The Quality of Randomized Clinical Trials in the Field of Surgery: Studies on Laparoscopic versus Open Appendectomy as an Example

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Key Words

Laparoscopic appendectomy · Open appendectomy · CONSORT

Abstract

Background: The field of surgery undergoes rapid renewal and introduction of surgical techniques and instruments. Thus, the quality of the randomized clinical trials in this field should be evaluated. We assessed the quality of randomized trials comparing laparoscopic versus open appendectomy as a model. **Method:** Using MEDLINE and EMBASE, 42 first-time published randomized clinical trials in the English language met the inclusion criteria. Factors related to the methodological quality, e.g. blinding, sample size calculation and intention-to-treat analysis, were reviewed. **Results:** Method of random number generation was described in only 15 (36%) of the studies, i.e., it was not clear if the remaining two thirds of the studies were actually randomized or not. Although not using blocking, the trials often reported similar sample size in the intervention and control groups. Proper concealment of the allocation status was reported in almost half of the studies. None of the trials was judged to use proper double-blinding measures. Sample size calculation was present in one of five trials and half of the studies performed analysis according to intention-to-treat. **Conclusions:** It seems that surgical trials do not always follow the basic methodological guidelines to maintain the high quality of

randomized clinical trials. Compliance with the CONSORT statement and transparency in result reporting is strongly recommended to improve the quality of randomized trials in the field of surgery.

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Introduction

Randomized clinical trials (RCTs) are the gold standard in evidence-based medicine. To maintain the high quality, there are several guidelines that must be followed [1]. The field of surgery undergoes rapid introduction and renewal of surgical techniques and instruments. Thus, it is important that the efficacy and safety of these techniques and instruments are properly evaluated. Acute appendicitis is a common indication of abdominal surgery with a life-time incidence between 7 and 9% [2]. In the early 1980s, Semm [3] introduced a laparoscopic technique for appendectomy and since then, this approach has gained popularity at the expense of open appendectomy. The possible benefits of laparoscopic appendectomy over open appendectomy have been studied in numerous RCTs.

We used this area of research as a model to review the quality of RCTs in the field of surgery and to discuss how the study design should be improved to ensure the high standard of randomized controlled trials.

Methods

Inclusion Criteria

RCTs that compared laparoscopic and open appendectomy between 1983 (first report on laparoscopic appendectomy [3]) and September 2008, irrespective of the study outcome, were included in this paper. Only the first-time published original articles in the English language were considered eligible.

Sources of Data

Using MEDLINE and EMBASE, a literature search was carried out to identify relevant papers. Search terms used were [open] + [laparosc*] + [appendectomy] + [random*].

Identification of Relevant Papers

On the 25th of September 2008, 110 citations were available, 49 of which were RCTs comparing open and laparoscopic appendectomy. Of these, 7 were omitted (3 were not accessible through the internet network of the university library of Karolinska Institutet and no contact information was available to contact the first authors in order to receive reprints of the papers [4–6]; four other studies used the material of an already published RCT [7–10]). As a result, 42 [11–52] papers remained for inclusion in this study.

Data Extraction

Trial characteristics and factors related to the trial quality, namely randomization procedure (method of random number generation, blocking, concealment, blinding), sample size calculation and intention-to-treat (ITT) analysis, were extracted. Jadad score [53] was used to evaluate the overall quality of the included papers.

Results

Baseline Characteristics

Baseline characteristics of the included trials are shown in table 1. Almost half of the studies were conducted after the year 2000 ($n = 19$, 45%). Europe was the most frequent study setting ($n = 23$, 55%). The median sample size was 90 (11–583). Four studies included only males [11, 12, 18, 44], four included premenopausal women only [19, 21, 26, 39] and five included exclusively children [17, 22, 24, 25, 43]. No trial reported registration of the trial protocol.

