Supervised Exercise Is Equivalent to Endovascular Revascularization for the Treatment of Intermittent Claudication

Spronk S, Bosch JL, den Hoed PT, et al. Intermittent claudication: clinical effectiveness of endovascular revascularization versus supervised hospital-based exercise training—randomized controlled trial. Radiology 2009;250:586–95.

Study Overview

Objective. To determine whether a structured exercise program is superior or inferior to endovascular revascularization for the treatment of symptomatic intermittent claudication.

Design. Single-center randomized controlled trial.

Setting and participants. 151 consecutive patients in the Netherlands with Rutherford category 1, 2, or 3 intermittent claudication symptoms, maximum pain-free walking distance < 350 meters, ankle-brachial index (ABI) < 0.9 at rest (or decreased by > 0.15 with exercise), and at least 1 iliac or femoropopliteal stenosis creating a > 50% vessel diameter reduction (visualized by magnetic resonance angiography). Potential subjects were excluded if they had an abdominal aortic aneurysm, New York Heart Association class III or higher heart failure, ipsilateral stenoses of both the iliac and femoral arteries, isolated tibial artery disease, lesions deemed unsuitable for revascularization, or prior treatment for the lesion causing claudication (including prior exercise). Median patient age was 65 years and baseline comorbidities were evenly distributed between treatment groups.

Intervention. Subjects were randomized to either exercise or endovascular revascularization. Patients randomized to exercise received two 30-minute hospital-based supervised treadmill sessions per week for 24 weeks (with patients receiving median 32 of 48 prescribed sessions) as well as instructions to walk unsupervised for at least 30 minutes three times per week outside the hospital (with patients reporting median walking time 4.7 hours per week). Those randomized to endovascular revascularization received angioplasty with or without stent placement as clinically indicated according to the intervening radiologist, followed by usual care (including guideline-concordant instructions on lifestyle change). Patients were enrolled from September 2002 to September 2005 and followed for 12 months.

Main outcome measures. The primary outcome was "clinical success," defined as a symptomatic improvement by at least 1 unit on the Rutherford scale. Secondary outcomes were functional capacity (measured as ABI and maximum pain-free walking distance) and quality of life (measured using 4 dimensions of the Medical Outcomes Study 36-item short-form health survey [SF-36] and the Vascular Quality of Life Questionnaire). All outcomes were measured at 1 week after initiation of treatment, at 6 months, and at 12 months. Clinical success and functional capacity were evaluated by an observer blinded to treatment assignment.

Main results. At 1 week, clinical success was achieved for 88% of patients undergoing revascularization and 68% of patients starting exercise (adjusted odds ratio [OR], 39 [99% confidence interval {CI}, 11–131]). However, this difference diminished over time, with 6-month clinical success rates of 75% for revascularization and 77% for exercise (adjusted

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OR, 0.9 [99% CI, 0.3–2.3]) and 12-month rates of 68% and 65% (adjusted OR, 1.1 [99% CI, 0.5–2.8]). Mean ABI and maximum pain-free walking distance improved for both treatment groups at 6 and 12 months, but there was no significant difference in the degree of improvement. Quality of life scores on the SF-36 and Vascular Quality of Life Questionnaire improved at 6 and 12 months for both treatment groups, with no significant between-group differences in the degree of improvement. All analyses were performed on an intent-to-treat basis, but study results were robust in supplemental per-protocol analyses.

Conclusion. Though endovascular revascularization was more likely than structured exercise to produce early symptomatic improvements among patients with intermittent claudication, this advantage was no longer present 6 or 12 months after treatment. Both treatment strategies improved symptoms, functional capacity, and quality of life for the majority of patients. The initial choice of endovascular or exercise-based approaches to treating claudication may depend on their relative costs.

Commentary

Despite international guidelines recommending exercise training for the initial treatment of intermittent claudication, endovascular procedures have become an increasingly common approach to treating this condition [1]. The effectiveness of exercise—particularly supervised exercise—for treating claudication has been established by multiple trials [2–5]. A prior trial directly comparing supervised exercise to endovascular treatments showed superior 6-year functional capacity among patients treated with exercise, but this trial was small and evaluated older endovascular techniques [6].

