Is permethrin 5% cream effective for rosacea?

Kocak M, Yagli S, Vahapoglu G, Eksioglu M, Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea: randomized double-blind placebo-controlled study. Dermatology 2002; 205:265–270.

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PRACTICE RECOMMENDATIONS

Permethrin 5% cream is a safe alternative for the topical treatment of papulopustular rosacea.

Permethrin 5% cream is superior to metronidazole 0.75% gel and placebo in decreasing *Demodex folliculorum,* and is as effective as metronidazole 0.75% gel in treating erythema and papules.

BACKGROUND

The skin mite *D folliculorum* has been implicated as a cause of rosacea. However, other possible causes include a genetic predisposition, psychogenic factors, gastrointestinal diseases, and seborrhea. Permethrin is a topical insecticide effective against a wide variety of arthropods, including *D folliculorum.*

POPULATION STUDIED

These researchers studied 63 patients, ages 20 to 80 years, with papulopustular rosacea. The duration of disease was 0.17 to 15 years (mean 2.9 years). Study participants were selected from an outpatient dermatology clinic in Ankara, Turkey; 48 women and 15 men. A diagnosis of papulopustular rosacea was based on clinical and histopathological findings. Patients were eligible if they had at least 10 inflammatory papules or pustules. Exclusion criteria were erythematotelangiectatic rosacea, fulminant rosacea, systemic treatment of the eyes, and use of oral anticoagulants.

STUDY DESIGN AND VALIDITY

This study was a randomized, double-blind trial in which patients with papulopustular rosacea were assigned to one of three topical treatments: permethrin 5% cream, metronidazole 0.75% gel, or placebo. Patients were provided with and encouraged to use sunscreen. All patients were followed for a total of 60 days. The authors did not specifically state whether the treatment allocation was concealed or if all patients completed the study.

Patients received 2 months of treatment given twice a day and were evaluated on days 15, 30, 45, and 60. At each assessment, mean scores were obtained for erythema, telangiectasia, edema, rhinophyma, and medication side effects.

The weaknesses of this study are that the authors did not state whether the treatment allocation was concealed or if all patients completed the study. Interpretive scoring for erythema was subjective, and it is not clear

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

whether the same physician scored this value at each assessment.

Also, the more accurate and sensitive standard to determine the number of *D folliculorum* is a skin surface biopsy. These researchers chose to do skin scrapings because it was less invasive and subjects were going to be evaluated 5 times. Consequently, the data pertaining to *D folliculorum* cannot be compared with other studies using the standard biopsy.

OUTCOMES MEASURED

The primary outcomes for this study were the change in the number of papules and pustules, change in erythema scores (assessed on a scale from 0 to 3), and counts of *D folliculorum.* Comparisons were made based on change from baseline at day 0 to day 60, with additional analyses comparing changes at each assessment on days 15, 30, 45, and 60. Secondary outcomes included telangiectasia, edema, rhinophyma, and side effects of the topical treatments.

RESULTS

Using intention-to-treat analysis, permethrin 5% cream was as effective as metronidazole 0.05% gel and significantly superior to placebo at improving erythema (change from a baseline score of 2.60 to 1.34), papules (change from baseline count of 6.04 to 1.73), and pustules (change from baseline count of 2.30 to 0.56).

Permethrin 5% cream was more effective at suppressing *D folliculorum* than metronidazole 0.05% gel. Permethrin cream began showing effective changes in erythema, papules, number of *D folliculorum* on day 15, and pustules on day 45. This positive outcome continued throughout the 60-day study.

Metronidazole did not show a significant effect on *D folliculorum* until days 45 to 60. Neither permethrin nor metronidazole had any significant effect on telangiectasia or rhinophyma. No complications or side effects with any of the topical treatments were reported.

Is imiquimod effective and safe for treatment of actinic keratosis?

Stockfleth E, Meyer T, Benninghoff B, et al. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. Arch Dermatol 2002; 138:1498–1502.

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PRACTICE RECOMMENDATIONS

Imiquimod 5% cream, applied 3 times per week for 12 weeks, is effective for treatment of actinic keratosis. Severe erythema and other local reactions occurred in almost everyone receiving treatment, due to imiquimod's immune system–modulating effects.

The 25 patients in the treatment group tolerated these adverse effects well. Despite these effects, imiquimod can be used as an alternative to traditional cryotherapy for the treatment of actinic keratosis among selected, motivated patients.

