Emergency Medicine Journal Club
Wednesday, March 30, 2016

The March EM journal club is sponsored by RCRMC, and will be held in the upstairs room at Mu Restaurant (309 W. State Street, Redlands) on Wednesday, March 30 from 6 to 9 pm. **No preparation is required for this journal club. Just bring an electronic or paper copy of this handout with you.** This is the second of a two part journal club series called:

Critically Evaluating the Emergency Medicine Literature

Part 2: Randomized Controlled Trials

In October we did Part 1, which covered Case Reports, Chart Reviews, Observational Studies, and Clinical Decision Rules. Some key points that apply to studies of all formats:

General Principles to Appraising the Medical Literature

- Journal source: Is it trustworthy?
- Population: Did they study the correct type of patient, or the correct severity of disease?
- Sample size: Is the study large enough to be (or at least feel) convincing?
- Outcome: Is the outcome something that actually matters? Disease-oriented outcomes versus patient-oriented outcomes?
- Face validity: Is the outcome believable?
- External validity: Are the results likely to be valid in a different setting?
- Statistical significance versus clinical importance

Biases

- Selection bias: Are study subjects different somehow from all those with the disease to be studied? Was study subject recruitment not representative?
    - Referral bias: Are patients seen by (or referred to) consultants different than those who aren't?
    - Work-up bias: Are patients getting the testing different from those who don't?
    - Spectrum bias: Is the appropriate spectrum of disease being evaluated?
- Review / interpretation bias: Could the investigator's personal views change how the results are coded or analyzed?
- Incorporation bias: Is the item tested being used to establish the outcome?
- Publication bias: Is the article more likely to be published because of the outcome?

Research Designs Summary

Research Design	*Strengths*	*Weaknesses*
Case Report	Easy to read and interpret	Highlight the atypical and bizarre
Chart Review	Can study rare conditions, accrue large sample sizes	Depend on quality of chart documentation
Observational Study	Can accrue large sample sizes	Comparisons challenged by confounding variables
Clinical Decision Rule	Can inform diagnosis and testing	Most are insufficiently accurate and reliable, and do not improve upon clinical judgment alone
Randomized Controlled Trial	Strongest comparative format	Hard to accrue large samples, requires informed consent

SCENARIO #1: The simplest randomized controlled trial … *New Engl J Med* 1985; 312:1197.

REMOVING COCKROACHES FROM THE AUDITORY CANAL: CONTROLLED TRIAL

To the Editor: A recent case seen in an emergency department of a large urban hospital may have finally settled the tormenting and age-old question concerning the best method of removing *Periplaneta americana*, the common cockroach, from the ear canal. Numerous methods have been described in the medical literature, the most popular of which appears to be placement of mineral oil in the canal and subsequent manual removal of the creature.[1] More recently, lidocaine spray has been suggested as a more effective approach to this problem.[2]

A patient recently presented with a cockroach in *both* ears. The history was otherwise noncontributory. We recognized immediately that fate had granted us the opportunity for an elegant comparative therapeutic trial. Having visions of a medical breakthrough assuredly worthy of subsequent publication in the *Journal*, we placed the time-tested mineral oil in one ear canal. The cockroach succumbed after a valiant but futile struggle, but its removal required much dexterity on the part of the house officer. In the opposite ear we sprayed 2 per cent lidocaine solution. The response was immediate; the roach exited the canal at a convulsive rate of speed and attempted to escape across the floor. A fleet-footed intern promptly applied an equally time-tested remedy and killed the creature using the simple crush method.

However humble the method, and despite our small study population, we think we have provided further evidence justifying the use of lidocaine for the treatment of a problem that has bugged mankind throughout recorded history.[3]

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General Issues with Randomized Controlled Trials

Randomization

- Sequence generation: Method used to generate the random allocation sequence?
- Allocation concealment mechanism, e.g., sequentially numbered containers or envelopes?
- Implementation: Who assigned participants to interventions and how?