The current investigation by Spronk and colleagues presents results from a recent single-center randomized controlled trial comparing supervised exercise to endovascular revascularization for the treatment of intermittent claudication. Patients receiving endovascular revascularization had superior improvements in symptoms and functional capacity 1 week after beginning treatment, but there were no differences between endovascular revascularization and exercise at 6 or 12 months. There were also no 6- or 12-month differences in quality of life measures between the treatment groups. Though the trial was not designed to test differences in adverse outcomes of treatment, 7 patients receiving endovascular revascularization experienced minor complications of treatment (hematoma or small arterial dissection). No patients receiving exercise experienced a complication.

This study has limitations. First, nearly half of examined patients with claudication were ineligible for enrollment, with the most common reason for exclusion being vascular lesions deemed unsuitable for endovascular treatment. This high degree of patient selection on endovascular "suitability" criteria may lead to overestimation of the relative effectiveness of endovascular revascularization among the general population of patients with intermittent claudication. Second, the trial's enrollment design was based on a power calculation designed to detect a very large difference in functional improvement between the treatment groups (equivalent to the functional difference between patients with and without intermittent claudication). This expectation of such a large difference in effectiveness may have severely limited the study's power to detect smaller but clinically meaningful differences between the treatments. Third, the impressive 68% of patients reporting improved claudication symptoms after just 1 week of exercise raises questions about the reliability and validity of this measure (especially with this degree of improvement remaining essentially unchanged at 12 months). Fourth, the trial was not powered to assess differences in treatment effectiveness among patient subgroups with differing locations and degrees of arterial stenosis. Finally, costs of care were not examined.

Applications for Clinical Practice

This study provides important evidence for the relative clinical effectiveness of 2 competing approaches to treating intermittent claudication: at 6 and 12 months, there appears to be essentially no difference in the outcomes achieved by supervised exercise and endovascular revascularization. Given the medium- and longer-term interchangeability of these therapeutic options, health systems managers may be justified in letting cost-based approaches determine the preferred treatment option.

—Review by Mark W. Friedberg, MD, MPP

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Smoking Linked to Increased Risk of Pancreatitis

Tolstrup JS, Kristiansen L, Becker U, Grønbaek M. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch Intern Med 2009;169:603–9.

Study Overview

Objective. To assess the independent effects of smoking on risk of pancreatitis.

Design. Observational population-based cohort study.

Setting and participants. Participants came from the first 3 examinations of the Copenhagen City Heart Study (CCHS), a prospective cohort study performed in 1976–1978, 1981–1983, and 1991–1994. The CCHS included participants who were randomly chosen from the general population of Copenhagen. Overall, 18,035 individuals participated in 1 or more examinations of the CCHS. For this study, 9573 women and 8332 men with recorded smoking status were followed for a mean of 20.2 years.

Data collection. Subjects completed a self-administered questionnaire regarding smoking, alcohol intake, physical activity, education level, and income. At the clinic visit, physical examinations were performed including measurement of height, weight, expired carbon dioxide, and forced expiratory volume in 1 second. At each subsequent survey examination, participants were asked whether they were current or past smokers and about duration of smoking (in years). Current smokers were further asked about the usual amount tobacco used in daily cigarettes, cheroots, cigars, and pipes.

Main outcome measure. The primary study endpoint was acute or chronic pancreatitis incidence. Pancreatitis diagnosis and cause of death information was obtained from the Danish Hospital Discharge Register and the Danish Registers of Causes of Death. Information about pancreatitis-related cases among the study participants in these registries was identified through linkage by the unique identification number allocated to every Danish inhabitant by the government.