BACKGROUND

Actinic keratosis is a precancerous skin lesion commonly found on areas frequently exposed to the sun. Among aging Americans, these lesions are regularly identified and treated in the clinical setting with cryotherapy. This manufacturer-sponsored study evaluated the efficacy and safety of 5% imiquimod (Aldara) cream for the treatment of actinic keratosis.

POPULATION STUDIED

Patients were selected from a dermatology practice in Germany. Of 52 patients screened, 36 men and women with histopathologically diagnosed actinic keratosis were enrolled. Study patients were ages 45 to 85 years. Each patient had 3 to 10 actinic keratosis lesions on the scalp, forehead, dorsal forearm, neck, or dorsal hand.

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Patients were excluded if they were receiving immune modulators (including imiquimod) or were recently treated for a viral or bacterial infection. Patients with cardiovascular, hematologic, hepatic, neurologic, renal, endocrine, vascular, or gastrointestinal conditions were also excluded.

STUDY DESIGN AND VALIDITY

The study was a randomized, double-blind, vehicle-controlled clinical trial. Histopathologic diagnosis was confirmed in 36 enrollees. The imiquimod group had 25 patients, while the vehicle cream control group had 11 patients. Masking of patients, physicians, and outcome assessors was appropriate, as was allocation concealment.

Each patient applied the cream 3 times per week for 12 weeks. The cream was left on for 8 hours at a time. Patients were assessed at 2, 3, 6, 9, 12, and 14 weeks. Enrollees were also evaluated 1 year after treatment. Among patients with severe reactions, application was reduced to 1 or 2 times per week. Rest periods were also allowed.

Analysis was by per-protocol basis rather than by intention-to-treat, so only 36 of 52 patients were included in the final results. Some were excluded for misdiagnosis, and 2 each from the control and treatment group were excluded for noncompliance (the reasons were not given). Despite lack of intention-to-treat analysis, this study would have likely been statistically significant had all potential enrollees been included.

OUTCOMES MEASURED

The number and appearance of lesions were evaluated during and after treatment. Clinical clearance was confirmed by histopathology. All adverse reactions were recorded.

RESULTS

Twenty-one participants (84%) of the treatment group experienced complete clinical and histological clearance; 2 additional participants (8%) had partial clearance. Among the 11 control group patients, there was no reduction in the size or number of lesions.

Recurrence of actinic keratosis was observed in 2 patients (10%) 1 year after treatment. Adverse effects were seen in almost all treated patients. Severe erythema was noted in more than 80% of patients. Even after treatment at 14 weeks, about half the participants had persistent erythema.

A majority of patients also experienced moderate erosions, flaking, ulcerations, and scabbing. In the treatment group, 18 patients reduced treatment frequency to 1 or 2 times per week for varying lengths of time because of adverse effects.

Does C-reactive protein predict cardiovascular events in women better than LDL?

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347:1557–1565.

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PRACTICE RECOMMENDATIONS

C-reactive protein (CRP) is an independent predictor of a first cardiovascular event in women and appears to be a stronger predictor than low-density lipoprotein (LDL) cholesterol levels.

Unfortunately, this information does not lead directly to a therapeutic intervention. As an accompanying editorial stated, low carotenoid levels also predict cardiovascular events, but supplementation with beta carotene does not reduce an individual's risk.[1]

This study does not clarify whether CRP is a causative agent, a marker, or a result of cardiovascular disease. Our focus should remain on identifying and treating conventional risk factors until we better understand the exact role CRP has in therapeutic decisions regarding cardiovascular disease.

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Focus on treating conventional risk factors until CRP's role in clinical decisions becomes clear

BACKGROUND

A growing body of evidence suggests an important role for inflammation in cardiovascular disease. Nested case-control studies have shown a consistent association between CRP and cardiovascular events such as stroke or myocardial infarction (MI). People in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) were most likely to have benefit from lovastatin if they had elevated CRP.[2]

POPULATION STUDIED

The subjects were women enrolled in the Women's Health Study, an ongoing trial evaluating aspirin and vitamin E for the primary prevention of MI. These women were all older than 45 when enrolled from 1992 to 1995. There were 28,345 women who had blood drawn at the onset of the trial, but only 27,939 women (with a mean age of 54.7 years) had samples that could be evaluated. Forty percent were using hormone replacement therapy (HRT), 25% had hypertension, 12% were smokers, and 2.5% were diabetic.

STUDY DESIGN AND VALIDITY

This prospective cohort study followed the women for a mean of 8 years. Cholesterol and CRP levels from the more than 15,000 women not on HRT were used to create the population-based distributions. The researchers found the crude and risk-adjusted hazard ratio for each quintile of CRP levels compared with the lowest quintile value. They also evaluated the additive predictive properties of CRP, as well as LDL cholesterol, and measured the effect of adjusting the Framingham 10-year cardiovascular risk score with CRP levels.

