Research
442

Revised by
Deema · Fatima · Talal · Ahmed · Mohammed

Experimental Study Designs

Lecture No. 11

Objectives:

1. Explain the distinguishing features of an intervention study.
2. Identify the types of epidemiological questions that can be addressed by experimental studies.
3. Explain randomization.
4. Define "blinding" and explain its purpose.
5. Define placebo and explain why placebo is used.
6. Identify measures of association from experimental studies.
7. Discuss the potential strengths and limitations of experimental studies.

~ This lecture was presented by **Dr. Afnan Younis**
~ It is included in the **Midterm Exam**
~ We highly recommended reading the **Ayah** in the first page

Slides

Color code

Original text
Dr. Notes
Important
Golden note
Extra

Editing file

Introduction to experimental studies

Introduction

Before any new intervention (drug, diagnostic or therapeutic equipment) becomes a standard practice, assessment of its efficacy and safety in comparison to standard therapy should be undertaken.

سُورَةُ الحَجِّ

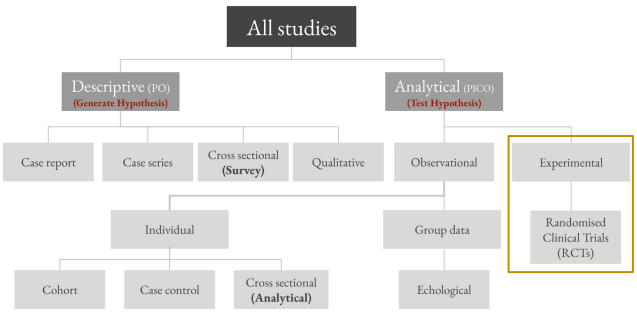
أَفَلَمْ يَسِيرُوا۟ فِى ٱلْأَرْضِ فَتَكُونَ
لَهُمْ قُلُوبٌ يَعْقِلُونَ بِهَآ أَوْ ءَاذَانٌ يَسْمَعُونَ بِهَا ۖ فَإِنَّهَا
لَا تَعْمَى ٱلْأَبْصَٰرُ وَلَٰكِن تَعْمَى ٱلْقُلُوبُ ٱلَّتِى فِى ٱلصُّدُورِ ﴿٤٦﴾

المختصر في التفسير

أفلم يَسِرْ هؤلاء المكذبون بما جاء به الرسول صلى الله عليه وسلم في الأرض؛ ليعاينوا آثار تلك القرى المهلكة، فيتفكروا بعقولهم ليعتبروا، ويسمعوا قصصهم سماع قبول ليتعظوا، فإن العمى ليس عمى البصر، بل العمى المُهْلِك المُرْدِي هو عمى البصيرة، بحيث لا يكون لصاحبه اعتبار ولا اتعاظ.

Analytical studies vs Experimental studies

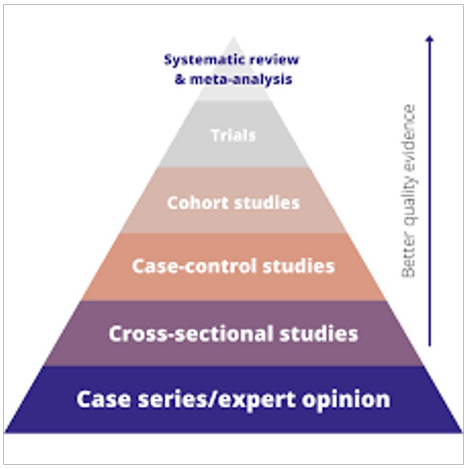
- Analytic studies must include a **comparison group** in order to measure the **association** between exposure and outcome and **test hypotheses** about exposure-outcome relationships.