Main results. Over a mean follow-up period of 20.2 years, 235 cases of pancreatitis occurred. In total, 68% of men and 58% of women were current smokers, and 19% of men and 15% of women were ex-smokers. The researchers observed a dose-response association between smoking and risk of acute and chronic pancreatitis in both men and women. The hazard ratio (HR) of developing acute or chronic pancreatitis was 1.5 (95% confidence interval [CI], 0.9–2.5) for those use used 1 to 14 g of tobacco daily, 2.5 (95% CI, 1.5–3.9) for those who used 15 to 24 g of tobacco daily, and 3.3 (95% CI, 1.9–5.8) for those who used more than 25 g of tobacco daily. Ex-smokers had an HR of 1.7 (95% CI, 1.0–2.7) for risk of pancreatitis. Pack-years of smoking had a similar dose-response relationship to pancreatitis risk. Alcohol intake was associated with an increased risk of pancreatitis (HR, 1.09 [95% CI, 1.04–1.14]) for each additional drink per day. Notably, the risk of acute and chronic pancreatitis associated with smoking was independent of both alcohol and gallstone disease. Overall, 46% of cases of pancreatitis were attributable to smoking in this cohort.

Conclusion. Among Danish men and women followed prospectively for 20 years, smoking was independently associated with increased risk of both acute and chronic pancreatitis in a dose-response fashion.

Commentary

Tobacco use remains the leading cause of preventable death in the United States [1]. The link between tobacco use and lung cancer, cardiovascular disease, COPD, and other cancers is well known. Recent research has linked tobacco to other important diseases, including diabetes [2], and as this study shows, acute and chronic pancreatitis.

The incidence of pancreatitis has increased over the past quarter century and the high associated mortality rate has not decreased [3,4]. Well-known causes of pancreatitis include gallstones and alcohol use. Previous data on smoking as an independent risk factor for pancreatitis are mixed [5–7]. Given the association between both smoking and alcohol use and smoking and gallstone formation, the independent relationship between smoking and pancreatitis may be difficult to disentangle using the case–control research methods that have been commonly used in past studies. However, experimental basic science studies do suggest a relationship between smoking and pancreatic cell damage [8,9].

This study sought to discern in a prospective population-based cohort whether smoking is independently related to

risk of pancreatitis. The investigators report a dose-response relationship between ex-smokers, light smokers, and heavy smokers and increased risk of pancreatitis. These findings expand upon the limitations present in earlier studies that were primarily case–control or flawed cohort studies, and are consistent with the basic science evidence. This current study is notable for its large size, detailed tobacco use questions, and linkage to a central registry of all discharges in Denmark that enabled complete follow-up for all participants. The large size and detailed information on the cohort participant discharge data also enabled the researchers to control for the effects of alcohol use and gallstone disease.

A few limitations to this study deserve mention. The study relied on linkage to a central administrative discharge database based on hospital claims. As such, the data were not clinically verified and only dealt with inpatient visits for pancreatitis, leading to the possibility of misclassification bias and missed outpatient visits for chronic pancreatitis. However, the authors conducted sensitivity analyses to explore these possibilities, without major changes in the results. In addition, external validity may be slightly compromised by the study's location in a small, homogenous Scandinavian country with a very high smoking rate at the time of the study (> 60%).

Applications for Clinical Practice

This large, well-done Danish study suggests that smoking is independently associated with a two- to threefold increased risk for acute and chronic pancreatitis. Clinicians should diligently screen all patients with acute and chronic pancreatitis for tobacco use and use evidence-based cessation methods, including repeated strong advice to quit, telephone quitlines, and medications, to help their patients quit smoking. Current smokers should also be counseled about their increased risk of pancreatitis and be made aware of symptoms that might suggest the onset of pancreatitis for which they should seek prompt medical attention.

—Review by Asaf Bitton, MD

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Factors Associated with Poor Analgesia When Using Intravenous Opioids for Acute Pain

O'Connor AB, Zwemer FL, Hays DP, Feng C. Outcomes after intravenous opioids in emergency patients: a prospective cohort analysis. Acad Emerg Med 2009;16:477–87.

Study Overview

Objective. To assess outcomes following administration of intravenous (IV) opioids in the emergency department (ED) and to identify clinical factors associated with poorer analgesic control.

Design. Prospective, observational cohort study.