This study used solid methods to evaluate the prognostic value of CRP. Follow-up was over 99% for the first 6 years. The population studied were all women, so generalizing these results to men will need further evaluation.

OUTCOMES MEASURED

The primary outcome was the ability to predict the occurrence of a first cardiovascular event, defined as nonfatal MI, nonfatal ischemic stroke, coronary revascularization procedures, or death from a cardiovascular disease. Standard definitions were used to determine whether patients had these events. They also analyzed the risks for developing each type of event individually.

RESULTS

The median CRP level was 1.52 mg/L and the median LDL was 123.7 mg/dL. The risk for a first cardiovascular event was linearly associated with increasing CRP levels. The adjusted relative risk of first cardiovascular event for increasing quintiles of CRP was 1.0 (the lowest quintile serves as the reference), 1.4, 1.6, 2.0, and 2.3. The adjusted risk for increasing quintiles of LDL was 1.0 (reference), 0.9, 1.1, 1.3 and 1.5. These findings are consistent with each type of event (stroke, MI, etc) as well as being independent of HRT usage.

They created a predictive model based on whether patients were above or below the median CRP and LDL levels. The adjusted relative risks for these groups were: low CRP and low LDL=1.0 (reference); low CRP and high LDL=1.5; high CRP and low LDL=1.5; high CRP and high LDL=2.1 (95% confidence interval=1.5–2.8).

Adding CRP information to the Framingham score (based on age, smoking status, blood pressure, diabetes, HDL and LDL levels) improved the predictive value of the score. Even with an identical score, patients with the highest quintile CRP level had a 1.9 times greater chance of a first cardiovascular event than patients in the lowest quintile.

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Does acetaminophen affect liver function in alcoholic patients?

Kuffer EK, Dart RC, Bogdan GM, Hill RE, Caper E, Darton L. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients. Arch Intern Med 2001; 161:2247–2252.

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PRACTICE RECOMMENDATIONS

Acetaminophen in doses of 4 g/d did not affect liver function of alcoholic patients in this randomized study.

These results do not rule out the possibility of acetaminophen-induced liver failure in alcoholic patients, especially patients with pre-existing liver disease or those who continue to drink. Patient-oriented outcomes (ie, studying chronic acetaminophen use in alcoholics to determine the incidence of developing hepatic failure) ultimately would resolve this controversy.

However, these data do cast doubt on the medical myth (based on case reports) that acetaminophen use in alcoholics causes hepatotoxicity.

BACKGROUND

Traditionally, acetaminophen use in alcoholics has been discouraged due to uncontrolled retrospective data (mostly case reports) that suggest drug-induced hepatotoxicity with therapeutic doses.

However, other available analgesic therapy options in alcoholic patients are limited. Nonsteroidal anti-inflammatory drugs are associated with much more common adverse gastrointestinal effects in this population, and opiate analgesic use incurs a risk of substance abuse. This study evaluated the effect of the short-term administration of full doses of acetaminophen on liver function in alcoholic patients.

These results do not rule out acetaminophen-induced liver failure in alcoholics, but they do cast doubt

POPULATION STUDIED

This study included 201 alcoholic patients at least 18 years of age who had entered an alcohol detoxification facility in Denver, Colorado. Patients were excluded if baseline laboratory values were abnormal (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels >120 U/L, international normalized ratio [INR] >1.5, or serum acetaminophen concentration >20 mg/L), if they had a history of ingesting more than 4000 mg/d of acetaminophen within 4 days of enrollment, an allergy to acetaminophen, were enrolled in any other trial within the previous 3 months, or were intoxicated with alcohol at the time the first dose of study medication was administered.

This patient population represented alcoholics in primary care who did not have evident liver dysfunction and had very recently stopped drinking.

STUDY DESIGN AND VALIDITY

This was a randomized, double-blind, controlled study. Allocation to treatment group (determined with computer software) was concealed from the investigator involved with patient evaluations and care.

Acetaminophen, 1000 mg, or an identical placebo was administered orally 4 times daily for 2 consecutive days. Laboratory studies (acetaminophen concentration, AST, ALT, γ–glutamyl transferase, and INR) were evaluated at baseline and on days 2 and 4. Alcohol concentrations were determined at initial presentation with the use of a breath alcohol analyzer. Patients were classified into 1 nutrition category (normal nutrition status, mild malnutrition, moderate malnutrition, or severe malnutrition), and body mass index was calculated.