Randomization Procedure

Different parameters related to the quality of the trials are summarized in table 2. The method of random number generation was clearly described in 15 (36%) of the RCTs. Of these, 7 (46%) used computer-generated randomization, 4 (26%) random number tables, 1 (7%) 'a master list with 10 repeating random numbers sequence', 1 (7%) coin toss, 1 (7%) admission code and 1 (7%) instrumental availability as the method of random number

generation. The remaining 27 (64%) did not mention the method of random number generation.

Six (14%) studies used blocking, all of which stated the size of the block (ranging from 4 to 52). In one study the size of the block alternated between 4 and 12. The study with a block size of 52 used one single block only. One (2%) study reported the use of stratified randomization based on age and gender in combination with blocking. Although not specifying the type of randomization, the remaining 36 (86%) most likely used simple randomization. The median difference between the sample size in the intervention and control group was 6% (0–167%). The study with a sample size difference of 167% had a pre-defined almost 2:1 randomization ratio. Five other studies only presented the number of participants in each group after post-entry exclusion of individuals from the study. However, the median difference in sample size did not change substantially when excluding these six trials (5% (0–47%)). The difference between the size of the intervention and control group in studies using blocking was 4% (0–13%). For studies with simple randomization excluding the trial with the 2:1 ratio, this figure was 8% (0–47%).

In 18 (43%) trials, there was no information about the presence of measures to conceal the allocation before randomization. Twenty studies (48%) provided this information. One (5%) study used central randomization, another (5%) used sealed, opaque, numbered envelopes, 2 (10%) had sealed, opaque envelopes without information about numbering of the envelopes, 12 (60%) reported sealed envelopes, 1 (5%) opaque envelopes, 2 (10%) stated 'envelopes' only and finally, 1 (5%) study used 'sealed assignment cards'. The remaining four (9%) trials did not have any allocation concealment (the allocation was based on coin toss, availability of the instruments for laparoscopic appendectomy, admission codes of the patients and which surgeon attending the call).

Seven (17%) RCTs reported blinding. Three used a wound dressing that covered the whole abdomen, 3 used wound dressings to resemble the incisional wounds after laparoscopic and open appendectomy, and 1 study reported the use of identical wound dressings, but did not specify if these were covering the entire abdomen or resembled the incisional wounds. The 3 first studies claimed to be double-blinded.

Statistical Analysis

Sample size calculation was performed in 9 (21%) studies and in all of them, the estimated number of participants was reached. The analyses were performed ac-