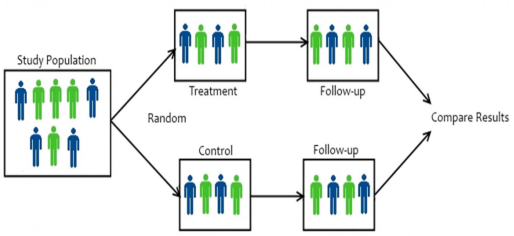
Experimental studies (trials):

- **A prospective study** comparing the effect and value of intervention(s) **against a control** in human beings.
- Experimental studies are similar in approach to cohort studies except that the **investigator assigns exposure.**

Randomized controlled trials



1. Comparison group (**controlled**)
2. Eligible participants (inclusion and exclusion criteria)
3. Similar baseline characteristics in both groups (randomization)
4. Decrease the psychological effect of participants and researchers (blinding/placebo)
5. Valid method to measure outcome
6. The gold-standard of clinical testing



Research questions that can be addressed by experimental studies

1. **Effectiveness and safety of interventions**
2. **Intervention, comparison, outcome**

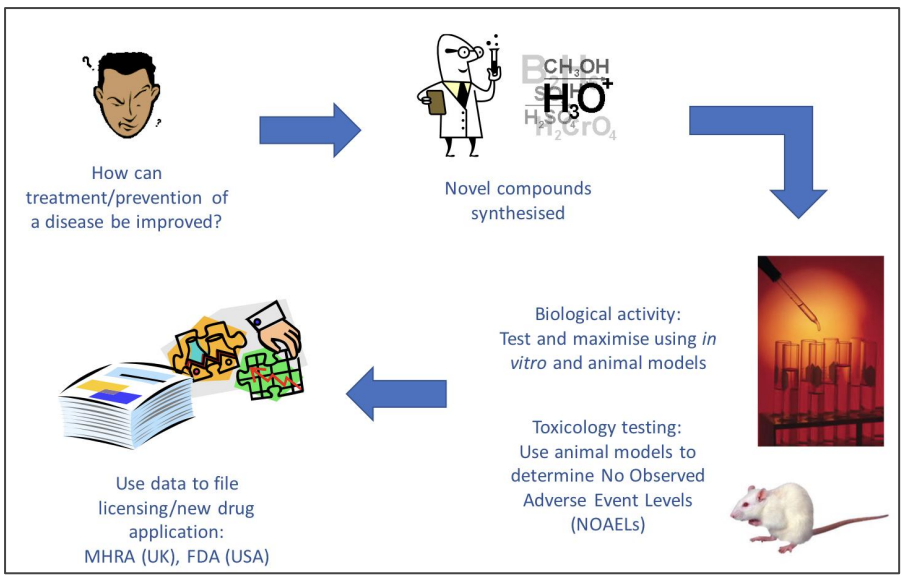
Examples of RCT questions

- Is a proposed intervention as effective as the established intervention?
- Does a proposed intervention have worse side effects than the established intervention?
- Which intervention for a specific condition results in less cost to a healthcare service?
- Which intervention are patients more likely to positively respond to?
- Which intervention provides longer-lasting benefit?

To know whether the new or old (standard) drug is more effective.

Studies done prior to any clinical trial

- Research in experimental animals is essential.
- Pharmacological and toxicological studies:
  - To establish that the new agent is effective and may be suitable for human use.
  - To roughly estimate the dose to be used in man.
- Clinical trials of new agents in humans pass through phases; **actual trial is phase III** and Phase IV is **post marketing surveillance.**

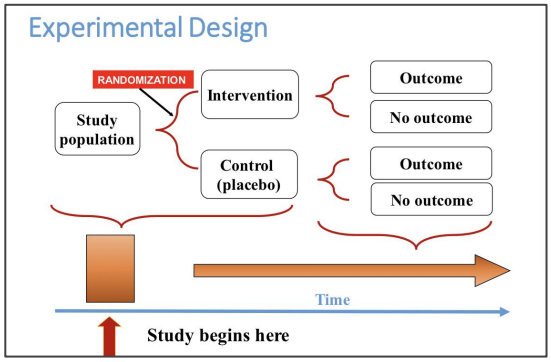


In phase 1 and 2 trials primarily aim to assess the **safety and dosage** range of the intervention in a small group of healthy volunteers or individuals