This was a well-designed study. Appropriate

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disease-oriented outcomes (changes in liver function tests) were evaluated. The selected acetaminophen regimen represents maximum daily dosing and the recommended first-line treatment of chronic pain conditions (eg, osteoarthritis).

Just after an alcoholic stops drinking (with negative serum ethanol serum concentrations) is when conversion of acetaminophen to its potentially hepatotoxic metabolite is highest. Therefore, the time of acetaminophen dosing in this study represented the period of greatest vulnerability. However, results apply only to short-term acetaminophen use in alcoholics without evident liver dysfunction. Alcoholic patients commonly seen in primary care may require acetaminophen therapy longer than 2 days.

OUTCOMES MEASURED

The primary outcomes measured were changes in liver function tests (AST, ALT, and INR) at baseline, 2 days after acetaminophen use, and 2 days after stopping acetaminophen.

RESULTS

Overall, 102 patients randomized to receive acetaminophen and 99 patients randomized to receive placebo completed the study. There were no statistically significant differences in demographic or baseline laboratory values between groups. Mean AST, ALT, and INR values did not differ between groups. Time-dependent changes in INR were not seen (P=.07).

Four patients in the acetaminophen group and 5 in the placebo group developed AST or ALT values greater than 120 U/L, but no values in any patient went above 200 U/L. The highest individual aminotransferase (197 U/L) and INR (1.75) values occurred in the placebo group. Post hoc subgroup analysis showed no increase in liver function among patients with low body-mass indexes or in patients classified as malnourished.

Are diuretics helpful in acute renal failure?

Mehta LM, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA 2002; 288:2547–2553.

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PRACTICE RECOMMENDATIONS

Although widely used to treat acute renal failure, diuretics may actually be harmful.

The results of this observational study demonstrated a higher risk of death and non-recovery of renal function when diuretics were initiated during the first week of hospitalization. It didn't matter whether a single or combination diuretic was used.

A randomized controlled trial would better answer this question by minimizing the inherent flaws in an observational study. Although this study doesn't conclusively prove that diuretics cause poorer outcomes, it certainly raises the possibility and should prompt us to think twice before initiating diuretic therapy for acute renal failure.

BACKGROUND

Diuretics continue to be widely used for treating acute renal failure despite the lack of supporting evidence. The ability to promote renal salt and water excretion with diuretics and extracellular volume overload in patients with acute renal failure influences the decision of many practitioners to use these medications.

This study evaluated the effects of diuretics on mortality, renal function, and length of hospital stay in hospitalized patients with acute renal failure.

POPULATION STUDIED

The authors studied 552 critically ill patients with acute renal failure in 4 California academic medical center ICUs. In patients without previous kid-

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ney disease, acute renal failure was defined as blood urea nitrogen >40 mg/dL or creatinine >2 mg/dL. In others, acute renal failure was defined as creatinine levels rising at >1 mg/dL compared with baseline. Patients were excluded if they had previous dialysis, urinary tract obstruction, or hypovolemia.

STUDY DESIGN AND VALIDITY

Patients in this prospective cohort study were placed into groups according to which day diuretics were initiated during the first week following consultation. Patients were also categorized as "ever" or "never" having received diuretics. Patients received 1 or more of the following: furosemide, bumetanide, metolazone, and hydrochlorothiazide.

The researchers monitored vital signs, urine output, blood urea nitrogen, and serum creatinine levels each day until hospital discharge. They calculated disease-specific severity-of-illness scores daily in the ICU based on the number of organ systems in failure.

Because these patient groups were given therapies not randomly assigned, the researchers adjusted for confounding variables with regression methods based on propensity scores of illness severity.

The study design used in this research limits our ability to draw conclusions regarding any true causal relationship between diuretic use and poorer outcomes. A randomized controlled trial is needed to definitively establish cause and effect.

Also, the results from this study of critically ill patients cannot be generalized to patients with less severe forms of acute renal failure. The results may not apply to patients in other medical institutions where management of acute renal failure and availability of dialysis differs.

OUTCOMES MEASURED

The primary outcomes were mortality, nonrecovery of renal function, and length of hospital stay.

RESULTS

Of the 552 patients included in the final sample, 294 (53%) died in the hospital. Of the 258 patients who survived, 17 required dialysis following discharge. Diuretics were used in 326 patients (59%).

Based on adjusted models, the use of diuretics was associated with a 68% increase in mortality (odds ratio [OR]=1.68: 95% confidence interval [CI], 1.06–2.64) and a 79% increase in the nonrecovery of renal function (OR=1.79; 95% CI, 1.19–2.68). Length of stay was not affected if diuretics were started on the first day of consultation (median 21.5 vs 22.5 days). However, diuretics initiated any other day during the first week prolonged hospital stays by a median of 4 to 10 days.