Table 1. Baseline characteristics of the included studies

Author	Publication year	Study setting	Number of patients	Age		Participants
				O	L	
Ricca [11]	2007	USA	52	31 ^a		overweight men
Tzovaras [12]	2007	Greece	78 ^b	22 (14–65)	26 (15–68)	men
Katkhouda [13]	2005	USA	268	28 (17–63)	29 (18–71)	>15 years
Olmi [14]	2005	Italy	252	23 (5–80)	25 (6–86)	all ages
Almagor [15]	2005	Israel	37	28 ± 13	35 ± 16	histologically confirmed diagnosis of AA
Moberg [16]	2005	Sweden	219	31 (15–83)	31 (15–71)	>15 years, randomized after laparoscopy
Oka [17]	2004	USA	517	11 (2–17)	11 (2–20)	children
Ignacio [18]	2004	USA	52	27 ± 9	28 ± 7	men
van Dalen [19]	2003	New Zealand	63	22 (16–51)	24 (16–45)	premenopausal women
Milewczyk [20]	2003	Poland	200	28 ^b	26	both gender
Al-Mulhim [21]	2002	Saudi Arabia	60	26 (14–42)	23 (14–35)	premenopausal women
Little [22]	2002	USA	129	10 (1–15)	12 (1–16)	children
Huang ^c [23]	2001	Taiwan	75	34 ± 12	32 ± 25	>12 years
Lavonius [24]	2001	Finland	43	12 (8–15)	12 (7–15)	children
Lintula [25]	2001	Finland	73	12 ± 3	11 ± 3	children
Larsson [26]	2001	Sweden	110	25 ± 8	25 ± 8	premenopausal women
Long [27]	2001	USA	200	not stated		>15 years
Pedersen [28]	2001	Denmark	583	27 (18–40) ^d	26 (18–40)	all ages
Nordentoft [29]	2000	Denmark	30	not stated		>18 years
Özmen [30]	1999	Turkey	70	28 (15–65)	23 (15–56)	all with suspected AA
Perner [31]	1999	Denmark	11	33 (18–53) ^e		not specified
Hellberg [32]	1999	Sweden	523	not stated		>15 years
Heikkinen [33]	1998	Finland	40	37 (15–59)	34 (15–72)	>14 years
Klingler [34]	1998	Austria	169	24 ^a	30	>14 years, <70 years
Macarulla [35]	1997	Spain	210	29 ± 15	27 ± 13	>12 years
Minne [36]	1997	USA	57	31 (14–55) ^d	31 (12–69)	≥12 years
Reiertsen [37]	1997	Norway	108	33 (18–59)	34 (18–56)	18–60 years
Kazemier [38]	1997	Netherlands	201	34 ± 18	31 ± 14	>11 years
Laine [39]	1997	Finland	50	28 (16–40)	27 (18–35)	premenopausal women
Hart [40]	1996	Canada	81	33 ± 17	29 ± 12	suspected AA
Mutter [41]	1996	France	100	27 (15–62)	29 (15–65)	≥15 years
Williams [42]	1996	USA	37	26 (10–45)	28 (14–43)	not specified
Lejus [43]	1996	France	63	11 ± 2	11 ± 2	children
Cox [44]	1996	Australia	64	25 (18–84)	25 (18–75)	males ≥18 years
Hansen [45]	1996	Australia	158	22 (13–66)	25 (14–89)	>12 years
Martin [46]	1995	USA	169	29 ^a	27	>14 years
Ortega [47]	1995	USA	253	25 ^a	26	only adults
Lujan [48]	1994	Spain	200	26 (7–70)	30 (7–84)	no exclusions
Frazer [49]	1994	USA	75	30 (10–68)	28 (10–70)	>9 years
Kum [50]	1993	Singapore	137	31 ± 7	33 ± 5	>12 years
Tate [51]	1993	Hong Kong	140	33 (29–37)	31 (28–35)	suspected AA
Attwood [52]	1992	Ireland	62	27 (15–67)	21 (12–39)	suspected AA

^a Distribution unclear; ^b only males (n = 78) randomized, females treated with laparoscopy only; ^c including a third arm with needlescopic appendectomy; ^d median and interquartile range; ^e total number of complications. O = Open appendectomy; L = laparoscopic appendectomy.

Table 2. Qualitative measures reported in RCTs comparing laparoscopic and open appendectomy