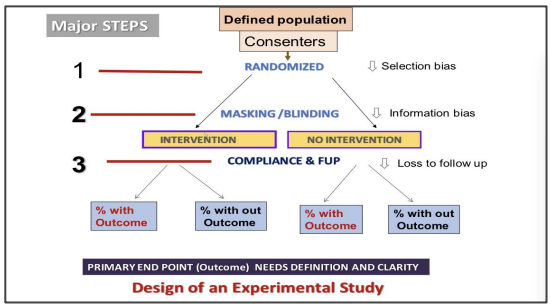
Experimental Design

Design of randomized control trial

1. Identify the **reference population** for generalization.
2. Select **study population** - sampling technique.
3. Define **inclusion/exclusion** criteria:
   a. The inclusion criteria for, who will be study participants
   b. The exclusion criteria are chosen to minimize potential dangers in being lost to follow up, hazardous effects (e.g. elderly patients, pregnant women, children).
4. Getting '**informed consent**' from the participants
5. **Random allocation** in experiment & control groups
6. **Follow up** for a specified period of time
7. The **outcomes** may be a cure, recurrence of the disease, survival, relief of pain, or reduction in blood pressure, etc.
8. The outcome measures are **compared** between the groups using appropriate statistical methods.



Getting informed consent occur **before** randomization!



Randomization

- Is the process of assigning clinical trial participants to treatment groups.
- Randomization gives each participant a known (**equal**) chance of being assigned to any of the groups.
- Successful randomization requires that group assignment cannot be predicted in advance.
- Tends to produce **comparable** groups.
- Removes **investigator bias.**
- **Statistical tests** will be valid.
- If predictable, **selection bias** will occur.
- Similarly if balance is not achieved for risk factors or prognostic factors **bias** will occur.

After we choose randomly, we should not expect their results, nor should we make any **predictions**.

Experimental Design, *cont.*

Methods of randomization

Fully Informed consent is to be taken before randomization.

1. Coin toss; not feasible.
2. Alternating assignments ABABAB; predictable , select an unpredictable method.
3. Block randomization: AABBAABB, AABABB, ...
4. Random digit table - better.
5. Random number producing algorithm (software) is the best.

For example; the first patient is in control group the second is in intervention group and so on.

TABLE 7-3. **A Table of Random Numbers**

	00–04	05–09	10–14	15–19
00	56348	01458	36236	07253
01	09372	27651	30103	37004
02	44782	54023	61355	71692
03	04383	90952	57204	57810
04	98190	89997	98839	76129
05	16263	35632	88105	59090
06	62032	90741	13468	02647
07	48457	78538	22759	12188
08	36782	06157	73084	48094
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Experimental Design, *cont.*

Baseline characteristics of patients in Placebo and (intervention) Pravastatin groups (NEJM 1996)

Characteristic	Placebo	Pravastatin
1. Mean Age (yrs)	59 (+-9)	59 (+-9)
2. Male Sex (%)	86	86
3. Race White (%)	92	93
4. Current Smoker (%)	21	21
5. Hypertension (%)	34	34
6. Diabetes Mellitus (%)	15	14
7. Body Mass Index (Mean)	28 (+-4)	28 (+-4)
8. Angina (%)	20	21
9. Medication Aspirin (%)	83	83
10. On Oral Hypoglycemic agent (%)	7	5

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS IN THE PLACEBO AND PRAVASTATIN GROUPS.*

