Att kritiskt granska en klinisk studie

- En enkel lathund…

10 punkter

- Hypotesen/frågeställning
- Randomiseringen
- Jämförelsegrupper
- Blindning
- Likabehandling
- Bortfall
- Klinisk relevans
- Statistisk styrka (power)
- Extern validitet
- Varia

Behöver jag kunna detta?

- Ja det behöver du
- Även i respekterade tidskrifter är antalet fel förvånansvärt högt
- För att kunna bibehålla oberoende krävs förmåga till kritisk granskning

Nåja, men hur gör man då?

- Använd:
  - → Sunt förnuft
  - → Klinisk kunskap
  - → Kritiska ögon
- Leta extra noga där det ofta finns fel
- Det är rätt svårt…

Exempel

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A CONTROLLED TRIAL OF ARTHROSCOPIC SURGERY FOR OSTEOARTHRITIS OF THE KNEE

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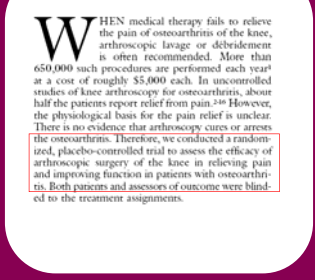
Steg 1 – Frågeställning

- Finns någon hypotes eller frågeställning specificerad alls?
- Är den tydlig?
- Har hypotesen klinisk signifikans?
- Stämmer hypotesen med studiens design?



WHEN medical therapy fails to relieve the pain of osteoarthritis of the knee, arthroscopic lavage or débridement is often recommended. More than 650,000 such procedures are performed each year[1] at a cost of roughly $5,000 each. In uncontrolled studies of knee arthroscopy for osteoarthritis, about half the patients report relief from pain.[2-16] However, the physiological basis for the pain relief is unclear. There is no evidence that arthroscopy cures or arrests the osteoarthritis. Therefore, we conducted a randomized, placebo-controlled trial to assess the efficacy of arthroscopic surgery of the knee in relieving pain and improving function in patients with osteoarthritis. Both patients and assessors of outcome were blinded to the treatment assignments.

Steg 2 – Randomisering

- Var studien randomiserad?
  - → Randomisering görs för att skapa jämförbara grupper med hänsyn tagen till såväl kända som okända "förvillelsefaktorer"
- Hur randomiserades studien?
  - → Om det inte står kan man anta att det genomförts felaktigt
  - → Till synes korrekta metoder såsom jämn och udda dag, eller födelsedag är helt förkastliga
  - → Vanligtvis används vag formulering om "sealed envelopes" – oftast helt OK

Steg 2 – Randomisering

- En tumregel är att randomisering skall vara:
  - → Helt oförutsägbar
  - → Helt opåverkbar

Randomization Process and Treatment Groups

Participants were stratified into three groups according to the severity of osteoarthritis (grade 1, 2, or 3; grade 4, 5, or 6; and grade 7 or 8). A stratified randomization process with fixed blocks of six was used. Sealed, sequentially numbered, stratum-specific envelopes containing treatment assignments were prepared and given to the research assistant. After the patient was in the operating suite, the surgeon was handed the envelope. The treatment assignment was not revealed to the patient.

Participants were randomly assigned to arthroscopic débridement, arthroscopic lavage alone, or the placebo procedure. One orthopedist performed all the operations. Patients in the débridement group or the lavage group received standard general anesthesia with endotracheal intubation. Patients in the placebo group received a short-acting intravenous tranquilizer and an opioid and spontaneously breathed oxygen-enriched air.

Steg 3 – Jämförelse-grupper

- Vilka jämfördes?
- Tips: se tabell 1
- Studiens olika grupper skall vara jämförbara vad gäller alla viktiga faktorer
- … men slumpen är aldrig perfekt
- Därför stratifierar man