Author	Method for random number generation	Blocking	Concealment	Blinding	ITT	Power analysis
Ricca [11]	unclear	unclear	unclear	measures taken	unclear	performed, number reached
Tzovaras [12]	unclear	unclear	unclear	unclear	yes	not stated
Katkhouda [13]	computer-generated	unclear	appropriate	measures taken	no	performed, number reached
Olmi [14]	admission code of the patients	unclear	inappropriate	unclear	unclear	not stated
Almagor [15]	unclear	unclear	unclear	unclear	yes	not stated
Moberg [16]	computer-generated	blocking	appropriate	measures taken	yes	performed, number reached
Oka [17]	surgeon attending the call	unclear	inappropriate	unclear	yes	performed, number reached
Ignacio [18]	unclear	blocking	unclear	measures taken	unclear	performed, number reached
van Dalen [19]	unclear	unclear	appropriate	unclear	yes	not stated
Milewczyk [20]	random number tables	unclear	unclear	unclear	yes	not stated
Al-Mulhim [21]	unclear	unclear	appropriate	unclear	unclear	not stated
Little [22]	unclear	unclear	appropriate	unclear	unclear	not stated
Huang [23]	unclear	unclear	unclear	unclear	no	not stated
Lavonius [24]	unclear	unclear	appropriate	unclear	unclear	not stated
Lintula [25]	unclear	unclear	appropriate	measures taken	yes	not stated
Larsson [26]	unclear	blocking	appropriate	unclear	no	not stated
Long [27]	random number tables	blocking	appropriate	unclear	yes	performed, number reached
Pedersen [28]	computer-generated	unclear	appropriate	unclear	no	performed, number reached
Nordentoft [29]	unclear	unclear	unclear	unclear	no	not stated
Özmen [30]	unclear	unclear	unclear	unclear	yes	not stated
Perner [31]	random number tables	unclear	appropriate	unclear	yes	not stated
Hellberg [32]	computer-generated	blocking	appropriate	unclear	no	performed, number reached
Heikkinen [33]	unclear	unclear	appropriate	unclear	no	not stated
Klingler [34]	unclear	unclear	unclear	unclear	no	not stated
Macarulla [35]	unclear	unclear	appropriate	unclear	no	not stated
Minne [36]	10 repeating random numbers on a master list	unclear	unclear	unclear	no	not stated
Reiertsen [37]	unclear	blocking	unclear	unclear	yes	performed, number reached
Kazemier [38]	unclear	unclear	appropriate	unclear	yes	not stated
Laine [39]	unclear	unclear	unclear	unclear	unclear	not stated
Hart [40]	computer-generated	unclear	appropriate	unclear	no	not stated
Mutter [41]	unclear	unclear	unclear	unclear	yes	not stated
Williams [42]	unclear	unclear	unclear	unclear	unclear	not stated
Lejus [43]	unclear	unclear	unclear	measures taken	yes	not stated
Cox [44]	unclear	unclear	unclear	unclear	yes	not stated
Hansen [45]	random number tables	unclear	appropriate	unclear	no	not stated
Ortega [47]	unclear	unclear	inappropriate	measures taken	yes	not stated
Lujan Mompean [48]	instrumental availability	unclear	inappropriate	unclear	yes	not stated
Fraze [49]	unclear	unclear	unclear	unclear	yes	not stated
Kum [50]	coin toss	unclear	inappropriate	unclear	no	not stated
Tate [51]	unclear	unclear	appropriate	unclear	yes	not stated
Attwood [52]	unclear	unclear	appropriate	unclear	yes	not stated

cording to ITT in 21 (50%) of the trials. In 10 (48%), the use of ITT analysis was specified in the statistical analysis or results section, and in 11 (52%), this information was retrieved by our review of the tables of results. The remaining 21 trials either did not perform ITT analysis ($n = 13$, 31%), or it was unclear whether such analysis was performed or not ($n = 8$, 19%).

Jadad Score

The overall quality of the RCTs was estimated by Jadad score. The score is between 0 and 5 with a higher score indicating higher quality. The median Jadad score of the included papers was 2 (0–3). Four studies (10%) had a score of 0, 16 (38%) scored 1, 15 (36%) scored 2 and 7 (16%) had a Jadad score of 3. None of the studies was considered to have appropriate measures of double-blinding (2 possible points).

Discussion

Overall, RCTs that compared laparoscopic and open appendectomy had low quality. A similar conclusion has been presented previously in a Cochrane meta-analysis by Sauerland et al. [54]. Unfortunately, we do not believe that the quality of surgical RCTs studying other treatments or diseases is so much different [55]. In order to improve the quality of randomized controlled trials in the field of surgery, there are some guidelines that should be followed.

Randomization reduces bias in treatment allocation, i.e., participants' baseline characteristics should not affect which treatment they will receive, and helps to balance the allocation groups for known and unknown prognostically important factors [1]. In this review, description of methods of random number generation was missing in almost two thirds of the trials. Although a minority, four (10%) of the trials reported the use of systematic methods, such as the admission code of the patients or coin toss, to decide the allocation. Such methods are not random and are sources of bias [56].