CHARACTERISTIC	PLACEBO (N = 2078)	PRAVASTATIN (N = 2081)
General		
Age (yr)	59±9	59±9
Sex (%)		
Female	14	14
Male	86	86
Race (%)		
White	92	93
Other	8	7
Country of residence (%)		
United States	66	66
Canada	34	34
Hypertension (%)	43	42
Current smoker (%)	21	21
Diabetes (%)	15	14
Body-mass index†	28±4	28±4
Blood pressure (mm Hg)		
Systolic	129±18	129±18
Diastolic	79±10	79±10
Cardiovascular status		
Months from myocardial infarction to randomization	10±5	10±5
Type of myocardial infarction (%)		
Q wave	61	61
Other	38	38
Angina (%)	20	21
Congestive heart failure (%)	4	4
CABG (%)	28	26
PTCA (%)	32	34
CABG or PTCA (%)	54	54
Thrombolysis (%)	40	42
Ejection fraction (%)	53±12	53±12
Medication use		
Aspirin (%)	83	83
Beta-blocker (%)	39	41
Nitrate (%)	33	32
Calcium-channel blocker (%)	38	40
ACE inhibitor (%)	14	15
Diuretic agent (%)	11	11
Insulin (%)	2.6	2.4
Oral hypoglycemic agent (%)	7	5‡
Estrogen (% of women)	10.3	8.4
Plasma lipids§		
Cholesterol (mg/dl)		
Total	209±17	209±17
VLDL	27±16	27±16
LDL	139±15	139±15
HDL	39±9	39±9
Triglycerides (mg/dl)	155±61	156±61

*Plus–minus values are means ± SD. Except for the use of oral hypoglycemic agents, differences between the groups were not significant. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, ACE angiotensin-converting enzyme, VLDL very-low-density lipoprotein, LDL low-density lipoprotein, and HDL high-density lipoprotein.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡P<0.05 for the comparison with the placebo group.

§To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

Blinding (Masking)

Prevent subjects and study personnel from knowing who is in which treatment group.

Types of masking (blinding):

1. Single blind
2. Double blind
3. Triple blind
4. Placebo characteristics

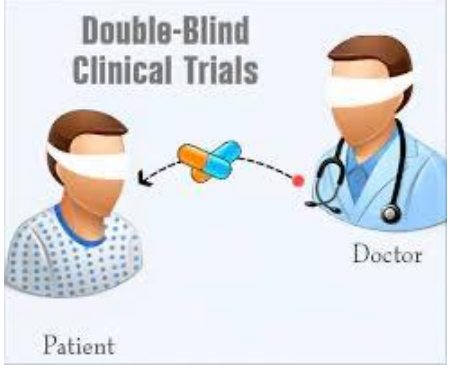
All To minimize information bias.

Single blinding: participant only.

Double blinding: participant and investigator.

Triple blinding: Participant, investigator and data analyst.

Double blind: Subjects not to know which group they are assigned to (for subjective symptoms like headache or pain) and Observer or data collector not to know which group a patient is in.



Experimental Design, *cont.*

Placebo

An inert substance that looks, tastes, and smells like the active agent.

A placebo can be a sugar pill, a water or salt water (saline) injection or even a fake surgical procedure.

Masking (blinding): Safety of participants

- Protection and safety of study participants is to be ensured.
- Minimization of risks, fear, pain and distress.
- Appropriate expertise is available at all trial sites.
- Study participants can contact appointed study team member at any time for any advice or reporting adverse effect (ensures compliance).

Checklist for sample size

- Estimate the outcome/event rate for control group by extrapolation from a similar population
- Define the primary outcome
- Difference in response rate to be detected (Define the smallest difference between intervention & control groups that will be of clinical significance)
- Adjust for the expected level of noncompliance

TABLE 8–4 Number of Patients Needed in Each Group to Detect Various Differences in Cure Rates; $\alpha = .05$; Power $(1 - \beta) = .80$ (Two-sided Test)

Lower of the Two Cure Rates	Differences in Cure Rates Between the Two Treatment Groups													
	.05	.10	.15	.20	.25	.30	.35	.40	.45	.50	.55	.60	.65	.70
.05	420	130	69	44	36	31	23	20	17	14	13	11	10	8
.10	680	195	96	59	41	35	29	23	19	17	13	12	11	8
.15	910	250	120	71	48	39	31	25	20	17	15	12	11	9
.20	1,090	290	135	80	53	42	33	26	22	18	16	12	11	9
.25	1,250	330	150	88	57	44	35	28	22	18	16	12	11	—
.30	1,380	360	160	93	60	44	36	29	22	18	15	12	—	—
.35	1,470	370	170	96	61	44	36	28	22	17	13	—	—	—
.40	1,530	390	175	97	61	44	35	26	20	17	—	—	—	—
.45	1,560	390	175	96	60	42	33	25	19	—	—	—	—	—
.50	1,560	390	170	93	57	40	31	23	—	—	—	—	—	—

Modified from Gehan E: Clinical trials in cancer research. Environ Health Perspect 32:31, 1979.