Comparison

- Two treatments: A versus B
- Treatment versus non-treatment
- Treatment versus placebo

Blinding

- Non-blinded, i.e., "open label"
- Single-blinded
- Double-blinded

Baseline data

- "Table 1" is a table contrasting baseline demographic and clinical characteristics, i.e., did the randomization work in generating otherwise similar groups?

Outcomes

- Primary outcome
- Secondary outcomes
- Trial registration, e.g., ClinicalTrials.gov
- $p<0.05$

SCENARIO #2

In a famous 1976 BMJ study, British family physicians diagnosing acute myocardial infarction at house calls randomized patients to receive either home or hospital care. Great quote from study: "Women were excluded because home care for most would be difficult for social reasons." The 28-day mortality was lower in the home versus hospital group (12% versus 14%). They conclude that "Home care is a proper form of treatment" for acute myocardial infarction.

SCENARIO #3

A researcher wishes to compare antibiotics to placebo for acute otitis media in children. After making the diagnosis, each treating physician then flips a coin to determine treatment arm. After 100 children are enrolled the researcher finds a confounding dissimilarity in baseline fever between the two groups – more children were febrile in the group treated with antibiotics.

SCENARIO #4

A peds ED nurse who has recently taken training in hypnotism randomizes children requiring IV lines to receive either standard reassurance or standard reassurance plus hypnotism. He then rates the child's pain/distress on a 100 mm visual analog scale (0 = "no pain/distress", 100 = "worst possible pain/distress"). He finds significantly less pain/distress with hypnotism.

SCENARIO #5

Patients with acute migraine are randomized to receive either subcutaneous sumatriptan or no therapy, then 30 minutes later rate their pain on a 100 mm visual analog scale. There are significantly lower scores in the sumatriptan group.

SCENARIO #6

A multicenter study (NINDS) randomizes patients with acute stroke within 3 hours to receive either a thrombolytic or placebo, and concludes efficacy given that long-term outcome is 12% better in the thrombolytic group. A comparison of the two groups (not released with the initial study), however, showed that the thrombolytic group were less sick at baseline: the frequency of minimal or no disability (NIHSS 0 to 5) was 9% less in the thrombolytic group than in the placebo group.

SCENARIO #7

A multicenter study (NINDS) randomizes patients with acute stroke within 3 hours to receive either a thrombolytic or placebo, and prohibits aspirin or clopidogrel in either group.

SCENARIO #8

A researcher randomizes acute asthmatics to receive standard therapy with or without IV $MgSO_4$. The frequency of admission and relapse were similar between groups, but those with $MgSO_4$ showed statistically significant improvement in asthma severity scores after treatment.

SCENARIO #9

Kudenchuk PJ, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341:871-8.

In a randomized, double-blind, placebo-controlled study of out-of-hospital cardiac arrest with no response to 3 or more defibrillations, patients were assigned to receive amiodarone 300 mg IV (246 patients) or placebo (258 patients). Recipients of amiodarone were more likely to survive to be admitted to the hospital (44% vs. 34%, p=0.03). Mortality was similar between groups.

SCENARIO #10

A researcher studies the cosmetic outcomes of 500 children with wounds repaired using glue to 500 children with wounds repaired with sutures. Blinded plastic surgeons rate the cosmesis on a 100 mm visual analog scale, where 0 means "worst possible cosmesis" and 100 means" best possible cosmesis". The mean ratings are lower for glue than for sutures (77 mm versus 80 mm, p=0.04) and she concludes that glue closure is inferior to sutures.

SCENARIO #11

A researcher wonders whether pennies or quarters are more likely to roll "heads". He flips each of these coins 20 times and notes "heads" 6 out of 20 times for pennies and 13 out of 20 times for quarters, p=0.03. He concludes that quarters are more likely to roll "heads".

SCENARIO #12

A researcher wonders whether Drug A or Drug B is superior, and randomizes 20 patients into each group. He notes that 6 out of 20 improve with Drug A and 13 out of 20 improve with Drug B, p=0.03. He concludes that Drug B is significantly better than Drug A.

SCENARIO #13

Hoberman et al: Treatment of Acute Otitis Media in Children under 2 Years of Age. N Engl J Med 2011; 364:105-15.

