Diclofenac more effective than acetaminophen in osteoarthritis of the knee

Case JP, Baliumnas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis. A randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. Arch Intern Med 2003; 163:169–178.

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PRACTICE RECOMMENDATIONS

Diclofenac 150 mg/d is more effective in controlling osteoarthritis symptoms than acetaminophen 4 g/d in patients previously requiring an nonsteroidal anti-inflammatory drug (NSAID).

Since acetaminophen is less expensive and better tolerated, it is reasonable to attempt a 2-week trial in all patients prior to initiating treatment with NSAIDs.

BACKGROUND

A small number of studies have compared the effectiveness of acetaminophen with various NSAIDs, with some studies showing equivalence and others showing acetaminophen coming up short. These studies are the basis on which current clinical guidelines recommend acetaminophen over NSAIDs as initial therapy. This study evaluated the effectiveness of acetaminophen (Tylenol) and diclofenac sodium (Voltaren) compared with placebo in adults with osteoarthritis of the knee.

POPULATION STUDIED

The 82 patients in this study were men and women aged 40 to 75 years, recruited from a rheumatology clinic, with unilaterally symptomatic osteoarthritis of the knee. Patients had radiographic evidence of osteoarthritis (Kellgren-Lawrence grade ≥1) and medial compartment involvement.

Clinical criteria for entry were pre-enrollment ambulatory pain assessed by a visual analog score ≥30 mm on a 100-mm scale; moderate pain, assessed with 5-point Likert scale; or increased pain, evidenced by an increase of ≥10 mm on visual analog scale or ≥1 on Likert scale when taken off their previous analgesic during the initial 2 weeks of no treatment.

Furthermore, these patients had to be capable of independent ambulation without the use of a cane or walker and were within 1 standard deviation of weight for their height according to an actuarial life insurance table.

STUDY DESIGN AND VALIDITY

This research was a randomized, double-blind, placebo-controlled study. Initial allocation to treatment groups was concealed. After a 2-week washout period, patients were randomized to receive treatment with diclofenac (75 mg twice daily), acetaminophen (1000 mg 4 times daily), or matching placebo for 12 weeks. Follow-up visits were scheduled at weeks 2 and 12, at

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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.

which time pain and function were evaluated. Analysis of data was performed on an intention-to-treat basis.

This study was well done; however, some aspects deserve comment. This is a study of the comparative effectiveness of acetaminophen in a group of patients for whom acetaminophen already was shown not to work. All patients were recruited from a rheumatology clinic and had to have increased pain during the 2-week washout period, during which they were not allowed to take any of their previous pain medications.

Most of the patients (71%) were taking an NSAID alone or in combination with acetaminophen before the study started. Because acetaminophen has been advocated as first-line therapy for osteoarthritis for almost 10 years, these patients had very likely tried acetaminophen without success long before the study was started.

Also, there was a marked difference in tolerability between the 2 treatments. Of 82 patients, 21 withdrew prior to week 12. The patients that withdrew from the diclofenac group did so mainly due to adverse effects, whereas those that withdrew from the acetaminophen and placebo groups did so mostly due to ineffectiveness.

OUTCOMES MEASURED

The primary outcome was efficacy as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 2 and 12 weeks. This instrument assesses pain, stiffness, and function.

RESULTS

Only patients treated with diclofenac experienced a significant improvement in the primary outcome—the WOMAC—at week 2 (27%; P=.001) and week 12 (25.6%; P=.001) compared with baseline. The individual components (pain, stiffness, and function) of the WOMAC each showed clinical and statistically significant improvement compared with baseline scores at 2 and 12 weeks in the diclofenac-treated group only.

Predictably, when those patients who had previously taken an NSAID were analyzed, there was a significant response in the diclofenac-treated group but not in the acetaminophen or placebo groups. The response from acetaminophen was similar to that seen with placebo and was not significantly different from baseline scores.

Gabapentin helpful for hot flushes in postmenopausal women

Guttuso T, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: A randomized controlled trial. Obstet Gynecol 2003; 101:337–345.

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PRACTICE RECOMMENDATIONS

Gabapentin effectively decreases both the frequency and severity of hot flushes in postmenopausal women who report 7 or more hot flushes per day. Gabapentin, an anticonvulsant, is indicated by the US Food and Drug Administration as adjunct therapy in the treatment of partial seizures in epilepsy.

Although somnolence, dizziness, and peripheral edema are commonly experienced by patients taking this medication, gabapentin provides an effective treatment for reducing the number of hot flushes in women for whom hormone replacement therapy (HRT) is not recommended or desired.