Experimental design & analysis

Considering Methods in Analysis

Interim analysis

- **Reasons to stop trial when:**
  - **Beneficial effects appear earlier than expected**
  - **Harmful or adverse effects appear**

- **Primary end point evaluation**

Expressing results of a Clinical Trial

- Risk of death or complication (incidence)
- Relative risk
- Efficacy of vaccine (in vaccine trial) **For reading.**
  = disease incidence rate in vaccine takers / disease incidence rate in placebo takers
- Generalizability

Relative risk must come in exam

Relative risk: Measure of Association

Group	Outcome		Total
	Cured/Positive	Not Cured /Negative	
Intervention	a	b	a +b
Control	c	d	c +d

Relative risk (RR):

- Ratio of the incidence of an outcome in experimental group compared to that in the control group
- = (a/(a + b)) / (c /(c + d))

Experimental studies & analysis Cont.

Interpretation of Relative Risk

> 1	• Means that the odds of exposure Among cases is **greater** than the odds of exposure Among controls.	The exposure may be **a risk factor** for the disease.
= 1	• Means that the odds of exposure Among cases is **same as** the odds of exposure Among controls.	The exposure is **not associated** with the disease.
< 1	• Means that the odds of exposure Among cases is **lower** than the odds of exposure Among controls.	The exposure may be **protective** against the disease.

RR=1	Risk in exposed = risk in non-exposed No association
RR>1	Risk in exposed > risk in non-exposed Positive association, factor is associated with disease Larger RR → stronger association
RR<1	Risk in exposed < risk in non-exposed Negative association, factor is "protective"

Pravastatin Study Results (NEJM 1996)

Outcome	#	Placebo	#	Pravastatin
Death CHD	274	13.2%	212	10.2%
Fetal MI	207	10%	157	7.5%
Stroke	78	3.8%	54	2.6%

Calculate RR (incidence in exposed/Incidence in unexposed) for all outcomes what is exposure here?

Compliance of groups

- Differences in outcome in important subgroups
- Mortality differential when sub groups were analyzed for good compliance or bad compliance

Coronary drug Trial: Five year Mortality in Groups

	# of patients	Mortality (%)
Clofibrate Drug		
Poor Compiler	357	24.6
Good compiler	708	15
Placebo	2695	19.4

Experimental studies Cont.

Randomized Controlled Trials

Disadvantages:

- **Very expensive**
- Not appropriate to answer certain types of questions
  - it may be **unethical**, for example, to assign people to certain treatment or comparison groups

Potential Problems

- **Ethical considerations**
- **Selection bias**
- **Observer bias**
- **Watch the experimental group more carefully than the control group**
- **Reporting bias**

Ethics

- Superiority, noninferiority
- Informed consent (enrolling children right after diagnosis with leukemia)
- When should a trial be stopped earlier than planned (harmful beneficial effect)
- Confidentiality
- Data storage
- IRB

Terminology

- Protocol: The planned course of action for the clinical trial. The protocol is established prior to the start of the trial and states the number of participants, eligibility requirements, agents that will be used, dosages, duration, how data is collected, etc.
- Investigator: A researcher in a clinical trial.
- Sponsor: Responsible for funding the clinical trial.
- Institutional Review Board (IRB): An independent board of scientists, physicians, and nurses who review the clinical trial protocol to ensure patient safety.
- Informed consent: A patient's decision to participate in the clinical trial after being informed of the potential benefits and risks of participation. Participants may withdraw their consent at any time and leave the trial.
- Double blind: Term used to describe a clinical trial in which neither the patient nor the researcher knows which agents are being administered to which patients. This helps prevent bias.
- Intervention group: The group of participants receiving the new preventive or treatment agent that is being evaluated in the clinical trial.
- Control group: The group of participants receiving a standard treatment or placebo that is being compared to the new agent in the clinical trial.
- Randomization: Assigning participants by chance to either the intervention group or the control group. Randomization is often done with a computer.
- Placebo: An inactive substance that may be given to participants in a clinical trial.
- Follow-up: Monitoring of participants for a specified time after the clinical trial is completed.