When the sample size is small, simple randomization is not likely to result in treatment groups with equal size [1]. For instance, when 100 individuals are set to be randomized, the likelihood of having treatment groups with equal size using simple randomization is only 8% [1]. In the present review, the difference in sample size in unblocked RCTs was less than 10% and not different from those using blocking. This issue has also been reported by Altman and Doré [57]. In that study, 3 possibilities for

this finding was discussed, namely: (1) use of blocking without reporting it, (2) use of nonrandom methods for randomization, and (3) adding extra patients to one treatment arm to balance the groups. The second and third possibilities are associated with selection bias.

Proper concealment helps investigators to be unaware of the allocation sequence and reduces the bias in selection of the study participants [58]. Inadequately concealed trials have been shown to overestimate the effect of size by up to 40% [59]. More than half of the RCTs in this review either had inadequate measures of concealment or did not provide any information about the way the concealment was arranged.

Blinding of the allocation status is an acknowledged difficulty in surgical trials [60]. The results from unblinded RCTs have been shown to differ from those of RCTs with blinded outcome assessment [61]. In the surgical field, the most efficient way to double-blind the outcome assessment is the use of sham surgery. However, the ethical concerns of using sham surgery is worth being debated [62, 63]. In case of acute conditions such as acute appendicitis, the use of a sham procedure is not an option. In this review, 3 (7%) of 42 studies using an abdominal dressing to cover the entire abdomen reported being double-blinded. However, we find it difficult to believe that this measure was enough to provide sustainable double-blinding throughout the whole follow-up period. Some factors that may reveal the allocated intervention could be: (1) wound dressings are easily accessible to patients and could be removed, (2) a wound will always have some discharge which could locate the actual wound site and concomitantly unmask the surgical procedure, and (3) pain from the wound site could reveal the type of surgery. In case of RCTs comparing different surgical approaches, incisions to create identical postoperative wounds may be a possible solution. Of course, these wounds do not have to be as deep as wounds associated with a given surgical procedure.

Sample size must be calculated before a study is conducted to quantitatively estimate the precision of a randomized trial to study a given hypothesis [1, 64]. It could be argued that underpowered RCTs are unethical [65]. One strong argument is that by conducting a study with low statistical power, investigators will consume the trust of the study participants who have accepted the risks by being included in a trial [65]. Although meta-analyses may be a tool to pool the knowledge in a research field and improve the evaluation of the results, it must be kept in mind that underpowered studies are prone to bias [64]. Thus, the validity of meta-analyses' results could be com-

promised when pooling estimates of underpowered trials [64]. Furthermore, underpowered studies are prone to publication bias [64]. The absence of information about these studies also deteriorates the validity of a meta-analysis [64]. Thus, it is the responsibility of the investigators to make sure that a planned study has sufficient precision and statistical power to test a given hypothesis.

When analyzing the results of a randomized trial, investigators may be tempted to exclude some particular individuals, such as those erroneously included in a trial or those not adhering to the randomized allocation, from the final analysis. Exclusion of those wrongly randomized to an RCT could be excusable if such exclusion is not different with respect to the allocation status [66]. However, exclusion on other bases, such as non-adherence to the allocated treatment, could be substantially prone to bias [1, 66]. Thus, we recommend the use of ITT analysis

as the primary way of describing the results of a randomized controlled trial. Any analysis after post-randomization exclusion of participants should be defined as secondary, and the reason for exclusion must be thoroughly reasoned.

Conclusions

The quality of studies in the field of surgery needs to be improved. A tool to systematize trial planning and reporting is the CONSORT statement [67]. Moreover, registration of the trial protocol is another way that improves transparency in result reporting [68]. We believe that adherence to the recommendations in conducting RCTs and the two tools mentioned above will substantially improve the quality of RCTs in the field of surgery.