Setting and participants. The study was conducted in an urban academic ED between the hours of 8 AM and midnight from July 2004 to November 2006. Inclusion criteria

were age ≥ 18 years and receiving IV morphine or hydromorphone as the initial analgesic medication. Patients identified more than 2 hours after the opioid was administered were excluded. Other exclusion criteria were prior or simultaneous administration of any analgesic medication during the ED encounter or via emergency medical services, cognitive impairment that limited informed consent, unstable vital signs, or inability to speak English.

Study protocol. Trained research assistants screened triage diagnoses for potentially painful diagnoses and monitored potential subjects for IV opioid orders. Enrolled patients were interviewed before and 1–2 hours after analgesics and asked to score their pain on a verbal 0–10 scale with 0 = "no pain" and 10 = "worst pain possible." In the postanalgesic interview they were also asked if they desired additional analgesia and to rate their pain relief (1–5 scale) and treatment satisfaction (1–6 scale). The providers who ordered the opioid were asked to rate their concern about suspected "drug-seeking behavior" and "patient stability" using a 1–5 Likert scale with 1 = "not concerned" and 5 = "very concerned." A detailed medical record review was completed after the subject was discharged from the ED.

Main outcome measures. Poor analgesia, defined as (1) < 50% reduction of the initial pain score, and (2) postanalgesic pain score ≥ 7. An additional outcome measure was the development of opioid-related side effects, judged to be present if reported by the patient or nurse or documented in the chart (presence of naloxone orders, respiratory rate < 10/minute, systolic blood pressure < 90 mm Hg, or oxygen saturation < 90% during the 4 hours after IV initial opioid administration).

Results. 57% of the 691 patients studied failed to achieve a 50% reduction of their initial pain score, 36% had a postanalgesic pain score ≥ 7, 48% desired additional analgesia, and 23% had opioid-related side effects. Factors associated with poor analgesia included use of long-acting opioids at home, provider concern for drug-seeking behavior, and increasing age. An initial pain score of 10 was associated with a postanalgesic pain score ≥ 7. Black patients were less likely to achieve a 50% reduction of their initial pain score despite receiving similar initial and total equianalgesic doses. No risk factors evaluated in this study were associated with greater risk of opioid side effects.

Conclusion. ED patients who are older, black, already taking long-acting opioids, suspected of drug-seeking behavior, and who have higher initial pain scores are at risk of poorer analgesic control.

Commentary

Acute pain is one of the most common presenting complaints in the ED setting [1–3], yet despite the movement to increase quality of pain assessment and treatment, pain care continues to be inconsistent and inadequate in the ED [4–6]. Inadequate pain control has been attributed to the clinician paradigm of focusing on diagnosis as a priority instead of symptom treatment, lack of pain relief training, inadequate pain assessment, misconceptions, reluctance to prescribe opiates, and the widening "gap between deepening knowledge about pain and clinically adequate treatment [7]." Although surveys of ED patients indicate they expect complete relief of their pain [8], there are barriers that may preclude the ability to achieve this, including patient-related differences. These factors coupled with the emphasis of rapid diagnosis and treatment, ongoing professional perceptions of the dangers of opiate use or drug abuse, concerns about side effects, and the nursing and physician time required to rapidly and effectively titrate analgesia may limit the ability to provide or improve the quality of pain care in the ED.

This study by O'Connor et al demonstrates that in a patient population initially treated with only IV opioids, patient characteristics and clinician impressions are risk factors associated with difficulty in ultimately achieving pain control. Despite receiving similar initial and total equianalgesic dosages, patient race, age, initial pain scores, history of using long-acting opioids and clinician suspicion of the patient feigning symptoms to obtain narcotics are associated with the inability to reduce pain scores sufficiently. Awareness of these factors should be considered markers for increased risk of analgesic failure and thus prompt aggressive pain management efforts and frequent patient monitoring. The initial choice of opioid (versus nonopoiod) analgesic medication for the treatment of acute pain indicates that a clinician is making a strong attempt to relieve pain. This study found that even with the initial use of only opioid analgesia, many patients do not have a significant reduction in reported pain (reduction of follow-up pain scores to < 50% of initial scores). The use of opioid analgesic medication alone may not suffice in relieving acute pain, and alternate strategies (eg, prompt follow-up, monitored titration of medications) should be studied.