Patients who received diuretics at any time during that week had higher risk of death or nonrecovered renal function compared to patients who never received a diuretic (OR=3.12; 95% CI, 1.73–5.62). Patients with low urine output despite higher-dose diuretics died or needed dialysis sooner than patients who became nonoliguric with lower-dose diuretics. No significant differences in mortality, nonrecovery of renal function, and length of hospital stay occurred when comparing patients receiving combination diuretics vs single diuretics.

Is topical nifedipine effective for chronic anal fissures?

Perrotti P, Bove A, Antropoli C, et al. Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. Dis Colon Rectum 2002; 45:1468–1475.

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PRACTICE RECOMMENDATIONS

Patients in this study showed remarkable improvement when 1.5% lidocaine and 0.3%

nifedipine were applied twice daily for 6 weeks. This extremely safe, well tolerated, and effective treatment should provide family physicians with a reliable nonsurgical method for treating chronic anal fissures.

BACKGROUND

Acute anal fissures generally heal spontaneously with minimal or no intervention. Conversely, chronic anal fissures are traditionally treated with surgery. Therapies such as botulinum toxin, isosorbide dinitrate, and glyceryl tinitrate have shown some benefit, but their side-effect profiles are substantial. With the knowledge that topical nifedipine has been shown to relax smooth muscle, lower anal resting pressure, relieve pain, and heal acute anal fissures, these authors studied its effect on chronic anal fissures.

POPULATION STUDIED

Patients were recruited from the emergency surgery and gastroenterology center in Italy that conducted the study. Inclusion criteria were chronic anal fissure and age older than 18 years. Chronic anal fissure was assessed by clinical examination and a history of anal pain on defecation for longer than 2 months that did not resolve with stool softeners and simple anesthetic agents. Exclusion criteria were pregnancy, allergy to nifedipine or lidocaine, and complications warranting surgery.

STUDY DESIGN AND VALIDITY

This was a prospective, randomized, double-blind study. The control group received 1.5% lidocaine and 1% hydrocortisone acetate, and the treatment group received 1.5% lidocaine and 0.3% nifedipine. The ointments were applied every 12 hours for 6 weeks. The ointments were indistinguishable, and all parties were blinded with proper allocation concealment. Data analysis was by intention-to-treat. The groups were randomly assigned and had similar baseline characteristics.

The ethics committee required the control ointment to have hydrocortisone with lidocaine rather than a true placebo. It is possible that hydrocortisone was detrimental to healing and thus made the nifedipine ointment appear even better than it would have if compared with a true placebo. Also, the authors did not explain why clinical examination was done at 42 days, but manometric examination and clinical pain score was performed at 21 days. Overall this study was methodical and well-executed. Further, no patients were lost to follow-up.

OUTCOMES MEASURED

Healing of the chronic anal fissure was the primary outcome and was defined by anoscopy when epithelialization or formation of a scar was achieved at 42 days. Patients also subjectively rated pain as absent, modest, or persistent at day 21. Manometric studies were used as a secondary measure of clinical improvement and were measured at baseline and 21 days.

RESULTS

Of the 55 patients in the nifedipine group, 94.5% healed clinically at 42 days and 87.3% reported no pain at 21 days. Conversely, of the 55 patients in the control group evaluated at the same intervals, 16.4% healed and 10.9% reported no pain ($P<.001$; number needed to treat=1.3).

In the healed nifedipine group, 3 patients experienced a recurrence of their ulcers, and 2 were treated successfully with a second round of nifedipine. In the control group, 5 of the 9 who initially healed experienced a recurrence of the ulcer and also were treated successfully with nifedipine.

Mean anal resting pressure decreased by 11.0% in the nifedipine group but increased by 4.4% in the control group. After removal of blinding, 46 patients who were not healed in the control group were offered the nifedipine treatment. Of these, 38 healed with nifedipine ointment. No patients in the nifedipine group had any systemic side effects, whereas 1 patient treated with nifedipine and 3 in the control group had slight local hyperemia, which improved when treatment was completed.

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Is rate control better than rhythm control for atrial fibrillation in older high-risk patients?

AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347:1825–1833.