References

- Piantadosi S: Clinical Trials: A Methodologic Perspective. New York, Wiley-Interscience, 1997, p 121.
- Addiss DG, Shaffer N, Fowler BS, Tauxe RV: The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132:910–925.
- Semm K: Endoscopic appendectomy. *Endoscopy* 1983;15:59–64.
- Moirangthem GS, Arunkumar C, Marak AB, Lokendra K, Singh LD: A comparative study between laparoscopic versus open appendectomy. *JMS J Med Soc* 2008;22:58–62.
- Helmy MA: A comparative study between laparoscopic versus open appendectomy in men. *J Egypt Soc Parasitol* 2001;31:555–562.
- Bruwer F, Coetzer M, Warren BL: Laparoscopic versus open surgical exploration in premenopausal women with suspected acute appendicitis. *S Afr J Surg* 2003;41:82–85.
- Kald A, Kullman E, Anderberg B, et al: Cost-minimisation analysis of laparoscopic and open appendectomy. *Eur J Surg* 1999;165:579–582.
- Enochsson L, Hellberg A, Rudberg C, et al: Laparoscopic vs. open appendectomy in overweight patients. *Surg Endosc* 2001;15:387–392.
- Hellberg A, Rudberg C, Enochsson L, et al: Conversion from laparoscopic to open appendectomy: a possible drawback of the laparoscopic technique? *Eur J Surg* 2001;167:209–213.
- Lintula H, Kokki H, Vanamo K, Antila P, Eskelinen M: Laparoscopy in children with complicated appendicitis. *J Pediatr Surg* 2002;37:1317–1320.
- Ricca R, Schneider JJ, Brar H, Lucha PA: Laparoscopic appendectomy in patients with a body mass index of 25 or greater: results of a double blind, prospective, randomized trial. *JLS* 2007;11:54–58.
- Tzovaras G, Liakou P, Baloyiannis I, et al: Laparoscopic appendectomy: differences between male and female patients with suspected acute appendicitis. *World J Surg* 2007;31:409–413.
- Katkhouda N, Mason RJ, Towfigh S, Gevorgyan A, Essani R: Laparoscopic versus open appendectomy: a prospective randomized double-blind study. *Ann Surg* 2005;242:439–448; discussion 448–450.
- Olmi S, Magnone S, Bertolini A, Croce E: Laparoscopic versus open appendectomy in acute appendicitis: a randomized prospective study. *Surg Endosc* 2005;19:1193–1195.
- Almagor M, Mintz A, Sibirsky O, Durst A: Preoperative and postoperative levels of interleukin-6 in patients with acute appendicitis: comparison between open and laparoscopic appendectomy. *Surg Endosc* 2005;19:331–333.
- Moberg AC, Berndsen F, Palmquist I, Petersson U, Resch T, Montgomery A: Randomized clinical trial of laparoscopic versus open appendectomy for confirmed appendicitis. *Br J Surg* 2005;92:298–304.
- Oka T, Kurkchubasche AG, Bussey JG, Wesselhoeft CW Jr, Tracy TF Jr, Luks FI: Open and laparoscopic appendectomy are equally safe and acceptable in children. *Surg Endosc* 2004;18:242–245.
- Ignacio RC, Burke R, Spencer D, Bissell C, Dorsainvil C, Lucha PA: Laparoscopic versus open appendectomy: what is the real difference? Results of a prospective randomized double-blinded trial. *Surg Endosc* 2004;18:334–337.
- van Dalen R, Bagshaw PF, Dobbs BR, Robertson GM, Lynch AC, Frizelle FA: The utility of laparoscopy in the diagnosis of acute appendicitis in women of reproductive age. *Surg Endosc* 2003;17:1311–1313.
- Milewicz M, Michalik M, Ciesielski M: A prospective, randomized, unicenter study comparing laparoscopic and open treatments of acute appendicitis. *Surg Endosc* 2003;17:1023–1028.
- Al-Mulhim AS, Al-Mulhim FM, Al-Suwaiygh AA, Al-Masaud NA: Laparoscopic versus open appendectomy in females with a clinical diagnosis of appendicitis. *Saudi Med J* 2002;23:1339–1342.
- Little DC, Custer MD, May BH, Blalock SE, Cooney DR: Laparoscopic appendectomy: an unnecessary and expensive procedure in children? *J Pediatr Surg* 2002;37:310–317.
- Huang MT, Wei PL, Wu CC, Lai IR, Chen RJ, Lee WJ: Needlescopic, laparoscopic, and open appendectomy: a comparative study. *Surg Laparosc Endosc Percutan Tech* 2001;11:306–312.
- Lavonius MI, Liesjarvi S, Ovaska J, Pajulo O, Ristkari S, Alanen M: Laparoscopic versus open appendectomy in children: a prospective randomised study. *Eur J Pediatr Surg* 2001;11:235–238.