BACKGROUND

Although HRT is effective in reducing hot flushes, recent data from the Women's Health Initiative and other concerns about estrogen use have limited its use in postmenopausal women. Safe, effective, and well-tolerated therapies for hot flushes would be welcomed.

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Gabapentin decreases the severity and frequency of hot flushes, but not as effectively as HRT

POPULATION STUDIED

The investigators enrolled 59 postmenopausal women who reported a daily average of 7 or more hot flushes. Study participants were recruited by advertisements and from a local news program about complementary hot flush therapies.

Hot flushes were defined as the sudden onset of heat sensation accompanied with sweating that spontaneously resolved within 1 hour. At least 1 daytime hot flush per day was required. Patients were excluded if they had recent surgical menopause, recent treatment with HRT, or impaired renal function.

STUDY DESIGN AND VALIDITY

In this randomized, double-blind trial, subjects were assigned to receive 12 weeks of therapy with gabapentin 300 mg capsules 3 times daily (900 mg/d), or matching placebo.

Subjects recorded frequency and severity of hot flushes in a diary, rating each on a scale of 1 to 7. Daily frequency was calculated by adding the number of hot flushes recorded in a week and dividing by the number of days in that week on which hot flushes were recorded. A daily hot flush composite score was calculated by adding the severity scores over 1 week and dividing by the number of days in that week for which hot flushes were recorded.

This randomized, double-blind prospective study used concealed allocation, and analysis was by intention-to-treat. Eighty-seven percent of the patients receiving gabapentin completed the study, as did 96% of those receiving placebo.

Relative weaknesses include some missing data for certain weeks (the authors used the last observation carried forward) and a reported financial interest that the principal investigator had in the use of gabapentin for hot flushes.

A major limitation of this study is that there may have been a profound placebo response in the patients treated with gabapentin. Half of the patients receiving the drug experienced a side effect, and these side effects could have augmented the already profound placebo response (29% in the control group). A longer study (6–12 months) would have helped determine whether any placebo effect waned, giving us a truer approximation of the effect of gabapentin.

OUTCOMES MEASURED

The primary outcome measure for the double-blinded portion of the study was the percentage change in hot flush frequency from baseline to treatment week 12. Secondary outcome measures included changes in the hot flush composite scores from baseline to week 12.

RESULTS

The gabapentin group experienced a 45% decrease in mean hot flush frequency, compared with a 29% decrease in the placebo group (from 10.8 to 5.9 per day in the gabapentin group and from 10.3 to 7.3 per day in the placebo group; P=.02). The gabapentin group experienced a 54% decrease in the mean hot flush composite score, compared with a 31% decrease in the placebo group (44.9 to 20.5 vs. 39.5 to 27.3; P=.01). This is a significant change, but certainly less than the 90% efficacy that has been observed with HRT.

Fifty percent of patients in the gabapentin group reported at least 1 adverse event, compared with 28% in the placebo group. The most common adverse effects reported with gabapentin were somnolence (20% of patients) and dizziness (13%). Thirteen percent of patients in the gabapentin group withdrew due to adverse effects, compared with 3% of patients in the placebo group. Measured serum protein levels decreased significantly in the gabapentin group compared with the placebo group (P=.05).

Low-carbohydrate diet effective for adults

Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrin Metab 2003; 88:1617–1623.

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PRACTICE RECOMMENDATIONS

Very-low-carbohydrate diets result in more weight loss than low-fat/low-calorie diets after 6 months, with no adverse impact on lipids, bone density, or blood pressure. Low-carbohydrate diets should be considered in otherwise healthy obese patients who are interested in this particular strategy for weight loss or who have failed other attempts.

BACKGROUND

The incidence of obesity and obesity-related illnesses continues to rise in the United States, along with the costs of caring for these conditions. No approaches for weight loss have proven effective for the long term.

Given this situation, many patients turn to unproven alternative weight-loss diets, such as very-low-carbohydrate (eg, Atkins) diets, despite potential theoretical adverse effects on cardiovascular and metabolic risk factors. These adverse effects, however, remain unproven; in addition to the present study, 2 other recent studies have addressed these concerns.

A meta-analysis of 94 studies in adult patients found no adverse impact of low-carbohydrate diets vs low-fat diets but could not draw any conclusions about superiority.[1] Another short (12-week) randomized trial in adolescent patients found improved weight loss with no adverse impact on lipids.[2] While 6 months is not a long-term trial, the present study is the longest randomized trial to date.