These researchers randomized 291 children 6 to 23 months of age with acute otitis media (diagnosed with the use of stringent criteria) to receive amoxicillin–clavulanate or placebo for 10 days. They report 4 "primary" outcomes, and based upon 3 of the 4 being statistically significant they conclude that antibiotics are effective for this condition.

Time to resolution of symptoms (first AOM-SOS score of 0 or 1)	p=0.14
Time to the second of two successive recordings of that score	p=0.04
Mean AOM-SOS score over the first 7 days	p=0.02
7-day weighted mean AOM-SOS scores	p=0.01

However, post-publication critics noted that in the original pre-study ClinicalTrials.gov trial registration the only primary outcome was "time to resolution of symptoms", i.e., the first item. One of the remaining 3 outcomes was not in the original protocol and the other two were explicitly identified as secondary outcomes. Thus, if the study were reported to retain the original pre-specified primary outcome, then antibiotics were not significantly superior to placebo.

SCENARIO #14

A non-registered multicenter study (NINDS) randomizes patients with acute stroke within 3 hours to receive either a thrombolytic or placebo, and reports as a primary outcome statistically significant 12% improvement at 3 months. Non-significant secondary outcomes were improvement at 24 hours and mortality at 3 months.

SCENARIO #15

A small manufacturer-supported randomized trial (n = 200) in the *New England Journal of Medicine* suggested that a new proprietary human IgM monoclonal antibody to endotoxin ("Centoxin") could almost halve mortality due to gram-negative sepsis.[1] The New York Times estimated that this would be a multi-billion dollar product for its maker. A subsequent randomized trial of more than 10-fold larger sample size[2] found no such benefit, and indeed a trend towards increased mortality.

1. Ziegler. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. *N Engl J Med.* 1991;324:429-436.
2. McCloskey: Treatment of septic shock with human monoclonal antibody HA-1A: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1994;121:1-5.

SCENARIO #16

In a double-blind, placebo-controlled study of 273 patients with suspected acute MI, magnesium sulfate IV was associated with a reduction in 1-year death rate (20% versus 32% for placebo, p = 0.018). It is concluded that intravenous Mg should be adopted as part of the routine treatment of these patients. *Clin Cardiol* 1988; 11:377.

SCENARIO #17

A researcher wonders whether supplemental oxygen is truly helpful in severe carbon monoxide poisoning, and randomizes 40 such patients to receive either 100% oxygen or room air (both by non-rebreather for blinding). She found that 7 out of 20 receiving oxygen died and 13 out of 20 receiving room air died, p=0.06. She concludes that there is no statistically significant difference between oxygen or room air for severe carbon monoxide poisoning.

SCENARIO #18

Bansal: Tap water for irrigation of lacerations. *Am J Emerg Med* 2002; 20:469-72.

These authors randomized adults with simple lacerations to irrigation with tap water versus sterile normal saline before repair. At a 48 hour check, wound infections were found in 2 of 24 patients in the saline group and 2 of 21 patients in the tap water group, p=0.643. The authors conclude that tap water irrigation appears a safe substitute for sterile normal saline.

	Wound Infection +	Wound Infection -	
Tap H_2O	**2** 9.5% (1%, 30%)	**19**	21
NS	**2** 8.3% (1%, 27%)	**22**	24
	4	41	45

Effect size 1.2% (-16%, 19%)

What if the same 1.2% effect size trend persisted in larger samples?

n	*Effect size (95%CI)*
45	1.2% (-16%, 19%)
100	1.2% (-9%, 13%)
1,000	1.2% (-3%, 4%)
10,000	1.2% (-0.1%, 2.3%)