- 25 Lintula H, Kokki H, Vanamo K: Single-blind randomized clinical trial of laparoscopic versus open appendectomy in children. *Br J Surg* 2001;88:510–514.
- 26 Larsson PG, Henriksson G, Olsson M, et al: Laparoscopy reduces unnecessary appendectomies and improves diagnosis in fertile women: a randomized study. *Surg Endosc* 2001;15:200–202.
- 27 Long KH, Bannon MP, Zietlow SP, et al: A prospective randomized comparison of laparoscopic appendectomy with open appendectomy: clinical and economic analyses. *Surgery* 2001;129:390–400.
- 28 Pedersen AG, Petersen OB, Wara P, Ronning H, Qvist N, Laurberg S: Randomized clinical trial of laparoscopic versus open appendectomy. *Br J Surg* 2001;88:200–205.
- 29 Nordentoft T, Bringstrup FA, Bremmelgaard A, Stage JG: Effect of laparoscopy on bacteremia in acute appendicitis: a randomized controlled study. *Surg Laparosc Endosc Percutan Tech* 2000;10:302–304.
- 30 Ozmen MM, Zulfikaroglu B, Tanik A, Kale IT: Laparoscopic versus open appendectomy: prospective randomized trial. *Surg Laparosc Endosc Percutan Tech* 1999;9:187–189.
- 31 Perner A, Bugge K, Lyng KM, Schulze S, Kristensen PA, Bendtsen A: Changes in plasma potassium concentration during carbon dioxide pneumoperitoneum. *Br J Anaesth* 1999;82:137–139.
- 32 Hellberg A, Rudberg C, Kullman E, et al: Prospective randomized multicentre study of laparoscopic versus open appendectomy. *Br J Surg* 1999;86:48–53.
- 33 Heikkinen TJ, Haukipuro K, Hulkko A: Cost-effective appendectomy. Open or laparoscopic? A prospective randomized study. *Surg Endosc* 1998;12:1204–1208.
- 34 Klingler A, Henle KP, Beller S, et al: Laparoscopic appendectomy does not change the incidence of postoperative infectious complications. *Am J Surg* 1998;175:232–235.
- 35 Macarulla E, Vallet J, Abad JM, Hussein H, Fernandez E, Nieto B: Laparoscopic versus open appendectomy: a prospective randomized trial. *Surg Laparosc Endosc* 1997;7:335–339.
- 36 Minne L, Varner D, Burnell A, Ratzer E, Clark J, Haun W: Laparoscopic vs. open appendectomy: prospective randomized study of outcomes. *Arch Surg* 1997;132:708–711; discussion 712.
- 37 Reiertsen O, Larsen S, Trondsen E, Edwin B, Faerden AE, Rosseland AR: Randomized controlled trial with sequential design of laparoscopic versus conventional appendectomy. *Br J Surg* 1997;84:842–847.
- 38 Kazemier G, de Zeeuw GR, Lange JF, Hop WC, Bonjer HJ: Laparoscopic vs open appendectomy: a randomized clinical trial. *Surg Endosc* 1997;11:336–340.
- 39 Laine S, Rantala A, Gullichsen R, Ovaska J: Laparoscopic appendectomy – is it worthwhile? A prospective, randomized study in young women. *Surg Endosc* 1997;11:95–97.
- 40 Hart R, Rajgopal C, Plewes A, et al: Laparoscopic versus open appendectomy: a prospective randomized trial of 81 patients. *Can J Surg* 1996;39:457–462.
- 41 Mutter D, Vix M, Bui A, et al: Laparoscopy not recommended for routine appendectomy in men: results of a prospective randomized study. *Surgery* 1996;120:71–74.
- 42 Williams MD, Collins JN, Wright TF, Fenoglio ME: Laparoscopic versus open appendectomy. *South Med J* 1996;89:668–674.
- 43 Lejus C, Delile L, Plattner V, et al: Randomized, single-blinded trial of laparoscopic versus open appendectomy in children: effects on postoperative analgesia. *Anesthesiology* 1996;84:801–806.