POPULATION STUDIED

Fifty-three moderately obese (body-mass index 30–35) adult women were randomized between May 2000 and January 2001 at the University of Cincinnati. The group included 13 African American and 30 Caucasian women who had a stable weight for at least 6 months. Subjects were excluded if they had atherosclerotic cardiovascular disease, hypertension, diabetes mellitus, hypothyroidism, substance abuse, pregnancy, or current lactation.

STUDY DESIGN AND VALIDITY

Subjects were assigned to a very-low-carbohydrate diet with *ad libitum* calories or to a low-fat, restricted-calorie diet for 6 months. The low-carbohydrate diet was restricted to <20 g of carbohydrate per day for the first 2 weeks and 40–60 g/d for the remainder of the study. The low-fat diet consisted of 55% carbohydrate, 15% protein, and 30% fat, with caloric prescriptions based on body size using the Harris-Benedict equations.

During the first 3 months, both groups kept weekly food diaries and received weekly nutritional counseling. Blood pressure, lipids, body-fat analysis, and bone density were checked at baseline, 3 months, and 6 months.

This was a well-designed randomized controlled trial with intention-to-treat analysis that adequately concealed allocation. Of the 53 women who started the study, 42 (79%) completed it. The study was designed to detect a 25% difference in weight loss and a 30% difference in low-density lipoprotein (LDL) cholesterol.

OUTCOMES MEASURED

Primary outcomes were weight loss and LDL cholesterol level. Other outcomes included body-fat analysis, lean body mass, blood pressure, total caloric intake, bone density, and various metabolic markers including other lipid levels, and insulin.

RESULTS

Patients using the very-low-carbohydrate diet showed significantly greater weight loss than the

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low-fat diet group at 3 months—7.6 kg (95% confidence interval [CI], 7.5–9.5) vs 4.2 kg (95% CI, 3.4–5.0), and at 6 months—8.5 kg (95% CI, 7.5–9.5) vs 3.9 kg (95% CI, 2.9–4.9). The low-carbohydrate group lost more fat mass and lean body mass than did the low-fat group.

While both groups showed improvement in blood pressure, lipids, insulin levels, and glucose over the course of the study, there were no differences between the groups. There was no change in bone density from baseline in either group. Interestingly, despite the unrestricted caloric intake in the low-carbohydrate group, both groups had similar reductions in caloric intake over baseline, approximately 450 kcal/d.

REFERENCES

1. Bravata DM, Sanders L, Huang J, et al. Efficacy and safety of low-carbohydrate diets. A systematic review. *JAMA* 2003; 289:1837–1850.
2. Sondike SB, Copperman N, Jacobson MS. Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factors in overweight adolescents. *J Pediatrics* 2003; 142:253–258.

Are early exposures linked with childhood peanut allergy?

Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. N Engl J Med 2003; 348:977–985.

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PRACTICE RECOMMENDATIONS

Peanut allergies are associated with intake of soy products in the first 2 years of life, a history of rashes over joints and skin creases (especially oozing, crusted ones), and use of skin creams containing peanut oil. Instructing parents to avoid peanut oil–containing creams and limiting soy milk or formula in the first 2 years of life may reduce sensitization.

BACKGROUND

The increase in peanut allergies over recent decades, as well as the potential seriousness of such allergies, prompted the authors to investigate possible sensitizing agents to avoid. A history of atopy and family history of peanut allergy have been suggested as predisposing factors. These findings had not been replicated previously.

POPULATION STUDIED

Children of pregnant women enrolled with the Avon (England) Longitudinal Study of Parents and Children made up the cohort of 13,971 preschoolers in this study. Using responses to prospectively collected questionnaires, investigators identified 49 children up to age 38 months with a clear history of adverse reactions to peanuts.

Later, 36 of these children were submitted to skin testing and peanut challenge, of which 23 were positive. Exclusion criteria included inability to locate subjects (n=2), previous anaphylaxis (n=2), and parents' refusal to consent (n=9).

STUDY DESIGN AND VALIDITY

Data reported in this study came from 2 sources. A portion draws on questionnaires collected from a large prospective cohort study. This portion includes data on exposure to soy products within the first 2 years of life, a history of rash over joints and skin creases, and a history of oozing, crusted rash. The remaining interview data were collected retrospectively through a nested case-control design within the cohort.

Two control groups were established for comparison with cases—a random sample of 140 children without peanut allergy and a random sample of 70 children with eczema whose mothers also had a history of eczema. This portion includes data on maternal peanut consumption in pregnancy and lactation as well as a history of exposure to peanut oil–containing skin creams.