Of the factors associated with poor analgesic control, only physician concern for drug-seeking behavior can be modified to improve pain care and clinical practice. The health care system will continue to encounter "drug-seeking" patients, including those who abuse drugs for recreational purposes, addicts who are unable to control their dependence, and pseudoaddicts who have chronic pain that has been inadequately managed. Despite drug-seeking behaviors that may elicit suspicion, many of these patients

have genuine pain. The onus is on the clinician to first manage the pain effectively and then to refer drug-seeking patients to appropriate psychosocial, rehabilitation, or chronic pain care treatment.

Limitations of the study include the single institution setting whereby findings may not generalize to other settings. Additionally, it is not known if the results observed in this study may be secondary to relatively low opioid doses ordered and administered to this cohort. While not the objective of this study, future research to determine optimal opioid dosing strategies in ED patients would be warranted.

Applications for Clinical Practice

Awareness of risk factors associated with the inability to reduce pain scores significantly may alert physicians to manage pain more aggressively. These factors include suspicion for drug-seeking behavior, older age, black race, already taking long-acting opioids, and having high initial pain scores.

—Review by Ula Hwang, MD, MPH

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Quadrivalent HPV Vaccine Moderately Efficacious in Preventing HPV Infection and Related Disease in Women Aged 24 to 45 Years

Munoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomized, double-blind trial. Lancet 2009; 373:1949–57.

Study Overview

Objective. To determine if the quadrivalent human papillomavirus (HPV) vaccine (types 6, 11, 16, 18) is efficacious in preventing HPV infection or related disease in women aged 24 to 45 years.

Design. Randomized, double-blind, placebo-controlled phase III trial.

Setting and participants. Women were recruited through health centers and primary care providers in 7 countries: Colombia, France, Germany, Philippines, Spain, Thailand, and the United States. Women were excluded if they were pregnant, had a history of genital warts or cervical disease, had prior surgery on the cervix, had a cervical biopsy within the last 5 years, or had HIV or were immunocompromised. Randomization was done separately for patients < 35 years old and those ≥ 35 years old. 1910 were assigned to the vaccine arm and 1908 to the placebo arm. Subjects were screened for immunity to the HPV serotypes through serum analysis at baseline. Infection with HPV was determined through Pap testing and HPV PCR (polymerase chain reaction) conducted on labial, vulvar, perineal, perianal, endocervical and ectocervial swabs at baseline and every 6 months following. Complete gynecologic exams were done at baseline, 7 months, 12 months, and yearly thereafter and external genital exams were conducted every 6 months.

The determination of efficacy was made using per-protocol efficacy (PPE) analyses, a population naive to relevant type (NRT) analysis, and intention-to-treat (ITT) assessment, with the PPE results reported as the primary efficacy results. Subjects were included in the PPE group if they were

seronegative to the relevant HPV type at baseline, had no evidence of HPV infection on PCR or biopsy samples from baseline to month 7, had all 3 vaccine or placebo injections during 1 year and had at least 2 follow-up visits after month 7. NRT subjects were those who were seronegative and PCR-negative to the relevant HPV type at baseline, had at least 1 vaccine or placebo injection, and had 1 or more visits after the baseline visit. ITT subjects included all women who had at least 1 injection and 1 or more follow-up visits.

Main outcome measures. The combined incidence of HPV infection for 6 months or more and HPV-associated disease (cervical, vulvar, or vaginal intraepithelial neoplasia; adenocarcinoma in situ; cervical, vulvar, or vaginal cancer; or genital warts) related to HPV 6, 11, 16, or 18 and to HPV 16 or 18 alone. The secondary endpoint included the combined incidence of infection related to HPV 6 or 11 for 6 months or more and cervical or external genital disease. Infection was defined as (1) the isolation of the same HPV type on 2 occasions at least 6 months apart or (2) HPV-associated disease found on biopsy with positive HPV testing in the visit before or after the biopsy was taken. Disease was defined as a tissue sample with 1 of the identified disease states. The intended duration of the study is 4 years.