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PRACTICE RECOMMENDATIONS

Mortality with atrial fibrillation is similar with rhythm control and rate control treatment. However, adverse drug events and hospitalizations are more frequent with rhythm control therapy. Rate control therapy for atrial fibrillation should be the primary treatment strategy for an older high-risk population, but should not be extrapolated to younger and healthier patients (eg, patients with lone atrial fibrillation). These findings are consistent with another smaller study of patients with recurrent persistent atrial fibrillation.[1]

BACKGROUND

The goal for managing high-risk patients who have atrial fibrillation traditionally has been to achieve and maintain normal sinus rhythm. This approach often requires multiple episodes of cardioversion and the chronic use of potentially toxic anti-arrhythmic drugs. However, rate control with chronic anticoagulation therapy is a potentially safer and more commonly used approach.

POPULATION STUDIED

This multicenter study included 4060 patients with atrial fibrillation, who were over the age of 65 years and had other risk factors for stroke or death (not described, but determined based on the judgment of the clinical investigators). At baseline, 50.8% had hypertension, 26.1% had coronary artery disease, and 23.1% had a history of heart failure.

Patients were included if they had atrial fibrillation that was likely to be recurrent, likely to cause illness or death if persistent, and required long-term therapy. Patients were not included if anti-coagulation therapy was contraindicated or if they were not candidates for either rate or rhythm control therapy.

STUDY DESIGN AND VALIDITY

In this unblinded study, patients were randomized to receive either rhythm control or rate control therapy and were followed for a mean of 3.5 years. Concealment of allocation to treatment group was not discussed. In the rhythm control group, the treating physician chose the anti-arrhythmic drug. Cardioversion and combination therapy were allowed if necessary. Amiodarone was used most frequently (62.8% used at any time) followed by sotalol (41.1%), propafenone (14.5%), and others.

At least 1 attempt at electrical cardioversion occurred in 18.1% of the rhythm control patients. In the rate control group, the treating physician selected digoxin (70.6% used at any time), beta-blockers (68.1%), diltiazem (46.1%) or verapamil (16.8%). These drugs were titrated to a resting heart rate of not more than 80 beats/minute (and not greater than 110 after a 6-minute walk test).

Combination therapy was allowed. Continuous anticoagulation with warfarin (goal of an international normalized ratio of 2.0 to 3.0) was mandated in the rate control group, and encouraged in the rhythm control group.

This was a relatively well-designed study, funded by the National Heart, Lung, and Blood Institute. Patients evaluated represent a commonly seen older primary care population with complicated atrial fibrillation. Appropriate disease-oriented outcomes (death, vascular events, adverse drug events) were evaluated.

Many patients originally randomized to one therapy group eventually used medications from the other therapy group. This was more frequent in the rhythm control group than in the rate control group (27.3% vs 11.6% after 3 years, and 37.5% vs 14.9% after 5 years). The percentage of

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patients maintaining sinus rhythm in the rhythm control group declined with time (82.4% at 1 year, 73.3% at 3 years, and 62.6% after 5 years).

Although the investigators required an age of at least 65 years for inclusion, 969 patients (24%) were less than 65 years old. The lack of concealed allocation during the enrollment process might have allowed for selective enrollment of patients that favored one treatment over another.

OUTCOMES MEASURED

Overall mortality was the primary endpoint. A composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest was the secondary endpoint. Hospitalizations and adverse drug events were other outcomes measured.

RESULTS

There was no statistical difference in mortality (26.7 and 25.9 %, rhythm and rate control groups, respectively; P=.08) or in the composite secondary endpoint mortality (32.0 and 32.7%, rhythm and rate control groups, respectively; P=.33). Hospitalizations were more frequent in the rhythm-control group as compared with the rate-control group (80.1% vs 73.0%; P<.001). Adverse drug effects such as pulmonary events, gastrointestinal events, bradycardia, prolonged corrected QT interval, and Torsade de pointes were all statistically higher in the rhythm-control group (P<.07 for all). Continuous warfarin therapy was frequently used in both groups (85% and approximately 70%, rate and rhythm control groups, respectively).

The rates of stroke were similar between groups (approximately 1% per year). Subanalyses revealed statistically fewer deaths with rate-control in patients 65 or older, in coronary disease, and in heart failure.

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Are ionized wrist bracelets better than placebo for musculoskeletal pain?

Bratton R, Montero D, Adams K, et al. Effect of "ionized" wrist bracelets on musculoskeletal pain; A randomized, double-blind, placebo-controlled trial. Mayo Clin Proc 2002; 77:1164–1168.

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PRACTICE RECOMMENDATIONS

As a result of a profound placebo effect, this study showed that Q-Ray ionized wrist bracelets were not superior to placebo bracelets in self-reported pain improvement among patients with musculoskeletal pain.