The data derived through the prospective cohort study are the most reliable, as they are not subject to selection, interviewer, and recall biases,

which threaten the validity of case-control studies. In this report, the data from the case-control study are also very strong. The nested design protects against selection bias, the interviewers were blinded, and the presence of peanut oil in certain creams is not common knowledge.

One overall limitation was the inability to confirm a peanut allergy in 13 of the 49 initially identified cases. The authors dealt with this by reporting results on both the positive peanut-challenged cases (n=23) and the original 49 cases identified.

OUTCOMES MEASURED

The outcome studied was development of peanut allergy as documented through response to questionnaires and confirmed by positive double-blind, placebo-controlled oral peanut challenge.

RESULTS

Independent factors associated with peanut allergy included consumption of soy milk or formula (adjusted odds ratio [AOR]=3.15; 95% confidence interval [CI], 1.27–7.80); rash over joints or skin creases (AOR=3.88; 95% CI, 1.36–11.04); oozing, crusted rash (AOR=24.62, 95% CI, 5.47–110.87); and use of creams containing peanut oil during the first 6 months of life (AOR=8.34, 95% CI, 1.05–66.1).

Sensitization during pregnancy did not seem to be a factor, as there was no peanut-specific immunoglobulin E identified in cord blood samples saved from the children with positive peanut challenge. There was also no significant difference in maternal peanut intake during pregnancy. No significant relationship was found between use of peanut oil–containing breast creams or maternal peanut ingestion during lactation and development of peanut allergy.

Tricyclics and opioids effective for the treatment of postherpetic neuralgia

Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002; 59:1015–1021.

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PRACTICE RECOMMENDATIONS

Both tricyclic antidepressants (TCAs) and opioids are more effective than placebo for the treatment of postherpetic neuralgia.

Although there was a trend toward greater pain relief with opioids, their use was associated with a higher dropout rate. Since response to one medicine did not reliably predict response to the other, either may be tried for the treatment of postherpetic neuralgia.

BACKGROUND

Postherpetic neuralgia is defined as pain persisting at least 3 months following an acute episode of herpes zoster. TCAs and opioids have been shown to be effective for the treatment of this condition but they previously have not been compared with each other.

POPULATION STUDIED

The researchers enrolled 76 patients, with an average age of 71 years (range, 32–90 years), recruited from physician referrals and from advertisements. Treatment allocation was concealed from the enrolling researcher.

Adult patients were included if they had a persistent pain level of ≥4 on a subjective, self-reported pain rating scale from 0 to 10 for 3 months after the resolution of the rash caused by herpes zoster. Patients were excluded if they had a history of substance abuse, an allergy to opioids or TCAs, a recent myocardial infarction, glaucoma, pregnancy,

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dementia, or <6 month expected life span in a human immunodeficiency virus–positive patient.

STUDY DESIGN AND VALIDITY

This was a randomized, double-blind, crossover study with 3 arms comparing morphine, nortriptyline, and placebo in the same patient. There were three 8-week segments—a 4-week titration phase, a 2-week maintenance phase, and a 2-week tapering phase—followed by a 1-week washout period.

Nortriptyline was used in progressively higher doses up to a maximum of 160 mg/d. If this dose was not tolerated, desipramine could be substituted for nortriptyline. Sustained-release morphine (MS Contin) was dosed to a maximum of 240 mg, with methadone substituted if it was not tolerated.

The study design tried to mimic typical clinical practice by titrating the dose of pain medicine upward. The crossover design allowed the patients to be their own controls. The investigators demonstrated that there was no carryover from a previous treatment to the new drug, thereby validating the crossover design.

Almost half (42%) of the patients failed to complete the study, though the investigators still included the data they had for these patients in the overall analysis. This weakened the ability to truly compare treatments, but the conclusion that either treatment is better than placebo is very solid.

OUTCOMES MEASURED

The main outcome measure was pain relief, as measured on a 0 to 10 scale. A change in score of 1.4 was considered to be clinically relevant. Cognitive function was measured by the Wechsler Adult Intelligence Scale and the Hopkins Verbal Ability Test.

RESULTS

Treatment with morphine decreased pain scores an average of 1.9 out of a possible 10. Treatment with TCAs decreased pain scores by 1.4. Both treatments were significantly better than treatment with placebo ($P<.001$ for morphine and $P<.01$ for TCAs).