Table 1. Base-Line Characteristics of the Randomized Patients.*

Characteristic	Placebo Group (N=60)	Lavage Group (N=61)	Débridement Group (N=58)
Age (yr)	52.0±11.1	51.2±10.5	53.6±12.2
Male sex (%)	93.3	88.5	96.6
Race (%)			
White	60.0	59.0	61.0
Black	31.7	31.2	22.0
Other	8.3	9.9	17.0
Severity of osteoarthritis in knee (%)†			
Mild	28.3	27.9	30.5
Moderate	46.7	45.9	45.8
Severe	25.0	26.2	23.7
Analgesic use (%)‡			
Nonprescription	70.0	67.2	64.4
Prescription	21.7	21.3	15.3
Mean score on Knee Society Clinical Rating Scale§			
Knee symptoms	49.4	50.2	51.4
Function	62.2	62.4	57.6
Psychological attributes¶			
Anxiety	27.0±21.0	30.2±19.9	28.4±22.4
Depression	20.0±32.0	28.1±37.2	22.0±35.3
Expectations for benefit‖	3.5±1.0	3.5±0.9	3.6±1.1
Optimism	72.6±21.0	74.5±19.4	73.7±17.1
Satisfaction with general health	39.3±25.1	43.7±22.4	46.5±24.8
Social functioning	65.5±25.6	60.3±23.9	67.6±25.2
Somatization	11.3±12.7	9.6±12.4	10.0±10.7
Stress	28.4±29.7	26.1±18.2	27.9±18.8
Vitality	54.8±21.0	52.7±19.7	57.7±19.3

Naturlig variation

Viktig variabel – ingen skillnad

Steg 4 – Blindning

- Visste patienten, den behandlande läkaren eller eventuella bedömare om vilken behandling patienten får?
- Ibland svårt att blinda alla inblandade, exempelvis vid kirurgi
- Strävan skall vara att så få som möjligt skall veta vilken grupp patienten tillhör

Steg 5 – Likabehandling

- Vid randomiserade studier måste alla patienter behandlas lika vad gäller allt utom den studerade behandlingen. Detta gäller även:
  - → Vårdtid och tillgång till eventuella övriga läkemedel
  - → Återbesök till och övrig kontakt med läkare och annan sjukvårdspersonal
  - → Tillgång till olika hjälpmedel och annat som ej har med frågeställningen att göra
- Utöver detta är det viktigt att de jämförda doserna är ekvipotenta – dvs att inte ena gruppen får maxdos och placebogruppen får 1/2 eller 1/3 dos.

Steg 4 & 5

Placebo Procedure

To preserve blinding in the event that patients in the placebo group did not have total amnesia, a standard arthroscopic débridement procedure was simulated. After the knee was prepped and draped, three 1-cm incisions were made in the skin. The surgeon asked for all instruments and manipulated the knee as if arthroscopy were being performed. Saline was splashed to simulate the sounds of lavage. No instrument entered the portals for arthroscopy. The patient was kept in the operating room for the amount of time required for a débridement. Patients spent the night after the procedure in the hospital and were cared for by nurses who were unaware of the treatment-group assignment.

Postoperatively, there were two minor complications and no deaths. Incisional erythema developed in one patient, who was given antibiotics. In a second patient, calf swelling developed in the leg that had undergone surgery; venography was negative for thrombosis. In no case did a complication necessitate the breaking of the randomization code.

Postoperative care was delivered according to a protocol specifying that all patients should receive the same walking aids, graduated exercise program, and analgesics. The use of analgesics after surgery was monitored; during the two-year follow-up period, the amount used was similar in the three groups.

End Points

Study personnel who were unaware of the treatment-group assignments performed all postoperative outcome assessments; the operating surgeon did not participate in any way. Data on end points were collected 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months after the procedure. To assess whether patients remained unaware of their treatment-group assignment, they were asked at each follow-up visit to guess which procedure they had undergone. Patients in the placebo group were no more likely than patients in the other two groups to guess that they had undergone a placebo procedure. For example, at two weeks, 13.8 percent of the patients in the placebo group guessed that they had undergone a placebo procedure, and 13.2 percent of the patients in the lavage and débridement groups guessed that they had undergone a placebo procedure.

Steg 6 – Bortfall

- Tyvärr gör världen vad den kan för att förstöra för oss (?) forskare. Därför händer att patienter:
  - → Dör
  - → Tröttnar på att studeras
  - → Flyttar till Mallis
  - → Försvinner spårlöst
- Hur bör sådant bortfall hanteras?
- Är bortfallet randomiserat?

