Randomised Trials in Surgery: The Burden of Evidence

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Abstract: A randomised controlled trial (RCT) is considered the hierarchical peak of evidence-based medicine and a general demand for any result to be evaluated by RCTs has evolved. Yet, many advances in operative surgery do not result from RCTs and many controversies remain without an RCT being conducted. A randomised comparison of laparoscopic versus open liver resection has recently been called for. Using such a trial and others as examples, we examine the limitations of randomised design in skill-dependant interventions. Surgical procedures are skill-dependant, constantly developing, irreversible and traumatising. Additionally, placebo control is usually unethical and adequate blinding difficult or impossible to accomplish. Under these circumstances, surgeon and patient participation will be problematic and the resulting data will tend to have low external validity. While some of these obstacles can be modified, others will remain. Non-randomised, prospective cohort comparison has other weaknesses, but may add complementary data with good external validity. An alternative hierarchy of evidence is warranted in this field.

Keywords: Randomised Controlled Trial/RCT/Surgery/Skill dependent interventions/Learning curve/Cohort study/Evidence Based Medicine.

INTRODUCTION

A recently presented single-centre series of laparoscopically performed liver resections (LapLR) has shown reassuring results compared to a matched historical control group that underwent open liver resections (OpenLR) in the same centre [1]. There were fewer blood transfusions given and less need for opiates postoperatively in the laparoscopic group, as well as shorter time to oral diet and shorter length-of-stay [1]. The authors conclude that a randomised controlled trial (RCT) comparing LapLR to OpenLR is necessary to prove the potential benefits shown in their series.

Randomised controlled trials have clarified a number of important issues in surgery for primary or secondary malignancies. A large number of RCTs have compared laparoscopic to open colorectal surgery for cancer and several systematic reviews and meta-analyses have been conducted [2-6]. In many instances patient recruitment was slow and total costs to the communities are unknown. While level-1 evidence [7] is now available, most trials had shortcomings directly related to their design. Lack of blinding is the most obvious, but also insufficiently standardised interventions or lack of general applicability as a consequence of surgeons being either insufficiently trained; or too exclusive and few. These shortcomings were predictable. For comparison, an RCT recently established the superiority of an antecolic to a retrocolic gastrojejunostomy in pylorus preserving pancreateoduodenectomies [8].

These situations differ in some important aspects that have a direct bearing on the appropriateness or quality of an RCT. In this paper, we discuss whether an effort to perform an RCT, and hence achieve traditional level-1 evidence [7], is advisable for all surgical interventions.

The Randomised Controlled Trial

A well conducted, carefully controlled and adequately blinded RCT constitutes the highest level of evidence in the Evidence Based Medicine (EBM) hierarchy [7]. While non-randomised comparison of prospective cohort series may yield important data, one can only adjust for factors that are already known to influence the outcome. Adjusted for these factors, an association between intervention (exposure) and outcome may be shown - or not shown.

Randomisation is the one design that can adjust for all factors, known and unknown, and hence the best design to establish causal relationship between exposure and outcome.

Randomisation is one of the most important methodological principles in medicine. It was first used in its present form in the Medical Research Council’s trial showing the effect of streptomycin in severe tuberculosis in the UK following the Second World War, and published in 1948 [9-11]. Streptomycin had just been made available, supply was limited and the unpredictable natural course of tuberculosis was a confounder well recognized at the time [9-11]. This seminal trial very clearly illustrates the optimal setting for a successful RCT: to test an intervention that is novel (no one is prejudiced for, or against it), standardised (requires no technical skill to deliver), stable (unchanged properties during trial period) and easily tolerated (non-traumatising and...
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reversible), with an available placebo and where double (or actually triple) blinding is feasible. Read: a new drug!

The optimal target disease is, like tuberculosis, one where spontaneous improvements are probable and cannot confidently be attributed to intervention. A displaced fracture is the reversed situation: an anatomically healed limb after repositioning and plaster cast is not due to spontaneous improvement but a result of the intervention. We do not need an RCT to convince us and this is recognized in the EBM hierarchy as level 1c-evidence: “all-or-none” or “dramatic effect”.

The blinded testing of a new drug against an existing one, or against placebo, is what earned the RCT its impressive track-record and hence its position at the top of the EBM hierarchy. Evaluating a novel or modified surgical intervention is a different situation. Most obviously, placebo control (sham operations in animal research) is usually unethical and successful blinding difficult to accomplish. Less obvious, but equally important: most surgical procedures are skill-dependant and hence have a learning-curve. This challenges standardisation and implies that the timing of a trial (relatively to the learning curve) will affect patient accrual and the validity of the results.

challenges to RCTs in surgery
An RCT should not be attempted if it is unnecessary, inappropriate, inadequate or impossible [12], and this could be the case in 60% of surgical treatment questions [13]. It may also apply to Ito and co-workers’ call for an RCT to compare LapLR with OpenLR. One may argue that an explanatory trial is unnecessary and a pragmatic RCT is inadequate. Both designs might prove impossible as they will probably accrue patients very slowly.