- 44 Cox MR, McCall JL, Toouli J, et al: Prospective randomized comparison of open versus laparoscopic appendectomy in men. *World J Surg* 1996;20:263–266.
- 45 Hansen JB, Smithers BM, Schache D, Wall DR, Miller BJ, Menzies BL: Laparoscopic versus open appendectomy: prospective randomized trial. *World J Surg* 1996;20:17–20; discussion 21.
- 46 Martin LC, Puente I, Sosa JL, et al: Open versus laparoscopic appendectomy. A prospective randomized comparison. *Ann Surg* 1995;222:256–261; discussion 261–262.
- 47 Ortega AE, Hunter JG, Peters JH, Swanstrom LL, Schirmer B: A prospective, randomized comparison of laparoscopic appendectomy with open appendectomy. *Laparoscopic Appendectomy Study Group. Am J Surg* 1995;169:208–212; discussion 212–213.
- 48 Lujan Mompean J, Robles Campos R, Parrilla Paricio P, Soria Aledo V, Garcia Ayllon J: Laparoscopic versus open appendectomy: a prospective assessment. *Br J Surg* 1994;81:133–135.
- 49 Frazee RC, Roberts JW, Symmonds RE, et al: A prospective randomized trial comparing open versus laparoscopic appendectomy. *Ann Surg* 1994;219:725–728; discussion 728–731.
- 50 Kum CK, Ngoi SS, Goh PM, Tekant Y, Isaac JR: Randomized controlled trial comparing laparoscopic and open appendectomy. *Br J Surg* 1993;80:1599–1600.
- 51 Tate JJ, Dawson JW, Chung SC, Lau WY, Li AK: Laparoscopic versus open appendectomy: prospective randomised trial. *Lancet* 1993;342:633–637.
- 52 Attwood SE, Hill AD, Murphy PG, Thornton J, Stephens RB: A prospective randomized trial of laparoscopic versus open appendectomy. *Surgery* 1992;112:497–501.
- 53 Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- 54 Sauerland S, Lefering R, Neugebauer EA: Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2004;CD001546.
- 55 Diener MK, Blumle A, Szakallas V, Antes G, Seiler CM: Randomized and nonrandomized controlled clinical trials in a German surgical journal. *Chirurg* 2006;77:837–843.
- 56 Schulz KF, Grimes DA: Generation of allocation sequences in randomised trials: chance, not choice. *Lancet* 2002;359:515–519.
- 57 Altman DG, Doré CJ: Randomisation and baseline comparisons in clinical trials. *Lancet* 1990;335:149–153.
- 58 Schulz KF, Grimes DA: Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359:614–618.
- 59 Schulz KF, Chalmers I, Hayes RJ, Altman DG: Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–412.
- 60 Paradis C: Bias in surgical research. *Ann Surg* 2008;248:180–188.
- 61 Juni P, Altman DG, Egger M: Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;323:42–46.
- 62 Macklin R: The ethical problems with sham surgery in clinical research. *N Engl J Med* 1999;341:992–996.
- 63 Horng S, Miller FG: Is placebo surgery unethical? *N Engl J Med* 2002;347:137–139.
- 64 Schulz KF, Grimes DA: Sample size calculations in randomised trials: mandatory and mystical. *Lancet* 2005;365:1348–1353.
- 65 Halpern SD, Karlawish JH, Berlin JA: The continuing unethical conduct of underpowered clinical trials. *JAMA* 2002;288:358–362.
- 66 Fergusson D, Aaron SD, Guyatt G, Hebert P: Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–654.
- 67 Moher D, Schulz KF, Altman D: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987–1991.
- 68 Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG: Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291:2457–2465.