The improvement with opioids was almost significantly better than TCAs ($P=.06$). TCAs—but not opioids or placebo—significantly decreased all 3 measures of cognitive function. More people dropped out of the study while taking opioids (n=20) than TCAs (n=6) or placebo (n=1). Response to one drug did not predict response to the other.

Ephedra and ephedrine: Modest short-term weight loss, with a price

Shekelle PG, Hardy ML, Morton SC et al. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance. A meta-analysis. JAMA 2003; 289:1537–1545.

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PRACTICE RECOMMENDATIONS

Products containing ephedrine and ephedra promote a 0.6–1.0 kg/mo weight loss over 2 to 6 months. However, the impact of these products on long-term weight loss or athletic performance is uncertain. Their use is associated with a 2- to 3-fold higher rate of psychiatric symptoms, autonomic hyperactivity, upper gastrointestinal symptoms, and heart palpitations. Several serious adverse events—such as death, myocardial infarction, and stroke—have been reported, with a rate estimated at <0.1%.

BACKGROUND

The US Department of Health and Human Services requested an analysis of the past studies of products containing ephedrine and ephedra after the recent deaths of several high-profile athletes attributed to these products. Most trials

have been small, but several were similar enough to combine into a meta-analysis.

POPULATION STUDIED

The researchers analyzed controlled trials of products containing ephedrine and ephedra; the trials assessed weight loss over ≥8 weeks or measures of athletic performance. Published and unpublished studies were included. Due to the small number of athletic performance trials identified (n=7) and the heterogeneity of outcomes, the authors reviewed these studies individually.

All of the trials were analyzed for adverse outcomes, and results were pooled when possible. The researchers also reviewed published and unpublished individual case reports.

STUDY DESIGN AND VALIDITY

This was an extremely thorough meta-analysis, with several reviewers searching 9 databases and identifying unpublished evidence. The authors also tried to account for publication bias and the variable quality of the included articles.

For the individual case reports, serious adverse events included death, cardiac events, neurologic symptoms such as stroke, and serious psychiatric symptoms. The reviewers looked for evidence that recent consumption of a product containing ephedrine or ephedra had occurred, and that other potential causes had been excluded. If both these criteria were satisfied, the event was labeled a sentinel event.

The main limitations of the study stem from the quality of the available evidence. Most of the trials had follow-up of <20 weeks and did not demonstrate ideal randomization, blinding, or description of withdrawals. Not only was the follow-up time short, but no studies looked at outcomes after discontinuation.

Generalizability is also a concern, as the studies frequently excluded subjects with preexisting medical conditions, and no trials of athletic performance measured the effects of repeated use of the products.

OUTCOMES MEASURED

The primary outcome measures were monthly weight loss, various measures of athletic performance, and any adverse event. Aside from the serious adverse events listed above, other events were grouped into psychiatric symptoms, autonomic hyperactivity symptoms (such as tremor, insomnia, and sweating), upper gastrointestinal symptoms, palpitations, tachycardia, hypertension, and headache.

RESULTS

Fifty-two trials with 1706 patients were identified. Trials that assessed weight loss showed that ephedrine promoted weight loss of 0.6 kg/mo compared with placebo (95% confidence interval, 0.2–1.0) with a pooled average weight loss of 11% at 4 months. However, when only studies of moderate or high quality were included, this estimate decreased to 0.2 kg/mo.

The other trials with various ephedrine- and ephedra-containing products demonstrated a statistically significant monthly weight loss of 0.6–1.0 kg/mo compared with placebo, with no trials assessing weight loss beyond 6 months.

When used for athletic performance, neither caffeine nor ephedrine alone had an impact on parameters of exercise performance. However, in small trials the combination of these agents showed a 20% to 30% increase in oxygen consumption, time to exhaustion, or carbon dioxide production.

Among the 7 categories of adverse events, the pooled results demonstrated a statistically significant increase in psychiatric symptoms (odds ratio [OR]=3.64), autonomic hyperactivity (OR=3.37), palpitations (OR=2.29), and upper gastrointestinal symptoms (OR=2.15). Overall, 10% to 20% of participants reported such events. The risk of these events due to caffeine alone is not known.

The trials did not report any of the serious adverse events, and the pooled trials have at least 80% power to detect a serious adverse event rate of 0.1% or higher. The vast majority of case

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Ephedra and ephedrine may double or triple the rates of psychiatric symptoms and heart palpitations

reports of serious adverse outcomes were insufficiently documented to assess the likelihood of causation. Sentinel events included 5 deaths, 5 myocardial infarctions, 11 cerebrovascular accidents, 4 seizures, and 8 serious psychiatric cases. An additional 50 possible sentinel events were associated with recent consumption of products containing ephedrine or ephedra but had other possible causes.