Research articles from slides

Randomized Controlled Trial > J Cyst Fibros. 2006 Dec;5(4):261-3.
doi: 10.1016/j.jcf.2006.05.009. Epub 2006 Jun 27.

Open follow-up study of tobramycin nebuliser solution and colistin in patients with cystic fibrosis

David Adeboyeku [1], Sandra Scott, Margaret E Hodson

Affiliations + expand
PMID: 16807142 DOI: 10.1016/j.jcf.2006.05.009
Free article

Abstract

A previous study of tobramycin nebuliser solution (TNS) compared with colistin [C] in cystic fibrosis (CF) patients, chronically infected with pseudomonas, showed benefit for the TNS treated patients over one treatment cycle only. The current report is of an extension of that study. An open randomised cross-over study of TNS compared with C was conducted on 21 patients who had previously been on the 1 cycle study. They continued for a further 5 months and then crossed over to the alternate treatment. There was an advantage for TNS over C in FEV(1) % predicted change over time. The C slope was -0.88% per month and the TNS slope 0.35% per month (p=0.0002). This suggests advantages of TNS over C in a study with a small number of patients. Larger studies are required.

Randomized Controlled Trial > Psychol Med. 2006 Dec;36(12):1737-46.
doi: 10.1017/S0033291706008695. Epub 2006 Aug 29.

Online randomized controlled trial of brief and full cognitive behaviour therapy for depression

H Christensen [1], K M Griffiths, A J Mackinnon, Kylie Brittliffe

Affiliations + expand
PMID: 16938144 DOI: 10.1017/S0033291706008695

Abstract

Background: Effective internet-based programs for depression usually incorporate a componen that provides telephone or email contact. Open access websites, without such contact, show hig rates of attrition and poorer outcomes. The present study was designed as an exploratory investigation of the parameters that influence the effectiveness and retention of users on open access websites. We investigated whether brief cognitive behaviour therapy (CBT) was as effective as an extended version, whether add-on components of behaviour therapy or stress management contributed to positive outcomes, and whether longer programs were associated with greater attrition.

Randomized Controlled Trial > Gastroenterology. 2006 Dec;131(6):1674-82.
doi: 10.1053/j.gastro.2006.08.079. Epub 2006 Sep 1.

A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas

John A Baron [1], Robert S Sandler, Robert S Bresalier, Hui Quan, Robert Riddell, Angel Lanas, James A Bolognese, Bettina Oxenius, Kevin Horgan, Susan Loftus, Dion G Morton;

Abstract

Background & aims: In human and animal studies, nonsteroidal anti-inflammatory drugs have been associated with a reduced risk of colorectal neoplasia. Although the underlying mechanisms are unknown, inhibition of cyclooxygenase (COX), particularly COX-2, is thought to play a role. We conducted a randomized, placebo-controlled, double-blind trial to assess whether use of the selective COX-2 inhibitor rofecoxib would reduce the risk of colorectal adenomas.

Methods: We randomized 2587 subjects with a recent history of histologically confirmed adenomas to receive daily placebo or 25 mg rofecoxib. Randomization was stratified by baseline use of cardioprotective aspirin. Colonoscopic follow-up evaluation was planned for 1 and 3 years after randomization. The primary end point was all adenomas diagnosed during 3 years' treatment. In a modified intent-to-treat analysis, we computed the relative risk of any adenoma after randomization, using Mantel-Haenszel statistics stratified by low-dose aspirin use at baseline.

