgical randomized controlled trials (MEDLINE 1991–2000)

Subject	Number
RCT	650 (100.0%)
RCT, Medical ¹	363 (55.9%)
RCT, Surgical ²	287 (44.1%)
op vs. cons ³	20 (7.0%)
op vs. op ⁴	227 (79.1%)
others	40 (13.9%)

op = Operation; cons = conservation.

¹ Comparison of analgesic, anesthetic, antibiotic or adjuvant cancer treatment.

² Comparison of surgical procedures.

³ Comparison of surgical and conservation treatment regimes.

⁴ Comparison of different surgical procedures.

controls in the design of surgical trials [22]. If no sham operation is performed, investigators should be aware of bias through the placebo effect of all surgical procedures [23].

Furthermore, it remains difficult to standardize the tested surgical procedures because the procedures will evolve continuously and because the complications decrease as surgeons overcome the learning curve and gain increasing experience with a new procedure. The results vary with the individual surgeon because the participating operators vary in their surgical skill and experience (table 7). All participating surgeons should undergo appropriate training before the start of a randomized controlled trial to reach a certain minimum of standardization [24, 25].

Table 7. Differences between randomized trials for drugs and surgical procedures (from Bonchek [24])

Drug	Surgical procedure
Unchanging compound	Evolves continuously
Complications increase with use	Complications decrease with use
Results unrelated to physicians' skill	Results vary with operator
Placebo usually available	No placebo
Crossover rare	Crossover common

Yet, another source of bias in surgical trials is the blinding of patients and surgeons. Unfortunately, it is not always possible to blind all participants as effectively shown in the exemplary cited trial of Majeed et al. [26], where the same wound dressing was used for patients who underwent laparoscopic and small incision cholecystectomy. Especially if the primary outcome criteria are not recurrence of disease or even death, but variable symptoms or quality of life measurements, a lack of blinding procedures may bias the results of these trials. This bias can be minimized by assessment of the outcome of the procedure by independent investigators.

Furthermore, through overly restrictive exclusion criteria, the group of patients eligible for participation in a randomized controlled trial may comprise a misrepresentation of the typical patient population [27]. This can lead to a lack of generalizability, i.e. less external validity of the results. Although nonrandomized studies have a less selective recruitment process, their results are influenced through bias in the selection of treatment options by the preferences of the participating physicians. In addition, there is still a large inexperience in surgeons about clinical epidemiology and designing and performing a randomized controlled trial [28, 29].

Finally, the financial support for surgical clinical research is limited and there seems to be a lack of interest in funding of surgical trials [15]. Commercial funding for comparison of different surgical techniques is often not available, whereas quite all medical trials are supported by pharmaceutical companies [30, 31]. Therefore, the access to institutional financial resources should be simplified for clinical surgical research, and the lack of interest in funding surgical randomized trials should be battled in the near future.

Implementation of Results from Surgical Randomized Controlled Trials into Day-to-Day Surgical Decision Making

After improving the quality and quantity of randomized controlled trials in surgery, the next logical step must be a feasible transfer and the best possible implementation of the results into the day-to-day surgical decision making. In times of innumerable published papers, even in special fields of medicine every year, it is important for a physician to stay informed about the most recent developments in clinical medicine. The best way to assimilate all findings of evidence-based trials about a specific intervention is a systematic review [32]. The leading institution performing systematic reviews of published randomized controlled trials is the Cochrane Collaboration [33]. This international organization has the goal to improve the quality of health care by 'preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of health care interventions' (www.cochrane.org). By presenting these systematic reviews in the 'Cochrane Database of Systematic Reviews' in the Internet and quarterly in electronic format, there is a great accessibility of critical summaries of results of randomized controlled trials. Hence, the Cochrane Collaboration became the platform to find guidance for decision making in the day-to-day patient care based on the best evidence.

Conclusion

There is still no increase in well-designed clinical surgical studies that could form a rigorous evidence based on newly introduced procedures, and there are many established procedures supported only by nonexperimental evidence. To accurately assess the evidence for the clinical utility of these procedures, critical analysis is required [34]. Randomized controlled surgical trials are the essential cornerstone of this analysis.

However, randomized controlled trials may provide only low external validity secondly to several factors, including unrepresentative participating surgeons with particular interest in the topic, atypical settings and patients and the difficulty in applying trial results across surgical patient populations. Nevertheless, the randomized controlled trial to compare surgical procedures remains the best and only method creating solid evidence and is the most effective source to identify effects of therapeutic interventions on treatment outcomes. Despite the obvious difficulties in the realization of randomized con-

trolled trials in surgery, there should be an increase in randomized controlled surgical studies to develop and preserve high-quality surgical care in the future.

The surgical world has to work against accusations such as the following from the editor of *Lancet* [35]: 'Only when the quality of publications in the surgical literature has improved will surgeons reasonably be able to rebut the charge that as much as half of the research they undertake is misconceived.'

Hopefully, in the future, the following quote from Sackett [36], one of the leading forces of the EBM move-

ment, will apply to the clinical and research aspects of surgical care: 'As physicians, whether serving individual patients or populations, we always have sought to base our decisions and actions on the best possible evidence.' The highest available level of evidence, namely the randomized controlled trial, should support in particular surgical treatment decisions because they are often definite and irreversible. We have created a new center at our institution that is dedicated to quantitative clinical research and will continue to conduct randomized controlled trials in surgery.

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