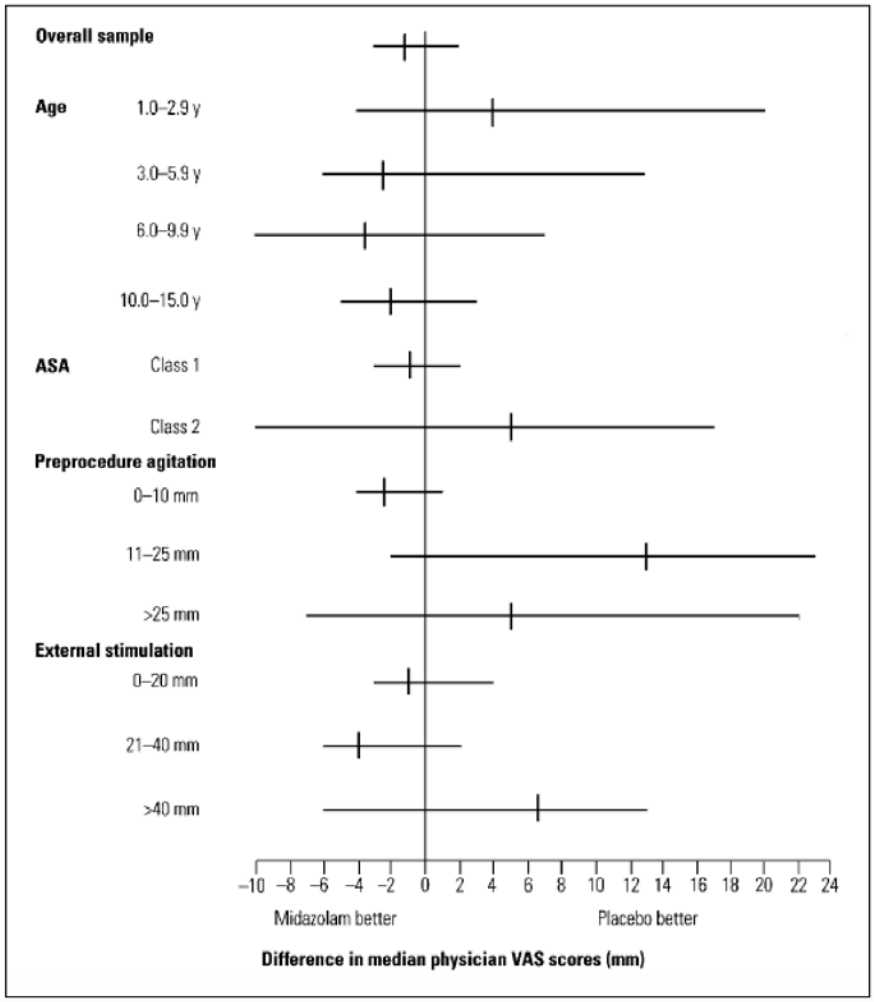
SCENARIO #19

Andolfatto: Ketamine-propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: a randomized double-blind trial. *Ann Emerg Med* 2012; 59(6):504-12

These authors randomized 284 adults needing procedural sedation to receive either ketofol (1:1) or propofol alone in double-blind fashion. They noted adverse respiratory events in 30% of those receiving ketofol and 32% in those receiving propofol alone, (difference 2%; 95% confidence interval -9% to 13%; p=.80), and conclude that ketofol does not reduce adverse respiratory events compared with propofol alone.