Heliox of minimal benefit in acute asthma

Ho AM, Lee A, Karmakar MK, Dion PW, Chung DC, Contardi LH. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: A systematic overview. Chest 2003; 123:882–890.

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PRACTICE RECOMMENDATIONS

This meta-analysis showed that heliox, a mixture of helium and oxygen, offers minimal benefit during the first hour of treatment, and this benefit is not sustained. More importantly, it was not demonstrated that there was a difference in important clinical outcomes. Patients on a traditional air-oxygen mixture do just as well in the medium to long term.

Hypoxemic patients are not suitable for heliox therapy. Therefore, heliox should not be used in place of traditional oxygen or oxygen-air mixtures in acute exacerbations of asthma.

BACKGROUND

During an asthmatic attack, not all patients respond to treatment with bronchodilators and corticosteroids. Heliox, because of its low density, flows more efficiently through constricted airways with less turbulence and resistance than oxygen or air-oxygen mixtures. Heliox has been studied with mixed results in acute asthma.

POPULATION STUDIED

The investigators included studies that enrolled adults and children with acute asthma requiring hospital treatment. They excluded studies of patients with disease but without acute exacerbations, and studies of patients with induced peripheral airway obstruction.

STUDY DESIGN AND VALIDITY

This was a meta-analysis of randomized controlled trials found by an extensive search of MEDLINE, EMBASE (the European MEDLINE), and the Cochrane Controlled Trials Registry. They also reviewed the reference lists of included articles, but excluded articles not in English. They identified 8 randomized controlled trials, 2 nonrandomized controlled trials, 4 before-after case series, and a case report. Only 4 randomized controlled trials were included in the meta-analysis.

Significant clinical and statistical heterogeneity among the study results prevented pooling of outcomes. Heterogeneity is a way to compare similarity of each study's outcomes. The quality of randomized controlled trials was assessed according to the level of allocation concealment (adequate, unclear, or inadequate), double-blinding, and withdrawals.

Meta-analysis was performed with common reported outcomes (lung function, hospital admission rate, oxygen saturation by pulse oximeter [SpO_2]) using a random-effects model, an appropriate method. A qualitative systematic overview was also performed so as not to miss any effects based on parameters that could not be pooled.

All the analyzed trials might have suffered from an important flaw: the entrainment of room

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Data were insufficient to show whether heliox can avert tracheal intubation or affect mortality

air during delivery of the test gases or while albuterol was being nebulized with the test gases, potentially diluting the beneficial effect of helium.

Also, blinding was reported in some of the articles to be difficult because of the high-pitched voice that results from breathing heliox.

OUTCOMES MEASURED

The primary patient-oriented outcomes were length of hospital stay, and incidence of tracheal intubation and mechanical ventilation.

Disease-oriented outcome measures were peak expiratory flow rate, peak expiratory flow rate as a percentage of predicted, forced expiratory flow rate between 25% and 75% of vital capacity, forced expiratory volume in 1 second, forced vital capacity, respiratory rate, clinical asthma scores dyspnea index/score, partial pressure (tension) of carbon dioxide (artery), alveolar-arterial oxygen tension gradient, and pulsus paradoxus.

RESULTS

Most studies failed to show any difference between groups after the first hour or so of treatment or any difference in important clinical outcomes. Data were insufficient to determine whether heliox can avert tracheal intubation, change intensive care and hospital admission rates and duration, or affect mortality.

Improvement in peak expiratory flow rates was greater with heliox than with air-oxygen, primarily in those patients with worse baseline peak expiratory flow rates. Three studies measured a dyspnea index and found a greater likelihood of improvement in the heliox group (weighted mean difference, 0.6; 95% confidence interval, 0.04–1.16).

Natural progesterone prevents preterm birth in high-risk pregnancies

da Fonseca EB, Bittar RE, Carvalho MHB, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003; 188:419–424.

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PRACTICE RECOMMENDATIONS

The administration of natural progesterone decreases both the number of episodes of uterine contractions and the incidence of preterm birth in women at high risk for preterm delivery.

Previous trials used synthetic (not natural) progesterone; another placebo-controlled clinical study would be of value to evaluate safety and effects of natural progesterone. These results do not apply to women at low risk for preterm birth because this study evaluated only high-risk patients.

BACKGROUND

Synthetic progesterone has been used to reduce the number of preterm births; this is the first study to evaluate the effects of natural progesterone. This form of progesterone may offer less teratogenic risk and fewer metabolic effects.