Results: Adenoma recurrence was less frequent for rofecoxib subjects than for those randomized to placebo (41% vs 55%; P < .0001; relative risk [RR], 0.76; 95% confidence interval [CI], 0.69-0.83). Rofecoxib also conferred a reduction in risk of advanced adenomas (P < .01). The chemopreventive effect was more pronounced in the first year (RR, 0.65; 95% CI, 0.57-0.73) than in the subsequent 2 years (RR, 0.81; 95% CI, 0.71-0.93). As reported previously, rofecoxib was associated with increased risks of significant upper gastrointestinal events and serious thrombotic cardiovascular events.

Randomized Controlled Trial > Fertil Steril. 2006 Dec;86(6):1669-75.
doi: 10.1016/j.fertnstert.2006.04.043. Epub 2006 Oct 30.

A comparison of oral and transdermal short-term estrogen therapy in postmenopausal women with metabolic syndrome

Micheline C Chu [1], Pippa Cosper, Gary S Nakhuda, Rogerio A Lobo

Affiliations + expand
PMID: 17074346 DOI: 10.1016/j.fertnstert.2006.04.043

Abstract

Objective: To determine whether it would be preferable to prescribe oral or transdermal estrogen to symptomatic postmenopausal women with metabolic syndrome (MBS).

Design: Prospective, randomized study.

Setting: Academic medical center.

Patient(s): Fifty obese postmenopausal women with MBS.

Intervention(s): Women were randomized to receive either oral E(2) (oE(2), 1 mg/d) or transdermal E(2) (tE(2), 0.05 mg/d) for 3 months. Fasting blood was obtained before and after treatment for glucose, insulin, lipid profiles, the adipocytokines (adiponectin, leptin, and resistin), and a gastric peptide (ghrelin). In addition, a 75-g 2-hour oral glucose-tolerance and intravenous insulin-tolerance tests were performed before and after E(2).

Main outcome measure(s): Changes in parameters of insulin resistance (IR), lipid profiles, and adipocytokine levels.

Result(s): Mean serum concentrations of E(2) in women using oE(2) and tE(2) were 39.1 +/- 5.6 and 49.2 +/- 28.6 pg/mL, respectively. After oE(2), there was a statistically significant worsening of IR markers, including an increase in baseline insulin (15.28 +/- 1.27 to 22.02 +/- 2.40 microU/mL), a

Summary

1. Experimental Studies like Clinical Trials are a powerful design
2. This design helps to estimate the superiority of one treatment on the other
3. Role in determining new methods of treatment, prevention, and diagnosis
4. Its randomization process helps to reduce selection bias
5. Masking reduces information bias
6. Efficacy of vaccines and **Number needed to treat** translate in setting health care priorities

القادة:

نواف التركي عبدالله الشهري لمتحمي

ريان الغنامي وهى ا

الأعضاء:

عبدالله التركي عبدالله المياح

محمد الزير عبدالله النجرس

عثمان الدريهم تركي العتيبي

عبدالعزيز القحطاني عبدالله القرني

ناصر الغيث عامر الغامدي

سعد السهلي سعد الاحمري

رائد الماضي معاذ آل صلام

سعود الشعلان محمد الحصيني

عبدالرحمن ابو بخيت

رغد الظفيف

ريما الجريبة

شهد البخاري

نوف الضلعان

أثير الاحمري

وعد ابو نخاع

ثراء الهويش

في الدوسري

منار الزهراني

Answer: Q1: B |Q2: D |Q3: B |Q4: C

MCQ:

Q1: Minimal bias is a .... to RCT

A. Limitation
B. Strength
C. Both
D. None of the above

Q2: Which one of the following is a disadvantage of RCT ?

A. Very expensive
B. Not appropriate to answer certain types of questions
C. It may be unethical, for example, to assign people to certain treatment or comparison groups
D. All of the above

MCQ:

Q3: Masking of treatment after randomization is?

A. Blocking
B. Blinding
C. Concealment of allocation
D. None of the above

Q4: Relative risk is used in which of the following ?

A. Cohort studies
B. RCT
C. Both
D. None of the above