ARTICLE:
Citation: Lin et al, Improved Outcomes in Patients With Acute Allergic Syndromes Who Are Treated With Combined H1 and H2 Antagonists. Annals of Emergency Medicine 36:5 November 2000
Country: USA
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PURPOSE:
• Research Question(s): What is / are the primary questions being addressed by this study? Usually found just before the methods.

**H1 and H2 blockade in treatment of acute allergic syndromes vs. H1 blockade alone.**

• Hypothesis: What is the anticipated outcome or alternatively, the null hypothesis (there will be no difference between groups).

They predicted that combined H1 and H2 blockade results in improved outcomes in patients treated for acute allergic syndromes compared with H1 blockade alone

DESIGN:
• Study Design:
Randomized, double blind, placebo Controlled

• Dependent / outcome Variable(s): What is the variable of interest / outcome being studied.

Resolution of urticaria, angioedema, or erythema at 2 hours after protocol treatment; also assessed were areas of cutaneous involvement, HR, BP, respiratory findings, and symptom scores

• Independent / research Variable: What is the variable that is modified among groups?

H2 blockers or placebo (specifically 50mg IV ranitidine)

SETTING / SUBJECTS:
• Research Setting: Inpatient / outpatient, rural / urban, academic / community, EM / non-em, etc.

ED patient population in urban academic medical center

• Subjects:
  • Study population: Who was studied (eg: all adults presenting with chest pain, all children with wheezing, etc).
ADULT patients >18 yrs old

- **Inclusion / Exclusion criteria:** Are there any important inclusion or exclusion criteria, especially those that may affect generalizability.

**Inclusion:** any of following after ingestion of food, or ingested/inhaled/injected drug, or contact with latex:
- Acute urticaria, acute angioedema, acute unexplained stridor, acute pruritic rash, no greater than 12 hours after onset

**Exclusions:** pregnant patients

- **Number (control / intervention groups):** Number of subjects in each group.

100 patients were set as sample size ultimately 91 analyzed (48 active, 43 placebo). One was inadvertently studied twice but his second study was discarded. Eight other patients withdrew after enrollment but before medication given.

- **Demographics:** Age, sex, race, etc.

Active vs. placebo:
- Age 32.3 and 31.7; 21/27 and 15/28 male/female respectively, predominantly white.
- No significant difference between study groups.

- **Attrition:** Did patients exit the study or were patients lost to follow up.

Yes 8 patients exited after enrollment but before medication administered

**METHODS:**

- **Interventions:** What, if any, interventions were performed among the study groups.

H1/H2 blockers at the outset

Supplemental medications such as epinephrine, steroids, bronchodilators, and additional antihistamine doses were administered at discretion of physician

- **Study Groups:** What were the various study groups (eg: control / placebo, intervention 1, intervention 2, etc)

**Active group** = 50mg diphenhydramine/ 50mg ranitidine
**Placebo** = 50mg diphenhydramine 50cc normal saline

- **Instruments:** What devices, special equipment, surveys, rating scales, etc. were utilized.

None aside from pre-printed symptom card form (None, mild, moderate, severe) and study specific form.

- **Data Collection:** Who collected data? What was their training? Was there consistency among data collectors? Were there changes to data collection / study protocol during the period of the study.

HR/BP/physical findings, side effects and symptoms assessed at baseline, 1, 2 hours; physical findings included urticaria, erythema, presence of angioedema, wheezing, stridor, abdominal distention or tenderness, hyperactive BS.
Information recorded on study specific form. To assess urticaria used a cartoon that was on this form. Symptom scores were checked with a pre-printed form that patients checked off.

Nine patients were found to have symptoms greater than 12 hours. These were included in an intention to treat analysis.

DATA ANALYSIS:
- **Level of Data:** Categorical (two or more categories without order, (ie: male / female)  
  Ordinal (hierarchical categories without set spacing, (ie: education level, death / discharge)  
  Interval (continuous data with set spacing, (ie: age, weight, hemoglobin)

**Categorical and ordinal**
- **Statistics Used:** What type of statistical tests were utilized (eg: T-test, ANOVA, regression analysis).
  Bivariate chi square, multivariate logistic regression, Greenhouse-Geisser adjustment for nonsphericity was applied. Normalized HR with logarithmic transformation.
  - **What, if any, variables were controlled for?** Do the results adjust for confounding variables?