Like many other studies involving the treatment of pain, the perception that the treatment would work profoundly improved its effectiveness. While the bracelet did not work better than placebo, many patients may experience less pain if they purchase and use it.

BACKGROUND

Currently, there are advertisements claiming that this ionized bracelet relieves musculoskeletal pain. This study compared the efficacy of ionized wrist bracelets and identical placebo wrist bracelets in treating musculoskeletal pain.

POPULATION STUDIED

The researchers studied a group of 610 adults (recruited from advertisements posted at the Jacksonville, Florida Mayo Clinic) with pain in at least 1 of 12 locations: neck, shoulders, elbows, wrists, hands, upper back, mid back, lower back, hips, knees, ankles, or feet. The mean age of the participants was 48 years; most were female (74.2%) and white (87.8%). Similar numbers of participants in both treatment groups had previously used ionized bracelets (4.5%), and about 80% believed the ionized bracelet would work.

STUDY DESIGN AND VALIDITY

The study was a randomized, placebo-controlled trial. Patients, researchers, and the bracelet manufacturer were blinded to the identity of the bracelets. Allocation was concealed during enrollment. The patients were randomly assigned to wear the ionized wrist bracelet or an identical placebo bracelet for 4 weeks. Patients wore the bracelets according to manufacturer's instructions. All 610 patients completed the study.

The project was well designed. Identical bracelets were provided by the same manufacturer. All of those who might have been biased in their assessment of effect had they known the identity of the bracelets were blinded to treatment assignment.

There are, however, several factors limiting the generalizability of the results to primary care patients. First, study participants were mostly middle-aged, white women recruited in a tertiary care center who believed that ionized bracelets work. Second, although similar percentages in both treatment groups reported pain and injury at specific locations, the duration and cause of pain were not disclosed. Additionally, the authors did not provide a discussion of the power calculation for the sample size necessary to find a difference if one existed.

OUTCOMES MEASURED

The authors measured 2 primary endpoints. The first was the change in pain score on a 10-point scale at 4-week follow-up at the location where baseline pain was most severe. The second endpoint was change in the sum total of pain scores for all locations after 4 weeks of bracelet use.

RESULTS

There was no significant difference between the 2 groups for either endpoint. The baseline pain score for all body locations for both groups was between 4.2 and 5.8 out of a possible 10; at 4-week follow-up the scores had decreased 1.3 to 2.6 points. Most (77%) individuals in both groups reported improvement in their maximum pain score and a similar percentage had an improved sum of pain scores.

An ionized bracelet is no better than placebo, but many patients may experience less pain with it

Does magnesium therapy early in acute MI reduce mortality?

Antman E, Cooper H, Domanski M, et al. Early administration of intravenous magnesium to high risk patients with acute myocardial infarction in the magnesium in coronaries (MAGIC) trial: a randomised controlled trial. Lancet 2002; 360:1189–1196.

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PRACTICE RECOMMENDATIONS

Short-term mortality is not reduced with early administration of intravenous magnesium in high-risk patients having an acute myocardial infarction (MI). There is no reason to give intravenous magnesium unless patients have other indications for repletion, such as a low magnesium level or arrhythmia responsive to magnesium therapy.

BACKGROUND

Research is conflicting regarding the usefulness of magnesium therapy in patients with acute MI. An early study of 2316 patients and a prior meta-analysis of 7 studies involving 1266 patients found reductions in acute MI mortality with intravenous magnesium therapy. However, a very large study of 58,050 patients showed no reduction in mortality, although magnesium therapy was given late in this study and the patients receiving it had a low mortality risk. This trial is the largest study to adequately address the role

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of magnesium therapy given early to patients at high risk of dying.

POPULATION STUDIED

The researchers enrolled 6213 patients with acute MI and at high risk for short-term mortality from 278 sites in 14 countries. The mean age was 70 years, 26% of patients had a previous acute MI, and 45% of participants were women.

Acute MI was defined as ischemic pain and ST segment elevation in contiguous leads or a new left bundle branch block. Patients were older than 65 years and candidates for reperfusion (n=1924) or any age but ineligible for reperfusion (n=4289). Exclusion criteria were treatment for acute MI within the previous 7 days, persistent hypotension, sustained bradycardia, advanced heart block, severe renal insufficiency, or current involvement in another trial.

STUDY DESIGN AND VALIDITY

Patients were randomly assigned to receive placebo (n=3100) or intravenous magnesium (n=3113). Magnesium therapy was initiated within the first 6 hour of symptoms, with a 2-g infusion administered over 15 minutes followed by a 17-g infusion over the next 24 hours. Doses were selected based on prior studies of safety and efficacy. All other treatment decisions were left to the discretion of the treating physician. Patients were followed for 30 days. The primary endpoint was 30-day mortality.