Subgroup Analyses: Example

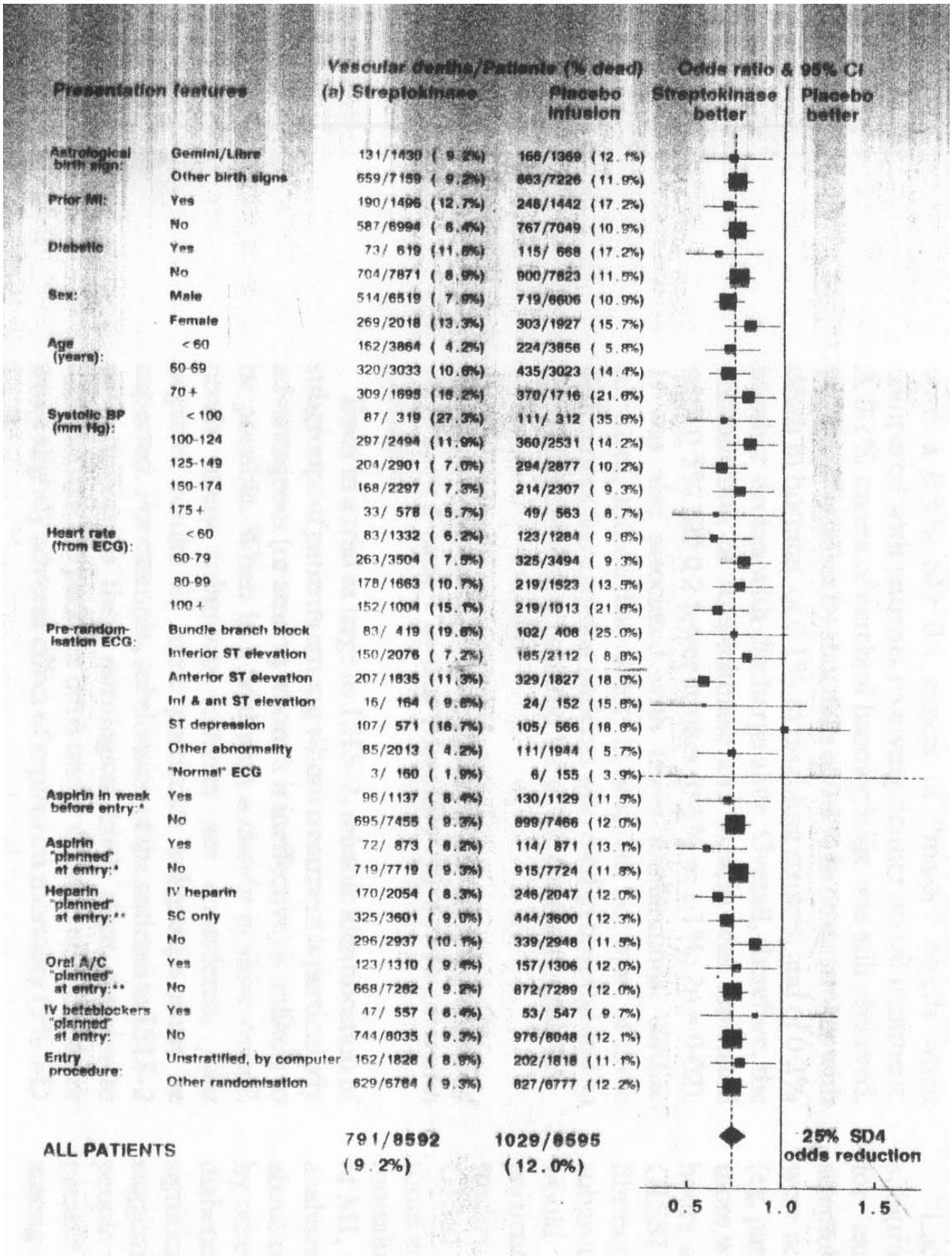
Sherwin: Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Ann Emerg Med. 2000 Mar 1;35(3):229–38.



SCENARIO #20

ISIS-2: Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988 13;2(8607):349-60.

Study: 17,187 patients entering 417 hospitals with suspected acute myocardial infarction were randomized to receive streptokinase, aspirin, both, or neither. Streptokinase alone and aspirin alone each produced a highly significant reduction in 5-week vascular mortality.