**RESULTS:**
- **Brief answers to research questions:** What were the conclusions made by the authors? Do they answer the original research questions? Do you think their conclusions are valid based on the data reported?

More than half reactions were attributed to food allergies. Significantly more patients in placebo group received additional anti-histamines (10pts placebo vs. 2 active treatment).

Number of patients with urticaria decreased somewhat in active treatment at 1 hour, but there was a significant difference of patients without urticaria at 2 hours (91.7% vs. 73.8 p= 0.02). Also number of areas involved with urticaria was significantly different at 2 hours.

They also attempted to analyze one outcome of “absence of both angioedema and urticaria” and found there was a significant difference at 2 hours in the active group compared to placebo (70.5 vs. 46.5% p0.02). However when absence of angioedema at 2 hours (irrespective of urticaria) was analyzed alone there was no significant difference between the two groups.

There was significant decrease in HR in both groups, with slightly greater, but not significant decrease in the active treatment group.

Symptom scores didn’t show a difference between the two groups.
Authors concluded that adding H2 blockers to H1 blockers results in additional improvement of certain cutaneous outcomes therefore they favor the recommendation of using combined approach for treatment of acute allergic syndromes.

- Additional findings: An any additional findings other than the primary research questions discussed? Were these expected or unexpected based on the study design?
  No
- Other possible explanation for findings: Are their other possible / probable explanations for the results other than those presented by the authors? Do the results correspond with the purpose of the study? Consider: sample size issues, measurement issues (did they measure the right outcomes?), attrition, treatment integrity (was the intervention always delivered exactly the same way?), and other issues you identify.

Results correspond with the study

- Limitations: Are their important limitations identified by the authors? Do you see any other important limitations? Do these limitations significantly alter the conclusion or the applicability of the study?
  Probably the most important limitation in my mind is whether H2 blockade is helpful in anaphylaxis and they couldn’t answer this based off study size. Ability to reverse hypotension and bronchospasm with addition of H2 blockade remains unproven.

Other limitations include:
  - Mild severity of reactions,
  - IV treatment rather than PO therefore it’s unclear if PO would see similar benefit.
  - Multiple non-protocol medications were given
  - No follow-up of patients

IMPLICATIONS FOR PRACTICE:

- Applicable to this clinical practice: Is the study population generalizable to the population likely to be affected by this intervention / outcome in your clinical practice? If not, what setting may this be applicable to?
  I believe this study population is generalizable to our practice. Although described as an urban population, patient population was a majority Caucasian with minority Hispanic and African American.

- Feasible (cost, resources, etc): Is this an intervention that would be reasonable to institute in clinical practice? Are instruments / medications available? Does the study adequately assess risks and unforeseen outcomes? Is the intervention cost / resource effective? Does the study account for cost / benefit? Are there more effective treatments available?
  Easily feasible in our clinical practice.
• **Clinically Relevant**: Is this intervention likely to make a clinically significant impact on your patients if instituted? That is, some interventions may show statistically significant changes without making an impact that is clinically important.

I am less than convinced on clinical relevance regarding these interventions. Although H2 blockers improve urticaria at 2 hours and when combining urticaria and angioedema there is improvement, I am not sure if that is completely relevant. When angioedema is analyzed alone there was no significant difference and there was no evidence to support this improves anaphylaxis, which would be the endpoints I’m most concerned about. Furthermore no symptom scores improved for patients therefore the only significantly difference was objective cutaneous improvement. On the converse, there is minimal to no downside to using H2 blockers and it would be very easy to do so. Thus until further evidence proves their lack of efficacy in anaphylaxis I would probably continue to use them.

**LEVEL OF EVIDENCE / DECISION FOR USE:**

- **Background**  
  Consider Replication  
  Ready for use

- **Level of Evidence**:
  - Ia Evidence obtained from meta-analysis of randomized controlled trials  
  - **Ib Evidence obtained from at least one RCT**  
  - IIa Evidence obtained from at least one well-designed controlled study without randomization  
  - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study  
  - III Well-designed non-experimental studies  
  - IV Expert committee reports, opinions of experts