Allocation was adequately concealed through a centralized randomization process. Random-ization was effective with similar patients in the control and intervention groups. Blinding also was well maintained throughout the study. The study was large enough, given the high short-term mortality, to find at least a 20% difference between the groups, if it existed. Analysis was by intention-to-treat, and only 5 patients were lost to follow-up. Overall, this study applies to most patients hospitalized with acute MI. There is no reason to suspect that findings would not generalize to patients at lower risk for short-term mortality.

OUTCOMES MEASURED

The primary endpoint was 30-day all-cause mortality as measured by patient contact, the medical record, or a death certificate. Predefined secondary endpoints included treatment for heart failure, defibrillation for ventricular fibrillation or sustained ventricular tachycardia, and treatment with a temporary pacemaker.

RESULTS

At 30 days, 475 patients (15.3%) in the magnesium group and 472 patients (15.2%) in the placebo group had died (odds ratio, 1.0; 95% confidence interval, 0.9–1.2). There was no treatment effect even after multivariate analysis to adjust for other factors affecting mortality. Also, the authors reported no statistically significant differences with magnesium therapy for any secondary endpoint.

What are the risks of long-term NSAIDs and COX-2 inhibitors?

Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ 2002; 167:1131–1137.

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PRACTICE RECOMMENDATIONS

This review presents an interesting new analysis of cyclo-oxygenase-2 (COX-2) inhibitor safety, concluding that long-term use results in more serious adverse events than traditional nonsteroidal anti-inflammatory drugs (NSAIDs).

The nonsystematic and retrospective properties of this analysis limit its validity. However, the fact that an evaluation of long-term data found some small harm to COX-2 inhibitors relative to traditional NSAIDs (number needed to harm=78 over 9 months) should give clinicians pause. Until better meta-analyses or new safety data are published, clinicians should prescribe

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COX-2 inhibitors long-term only for those patients deemed to be at high risk of ulcer complications.

BACKGROUND

Much of the widespread use of COX-2 inhibitors is due to the perception that they are safer than traditional NSAIDs. However, in terms of patient-oriented outcomes, their real safety is unknown.

The 2 major studies in this area, the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR), originally published results based on 6 months of data. However, as published in publicly available Food and Drug Administration (FDA) reports, these studies actually accrued a median of 9 months of data. The author of this review discusses the reasons for the differences in safety between the 2 classes of NSAIDs, and presents new analyses of their safety based on the longer study periods.

POPULATION STUDIED

The patient population being analyzed is the same as in the CLASS and VIGOR studies: adults with osteoarthritis and rheumatoid arthritis. The author reanalyzed results from these 2 studies only.

STUDY DESIGN AND VALIDITY

This was not a systematic review; no literature searches were performed or inclusion criteria described. The author apparently extracted data from the FDA's public reports on the full, long-term results of both the CLASS and VIGOR studies. These data were used to provide separate and pooled estimates of adverse events for each study.

A limitation of this review is that it only included 2 studies; however, these 2 studies are the largest trials published on this issue. Also, the author's definition of "serious adverse event" was not well defined, and retrospective examination of the data in the FDA's report could potentially lead to a biased analysis in favor of the author's viewpoint.

The author also did not consider any possible confounding variables or limitations of including the later data in the analysis. For example, in a letter to the editor,[1] the authors of the CLASS study stated that subjects in the traditional NSAID group dropped out earlier in the study. These patients were those at greater risk of complicated ulcers, resulting in a lower-risk group later on and biasing the long-term results. Nevertheless, these studies represent the best long-term data available on the safety of COX-2 inhibitors.

OUTCOMES MEASURED

The author reported total mortality, serious adverse events (death, hospital admission, life-threatening events), and complicated ulcers for each study individually and a pooled estimate for both studies (median duration of 9 months).

RESULTS

There was no significant difference in overall mortality between traditional NSAIDs and COX-2 inhibitors for either study or in the pooled estimate. The risk of serious adverse events was significantly higher (absolute risk increase =1.3%; number needed to harm [NNH]=78) in the pooled estimate as well as the rofecoxib study, but not in the celecoxib study. The risk of complicated ulcers was significantly lower in the rofecoxib study (absolute risk decrease=0.52%; NNH=192), but not in the celecoxib study or the pooled estimate. No *P* values or confidence intervals were presented.

REFERENCES

1. Silverstein F, Simon L, and Faich G. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA* 2001; 268:2398–2399.