The study sought to determine the role of natural progesterone to prevent preterm birth in high-risk pregnancies. The authors were especially interested in preventing preterm birth before 34 weeks, which is associated with poorer pregnancy outcomes.

POPULATION STUDIED

This study was performed in a tertiary medical center in Brazil. Included subjects had asymptomatic, high-risk, singleton pregnancies, and at least 1 previous spontaneous preterm birth,

prophylactic cervical cerclage, or uterine malformation. Subjects were randomized to receive progesterone or placebo. The median age of the women was about 27 years.

Patients excluded from the study had multiple gestation, fetal malformation, allergy to progesterone, missed follow-up, preterm rupture of membranes, or therapeutic premature delivery.

STUDY DESIGN AND VALIDITY

The researchers conducting this randomized, double-blind study enrolled 157 patients at high risk of preterm labor. Allocation to treatment may not have been concealed from the enrolling investigator. Progesterone 100 mg or placebo was administered daily by vaginal suppository from weeks 24 to 34 of gestation.

Uterine contractions were monitored by external tocodynamometer once a week for 60 minutes. Patients in preterm labor were hospitalized and treated with beta-mimetics. Both staff and patients were blinded until the last study patient delivered.

This was a well-designed study with appropriate power and statistically significant results. A weakness was the exclusion of 15 randomized patients from the final data analysis (90.4% follow-up). Although the analysis was not performed by intention-to-treat, no statistically significant difference in exclusion cause existed between the 2 groups. The results should be applied with caution to primary care populations as the study was performed on a group of high-risk patients at a tertiary care center, and the results probably do not apply to women at lower risk for preterm birth.

OUTCOMES MEASURED

The primary endpoint was preterm birth, defined as birth occurring before 37 weeks' gestation. Other outcomes were frequency of episodes of uterine contractions, episodes of preterm labor, and response to treatment with beta-mimetics.

RESULTS

The overall preterm birth rate was 21.1%. The incidence of preterm birth was lower in the progesterone compared with the placebo group (13.8% vs 28.5%; number needed to treat [NNT]=7). More women delivered before 34 weeks in the placebo group than in the progesterone group (18.6% vs 2.8%; NNT=7). Mean contraction frequency was less in the progesterone group compared with the placebo group (23.8% vs 54.3%; *P*=.0001).

No statistically significant difference in admissions for preterm labor existed between the 2 groups; but when beta-mimetics were used to treat preterm labor, more women in the progesterone group had their delivery delayed beyond 72 hours (85.7% vs 36.4%).

False-positive mammograms increase follow-up rates

Pinckney RG, Geller BM, Burman M, Littenberg B. Effect of false-positive mammograms on return for subsequent screening mammography. Am J Med 2003; 114:120–125.

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PRACTICE RECOMMENDATIONS

This population-based study found that women who had a false-positive mammogram had higher rates of rescreening at 18- and 30-month follow-up. In 10 years of annual screening, 50% of women will have a false-positive mammogram. However, the consequences of false-positives do not deter women from continued breast cancer screening.

When evaluating screening tests it is important to consider the effect of a false-positive test on the people being screened. The subsequent work-up for each false-positive may increase patient anxiety, total costs, and the risk of morbidity from unnecessary interventions.

CONTINUED

Women were less likely to return for screening if they had Medicaid insurance or were uninsured

BACKGROUND

Women enrolled in health maintenance organizations that use patient reminder systems have been shown to be more likely to receive subsequent mammography screening after a false-positive result. This study sought to determine screening follow-up rates in a population that did not receive reminders. It included women with and without health insurance.

POPULATION STUDIED

Women aged >40 years who had received mammograms in Vermont were identified during a 12-month period (in 1996 and 1997) through the Vermont Mammography Registry database. The index (initial) mammogram was defined as imaging that occurred during the enrollment period and was not necessarily the woman's first screening.

Of the 48,538 women receiving screening mammograms, 6694 were excluded due to breast cancer diagnosed within 1 year of screening, lack of procedural indication given on mammography order, prior history of breast cancer, breast cancer history unknown, or history of breast reduction, reconstruction, implant, or mastectomy.

STUDY DESIGN AND VALIDITY

A positive screening test was defined as a mammogram resulting in any recommendation other than routine screening, and a false-positive screen was defined as a positive mammogram that did not result in a cancer diagnosis within 1 year. Procedure dates, radiology reports, pathology reports, family history, medical history, and demographic characteristics are included within the statewide registry. The registry includes women regardless of insurance status, place of residence, or employment status.