Main results. These results represent interim results after a mean of 2.2 years of follow-up. Mean age of participants was 34.3 years. Hispanics comprised 43.2% of the sample while 31.2% were Asian and 20.6% were white. Baseline characteristics were similar in the vaccine and placebo groups. 33.5% and 32.8% were either immune to or had an active infection with at least 1 HPV serotype at baseline. Less than 2% were immune to or infected with more than 1 serotype. In the PPE group, vaccine efficacy for the primary endpoint (HPV infection and related disease from any serotype) was 90.5% (95% confidence interval [CI], 73.7%–97.5%; 4 cases in vaccine group, 41 in placebo). Efficacy against the second primary endpoint (HPV 16 or 18 infection and disease) was 83.1% (95% CI, 50.6%–95.8%; 4 cases in vaccine group, 23 in placebo) while efficacy against the secondary endpoint (HPV 6 or 11 infection and disease) was 100% (95% CI, 79%–100%; 0 cases in vaccine group, 19 in placebo). In the NRT and ITT analyses, vaccine efficacy was 74.6% (95% CI, 58.1%–85.3%; 20 cases in vaccine group, 77 in placebo) and 30.9% (95% CI, 11.1%–46.5%; 108 cases in vaccine group, 154 in placebo) for the primary endpoint. Safety was comparable between the groups with serious adverse events reported in 3 of the vaccine subjects and 7 of the placebo subjects.

Conclusion. HPV quadrivalent vaccine is moderately effective in preventing HPV infection and related disease among women aged 24 to 45.

Commentary

The quadrivalent HPV vaccine is currently recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) as part of the routine vaccination schedule for girls aged 11 to 12 years with catch-up vaccinations for girls and women up to age 26 years [1]. The recommendations arose from published data on the efficacy of the vaccine in preventing cervical and anogenital diseases among women under age 26 [2,3]. The vaccine was tested first in this younger age-group because most HPV infection is acquired by young women soon after becoming sexually active [4–6]. Initial data also demonstrated that the vaccine's efficacy was primarily achieved for women who were not exposed to HPV before vaccination [1–3], thus compelling the ACIP to recommend vaccination very early in life.

However, the cumulative, 5-year incidence of high-risk HPV infection in women between 30 and 44 years of age is still high—18.2% in one cohort of 1610 Colombian women [6]. A recent meta-analysis found evidence of a 2nd peak in prevalence of HPV infection after the age of 44 [7]. As a result, the manufacturer of the quadrivalent HPV vaccine, Merck, funded this study to determine whether efficacy extended to women older than the age-group for which the vaccine is currently approved.

The trial was well-conducted with very little loss to follow-up. The efficacy of the vaccine in preventing HPV infection and related disease appears to be strong, with 90.5% efficacy in the per-protocol analysis. Further data in this study show that immune responses to the vaccine were strong in this older population although slightly lower for HPV serotypes 6, 11, and 18 compared with younger populations.

Based on these results, which were most robust in the PPE group, a targeted vaccination strategy for those women known to be HPV-naive at baseline would seem logical. However, the clinical application of this study is significantly attenuated by the small absolute differences in endpoints between the intervention and placebo groups and the diminished efficacy in the intention-to-treat analysis, the group that most directly resembles the population encountered in practice. HPV testing is not considered part of routine cervical cancer screening except as a means to prevent unnecessary biopsies (reflex HPV testing for atypical cells of undetermined significance results) or to prolong the interval for Pap testing among women in monogamous relationships [8]. Mass vaccination of older populations does not appear to be supported by this study, and targeted vaccinations of HPV-naive populations would require proof of the clinical effectiveness and cost-effectiveness of HPV screening first.

Applications for Clinical Practice

The HPV vaccine is efficacious in preventing HPV-related diseases among women aged 24 to 45, especially if women

are HPV-negative at baseline. The absolute reduction in disease is small, and further research must determine whether HPV vaccination is cost-effective, either as a mass vaccination strategy or as a targeted strategy for those who are HPV-negative at baseline.

—Review by Jason P. Block, MD, MPH

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