A trial cannot answer all questions pertaining to a new intervention under scrutiny. It will be designed either to evaluate causality, i.e. whether the intervention may cause the desired outcome under optimal circumstances; or to evaluate feasibility, i.e. whether this is achievable in a general context and hence the effect of changing clinical practice “across the nation”. In the first instance, one gets an explanatory-, expert-, or efficacy trial dependant on adequate standardisation and absence of bias to ensure optimal internal validity. In the latter case, one gets a pragmatic-, feasibility-, or effectiveness trial, dependant on patients and surgeons being representative of the general community to produce generalizability, also referred to as external validity.

One design is not more important than the other; they produce reciprocally complementing data, and most clinical challenges need to have both issues assessed. It is the first issue however, that of causality, which has generally received most focus. And it is the question of causal relationship that an RCT is the supreme tool to answer. The success of high-quality RCTs to ascertain causal relationships has to some extent overshadowed the question of whether it transfers into a large or small treatment effect when generally applied [14].

This applies to all trials, but RCTs are more vulnerable because problems with standardisation and timing negatively affect patient accrual. And slow accrual is an Achilles’ heel of this design [15]. The reason for this is inherent in the method: experimentation, i.e. randomisation, implies that patients and surgeons cannot decide on treatment from preference, but must accept a random choice between options considered reasonably equal. If patients have a strong preference for one of the two, they are considered to lack equipoise, and will be difficult to recruit [15]. Surgeons may equally lack equipoise and be reluctant to participate [15]. If causality is the prime issue, an explanatory RCT should always be attempted. If feasibility of a nationwide change of practice is the aim, optimal generalizability must be sought and hence a design that ensures wide patient and surgeon recruitment. We have every reason to believe that only a very small minority of eligible patients participate in randomised trials [16].

Most trials are not absolutely explanatory or pragmatic; there is a balance between the two, but the nature of skill-dependant interventions with a learning curve implies that you cannot boost internal validity – which is generally the main priority – without losing external validity, and vice versa. This represents a fundamental difference from a drug-trial where standardisation and blinding is effortless and complete.

Randomisation is inappropriate if the target outcome (event) rate is extremely low, e.g. for certain rare complications to surgery, as this will necessitate a prohibitive number of patients to achieve statistical significance [17]. The difference in 5 year-survival after LapLR or OpenLR for liver metastasis is believed to be none or very small. An RCT will therefore require a very large number of patients and probably need more than 10 years to acquire conclusive statistical power [18]. Showing reductions by 50% for complications like bile leakage, liver failure or operative mortality is equally prohibitive, requiring 1300 to 6200 patients in each arm with a power of 0.90 and a two-tailed test [17]. If smaller, but clinically relevant effects are targeted, the increase in numbers needed will be exponential.

Learning-curve and the Timing of Trials
The technical success of any RCT depends on participants not having too strong preference (i.e. the presence of equipoise) for one of the alternatives as this will bar recruitment [15]. Lack of surgeon- and/or patient equipoise has halted trials where academical equipoise was considered to be present [19,20].

When an intervention has a substantial learning curve, yet another factor is introduced: an intervention performed at the beginning of the curve is different from one performed at the plateau-phase at a later time-point [21,22]. This adversely affects standardisation, but also equipoise changes over time as a novel technique becomes gradually refined and generally accepted in both the medical and the general society. Hence, deciding on the correct time to evaluate a novel intervention is difficult and affects both standardisation and patient accrual. Sufficient expertise must be achieved to perform a standardised procedure, but surgeon and patient equipoise must still be present [23]. As Buxton has observed on the timing of evaluation: “It’s always too early until, unfortunately, it’s suddenly too late” [24].
The absence of an optimal time-window for a trial (or one already lost) and a predictable lack of patient and surgeon equipoise could detrimentally slow patient accrual in a proposed RCT on laparoscopic versus open left lateral liver resections. The world-wide introduction of laparoscopic cholecystectomies without any RCTs is the most conspicuous example and illustrates the loss of a time-window, patient- and surgeon preference and also market forces at work.

Validity

The timing of a trial with a learning-curve also affects validity. Internal validity is reduced if the procedure under evaluation is not standardised within the trial. This will happen both as participating surgeons will position themselves differently on the learning-curve, but also because a complex procedure will be developed and refined as each surgeon moves onwards along the curve [25]. Standardisation can be increased through vigorous teaching and control [26], but it will always be a challenge in operative technique trials as improvisation is generally encouraged in surgery [27], and to some degree even a necessity for innovation [28]. External validity is reduced if the results have a low generalizability, as will be the case if only expert surgeons far out on the curve participate. Any time-point chosen for the trial will have its advantages and its problems, mostly in the balance between internal and external validity. In skill-dependant procedures with a learning curve, there will always be a trade-off between the two, and the choice will also affect patient accrual.