The use of registry data has the limitation of having no information on patients who did not follow-up for rescreening.

OUTCOMES MEASURED

The primary outcome measured was the likelihood of having received follow-up screening mammography 18 and 30 months after the index mammogram or diagnostic follow-up exam. Screening rates were further analyzed for differences according to various demographic variables, including age, insurance status, breast cancer risk factors, race, and education.

RESULTS

Of the 37,862 records with available mammography data, 3982 (10.5%) had a false-positive result. This false-positive rate was higher than previously reported rates of 4.4%–7.8%.

Among all women, those with a false-positive result were more likely to have undergone screening at 18 months (odds ratio [OR]=1.40; 95% confidence interval [CI], 1.30–1.51) and 30 months (OR=1.30; 95% CI, 1.18–1.44). Of women aged 40 to 49 years, 82.6% (95% CI, 80.6–84.5) of women with false-positive and 77.0% (95% CI, 76.2–77.7) of women with true-negative results had undergone screening mammography at 30 months.

In multivariate analysis, women aged <50 years or >65 years and women who did not graduate from high school were less likely to return for screening. Women who had any previous mammogram, a false-positive mammogram prior to the index study, and history of hormone replacement therapy were more likely to be rescreened.

At 18 months, women were less likely to return for screening if they had Medicaid insurance (OR=0.58; 95% CI, 0.54–0.64) or were uninsured (OR=0.53; 95% CI, 0.48–0.58) compared with women with any other form of insurance. Similar results were found at the 30-month interval.

Metoclopramide reduces nausea from emergency contraception

Ragan RE, Rock RW, Buck HW. Metoclopramide pretreatment attenuates emergency contraceptive-associated nausea. Am J Obstet Gynecol 2003; 188:330–333.

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PRACTICE RECOMMENDATIONS

This study provides good evidence that metoclopramide reduces the nausea and cramping associated with emergency contraception. The benefit, however, is small, and the effect of metoclopramide on the effectiveness of the emergency contraceptive is not known.

Clinicians may prescribe 10 mg metoclopramide along with combined estrogen/progestin emergency hormonal contraception. Results are likely to be similar with agents comparable to metoclopramide.

BACKGROUND

The effectiveness of emergency hormonal contraception is now well-established, but nausea and vomiting complicate its use and may limit drug absorption and patient compliance. This randomized trial assessed the effectiveness of metoclopramide in attenuating these side effects.

POPULATION STUDIED

The investigators enrolled 141 women presenting to a university health center for emergency contraception. Inclusion criteria were age >18 years, negative pregnancy test, unprotected intercourse within the past 72 hours, and no contraindications to emergency contraception. The authors identified participants as aged 18 to 25 years. The subjects were similar to those seen in family practice, but it would be helpful to have more clinical information, including age, medical/psychological history, and drugs used, including alcohol.

STUDY DESIGN AND VALIDITY

This was a randomized, placebo-controlled, double-blind study using concealed allocation. All participants received 2 doses of 0.5 mg levonorgestrel and 0.1 mg ethinyl estradiol 12 hours apart. Subjects received either metoclopramide 10 mg tablets or matching placebo to take 1 hour before each dose. At enrollment, participants were given a written 12-symptom survey to return by mail within 72 hours of completing treatment.

The methodology of this study was good. Strengths included prospective randomized design with concealed allocation and a reasonable placebo treatment. The major weakness was that there was no way to know what a clinically relevant difference might be on the symptom scales. Other weaknesses included the lack of clinical information at baseline or follow-up, limited power for relatively rare outcomes such as vomiting, response rates that were different between the treatment and control groups, and lack of attention to confounding factors such as psychological condition or use of other drugs.

OUTCOMES MEASURED

The primary outcomes were self-reported nausea (measured on a scale from 1 [least] to 10 [worst]) and vomiting (measured as none, once, more than once). Seven other symptoms were also assessed. Patient satisfaction, pregnancy rates, and cost were not assessed.

RESULTS

No comparison of groups at baseline was given. The overall response rate was 75%, although more controls than subjects returned their surveys (82% vs 63%). Patients receiving metoclopramide reported less nausea (3.22 vs. 4.41 on a 10-point scale; P=.01) and cramping (0.89 vs. 2.22 on a 10-point scale; P<.01) than those receiving placebo. There was no statistically significant difference between the treatment and control groups for all other symptoms, including vomiting, appetite, dizziness, and breast tenderness.