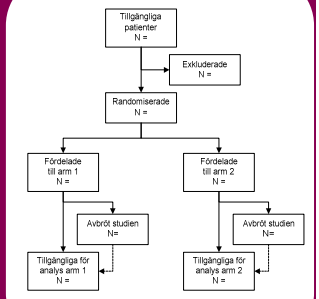
Steg 6 – Bortfall

- Den *korrekta* och allmänt accepterade metoden är att använda sig av så kallad intention-to-treat analys:
  - → Intention-to-treat innebär att man analyserar patienter som de har randomiserats, inte som de behandlats (konstigt nog…)

Steg 6 – Bortfall

- Hur en klinisk studie skall beskrivas finns beskrivet i den internationellt erkända CONSORT-förklaringen

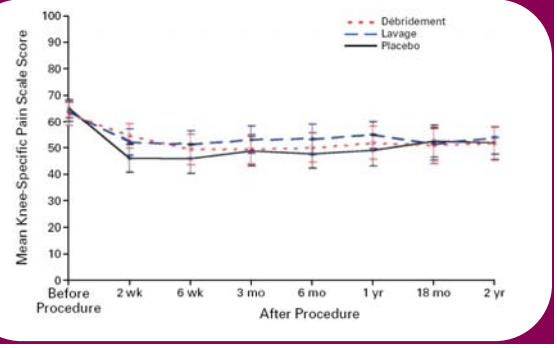
www.consort-statement.com



Steg 7 – Klinisk relevans

- Betyder resultatet något för dig?
  - → Använd kliniskt omdöme
  - → Kan resultatet bortförklaras av studiens sammanlagda svagheter?
  - → Statistisk signifikans?
  - → Numbers Needed to Treat (NNT)
- Ännu viktigare, betyder resultatet något för dina patienter?

Steg 7 – Klinisk relevans



Steg 7 – Klinisk relevans

Results At no point did either of the intervention groups report less pain or better function than the placebo group. For example, mean (±SD) scores on the Knee-Specific Pain Scale (range, 0 to 100, with higher scores indicating more severe pain) were similar in the placebo, lavage, and débridement groups: 48.9±21.9, 54.8±19.8, and 51.7±22.4, respectively, at one year (P=0.14 for the comparison between placebo and lavage; P=0.51 for the comparison between placebo and débridement) and 51.6±23.7, 53.7±23.7, and 51.4±23.2, respectively, at two years (P=0.64 and P=0.96, respectively). Furthermore, the 95 percent confidence intervals for the differences between the placebo group and the intervention groups exclude any clinically meaningful difference.

Steg 8 – Power

- Var studiens statistiska styrka (power) tillräcklig?
- Nämns poweranalys alls i studien?
- (Framför allt relevant om studien inte visar någon effekt av interventionen…)

Statistical Analysis

Our pilot study indicated that it would be feasible to recruit 60 patients per year. The trial was designed to have 90 percent power, with a two-sided type I error of 0.04, to detect a moderate effect size (0.55) between the placebo group and the combined arthroscopic-treatment groups in terms of body pain as measured by the SF-36-P at two years, with an enrollment of 180 patients and 16 or fewer lost to follow-up (i.e., 164 or more completing the two-year follow-up). The primary hypothesis was that the patients in two arthroscopic-intervention groups combined would report the same amount of knee pain at two years as the patients assigned to the placebo group.

Steg 9 – Extern validitet (generaliserbarhet)

- Är studiedeltagarna representativa för normala patienter?
- Skulle min patient ha kunnat ingå i studien?
- Tips: Jämför studiedeltagarna med det normala patientmaterialet vad gäller:
  - → Sjuklighet
  - → Ålder
  - → Könsfördelning
  - → Övriga sjukdomar

Steg 9 – Extern validitet

The principal limitation of this study is that our participants may not be representative of all candidates for arthroscopic treatment of osteoarthritis of the knee. Almost all participants were men, because the study was conducted at a Veterans Affairs medical center. We do not know whether our findings may be generalized to women, although uncontrolled studies do not indicate that there are differences between the sexes in responses to arthroscopic procedures.[8,10,13] A selection bias might have been introduced by the fact that 44 percent of the eligible patients declined to participate in the study. We be-

Steg 10 – Övrigt

- Studerades grupperna samtidigt?
  - → Exempel: sjukdomsbesvär kan vara säsongsbetonade
- Fanns tillräckligt med tid för att besvär skall hinna uppstå/försvinna?
  - → I en för kort studie kan resultat utebli eller accentueras
- Saknas någon outcome i studien?
  - → Exempelvis ”glömmer” forskare ibland att ta med viktiga faktorer som livskvalitet och smärta