Presentation features
Vascular deaths/Patients (% dead)
(a) Streptokinase
Placebo infusion
Odds ratio & 95% CI
Streptokinase better
Placebo better
Astrological birth sign: Gemini/Libra 131/1430 (9.2%) 166/1369 (12.1%)
Other birth signs 659/7159 (9.2%) 863/7226 (11.9%)
Prior MI: Yes 190/1496 (12.7%) 248/1442 (17.2%)
No 587/6994 (8.4%) 767/7049 (10.9%)
Diabetic Yes 73/ 619 (11.8%) 115/ 668 (17.2%)
No 704/7871 (8.9%) 900/7823 (11.5%)
Sex: Male 514/6519 (7.9%) 719/6606 (10.9%)
Female 269/2018 (13.3%) 303/1927 (15.7%)
Age (years): < 60 162/3864 (4.2%) 224/3856 (5.8%)
60-69 320/3033 (10.6%) 435/3023 (14.4%)
70+ 309/1695 (18.2%) 370/1716 (21.6%)
Systolic BP (mm Hg): < 100 87/ 319 (27.3%) 111/ 312 (35.6%)
100-124 297/2494 (11.9%) 360/2531 (14.2%)
125-149 204/2901 (7.0%) 294/2877 (10.2%)
150-174 168/2297 (7.3%) 214/2307 (9.3%)
175+ 33/ 578 (5.7%) 49/ 563 (8.7%)
Heart rate (from ECG): < 60 83/1332 (6.2%) 123/1284 (9.6%)
60-79 263/3504 (7.5%) 325/3494 (9.3%)
80-99 178/1663 (10.7%) 219/1523 (13.5%)
100+ 152/1004 (15.1%) 219/1013 (21.6%)
Pre-randomisation ECG: Bundle branch block 83/ 419 (19.8%) 102/ 408 (25.0%)
Inferior ST elevation 150/2076 (7.2%) 185/2112 (8.8%)
Anterior ST elevation 207/1835 (11.3%) 329/1827 (18.0%)
Inf & ant ST elevation 16/ 164 (9.8%) 24/ 152 (15.8%)
ST depression 107/ 571 (18.7%) 105/ 566 (18.6%)
Other abnormality 85/2013 (4.2%) 111/1944 (5.7%)
"Normal" ECG 3/ 160 (1.9%) 6/ 155 (3.9%)
Aspirin in week before entry:* Yes 96/1137 (8.4%) 130/1129 (11.5%)
No 695/7455 (9.3%) 899/7466 (12.0%)
Aspirin "planned" at entry:* Yes 72/ 873 (8.2%) 114/ 871 (13.1%)
No 719/7719 (9.3%) 915/7724 (11.8%)
Heparin "planned" at entry:** IV heparin 170/2054 (8.3%) 246/2047 (12.0%)
SC only 325/3601 (9.0%) 444/3600 (12.3%)
No 296/2937 (10.1%) 339/2948 (11.5%)
Oral A/C "planned" at entry:** Yes 123/1310 (9.4%) 157/1306 (12.0%)
No 668/7282 (9.2%) 872/7289 (12.0%)
IV beteblockers "planned" at entry: Yes 47/ 557 (8.4%) 53/ 547 (9.7%)
No 744/8035 (9.3%) 976/8048 (12.1%)
Entry procedure: Unstratified, by computer 162/1828 (8.9%) 202/1818 (11.1%)
Other randomisation 629/6764 (9.3%) 827/6777 (12.2%)
ALL PATIENTS
791/8592
(9.2%)
1029/8595
(12.0%)
25% SD4 odds reduction
0.5
1.0
1.5

SCENARIO #21

LLU IRB application: "Surgical wound care, prayer, spirituality, and healing"

"Under the aegis of Adventist Health, The Southern California Healthcare Network, the Northern California Network, Portland Adventist Medical Center, and Loma Linda University Medical Center are participating in this multi-site study in order to correlate superior outcomes in surgical wound care."

"Consenting patients [with elective bowel surgery] will be entered into a double-blind randomized protocol to assess the therapeutic effects of intercessory prayer." "Half of the participating patients will be used as a control group, for which no intercessory prayer will occur by designated Prayer Teams. The other group will, on a daily basis for fourteen days, be prayed for by Prayer Teams. The Prayer teams are composed of evangelical Christians from Boise, Idaho, and Loma Linda, California, and who have volunteered for this study."

"The specific variables which will be included in the intercessory prayer include: prayer for rapid recovery, prevention of complications such as infections and unplanned return to the OR, and death." "To monitor their intercessory prayer activities, each pray-er will keep a standardized prayer log in which they record the date, time, length of prayer, method of prayer, and identifier number of the patients for whom they prayed."

"Clinical outcomes will be correlated for those receiving and not receiving prayer from the prayer partners."