Narrow Inclusion Criteria

The degree to which a trial is pragmatic versus explanatory is influenced by the timing of the trial and choice of participants and can hence be manipulated. A very homogeneous sample of patients, e.g. without any co-morbidity, may be selected to boost standardisation in an explanatory trial, but this will automatically reduce external validity. Major, right-sided liver resections are considered challenging to perform laparoscopically and participating surgeons (and patients) are likely to be chosen with utmost care. Hence, neither patients nor surgeons will be representative. Data from patients that were for some reasons not invited, or who declined, are lost and these patients cannot be assumed to be similar to those participating [12]. It is important to acknowledge this as it is an inherent feature in experimentation that always results in a loss of external validity.

Bias

Bias is the conscious or subconscious skewing of information. Selection-bias occurs when a patient sample, believed to be representative, proves not to be. It is prevented by randomisation. Outcome-assessor bias acknowledges that any outcome assessor in a trial is prone to be influenced by pre-trial perceptions and colleagues’ preferences. This may affect interpretation of all data that are not completely objective, and few are. The only way to prevent this is blinding. While not impossible [29], blinding of a surgical access-techniques might be cumbersome and incomplete. Furthermore, blinding is not a magic bullet: it only prevents assessor bias. Two RCTs on laparoscopic versus open surgery (cholecystectomies and colonic resections) that are widely cited as examples of successful blinding, both concluded that laparoscopy did not result in shorter length-of-stay [29,30]. While previous trials with historical controls clearly had overestimated the benefit, few would subscribe to the conclusions of these RCTs today.

Is There an Alternative to RCT?

The difficulties in performing robust RCTs evaluating craft-based interventions are many and not unique to surgery. What makes surgery an area of concern in this respect is that “many of these challenges coincide” [23]. In the latest two decades, the influence from EBM has been strong and important. It is reasonably agreed that the methodological quality of trials in operative surgery tends to be low in too many instances [28]. It is important, however, that the virtues of the RCT in ideal conditions do not overshadow the fact that there are situations where an RCT might not be the best alternative. In these cases we might instead plan for high-quality, non-randomised, protocol-driven prospective comparison [31-34]. For the sake of our patients, we should use all data from our “biased surgical laboratory”. It should suffice to point to the overwhelming success of for instance congenital heart surgery. Without RCTs, the surgical mortality for these complex procedures have been reduced from prohibitive to almost nil [35,36], based almost exclusively on categorising and shearing observational data. Non-randomised cohort comparison will generally ensure an almost complete participation as interventions are provided according to preference. While the important issue of an unknown confounder and hence a risk of selection bias cannot be overstated, these observations will nevertheless provide the real-world effects of surgeons putting their craft of best performance into each technique. A recent systematic comparison found meta-analysis of well-designed non-randomised trials to be as good as RCTs [37].

The quality of observational (non-randomised) trials will improve with the adoption of core elements of RCT design like a publicly registered protocol, pre-defined entry criteria, rigid prospective inclusion, intention-to-treat analysis, complete follow-up etc. [38]. Good observational data will not obviate the need for an RCT, but provide robust and complimentary data alongside those of a possible future RCT [38].

Core elements of trial design that must be considered are shown in Fig. (1).

CONCLUSION

A well conducted RCT remains the most powerful tool to assess an intervention. It should always be considered, but there are situations where it is not particularly well suited. While surgical innovation cannot proceed without rigorous testing, evaluation and control, this must be performed with designs and against standards that acknowledge the challenges posed by key features of operative surgery [39,40]. These issues need not be irreconcilable. A mandatory participation in a national prospective database with patient characteristics and outcome for any major innovation in sur-
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**Fig. (1).** Suggested flow-chart for planning process taking into consideration the balance between causality and feasibility.

The technical technique may be proposed. Such a database should be financed and controlled by the health authorities for a limited number of years and may prove to new surgical procedures what the RCT has become in drug trials. For skill-dependent evidence and to a circular model as suggested by Walach change of paradigm, from today’s hierarchical pyramid of number of years and may prove to new surgical procedures financed and controlled by the health authorities for a limited scope.

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**CONFLICTS OF INTEREST**

The author(s) confirm that this article content has no conflict of interest.

**AUTHORS’ CONTRIBUTIONS**

KL: Conceived the general idea, wrote the first draft and outline of the argument and participated in redrafting and rewriting.

AH and TM: Critically read and revised the manuscript and added scientific and argumentative content.

All authors read and approved the final manuscript.

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