Should Radiofrequency Ablation Be First-line Treatment for Paroxysmal Atrial Fibrillation?


Study Overview

Objective. To compare radiofrequency ablation (RFA) with antiarrhythmic drugs in treating patients with paroxysmal atrial fibrillation as a first-line therapy.

Design. Randomized controlled trial.

Setting and participants. This multi-center study was conducted at 16 sites in 5 countries and enrolled 127 patients between July 2006 and January 2010. Adult patients < 75 years old with a history of paroxysmal atrial fibrillation who had at least 1 episode of symptomatic paroxysmal atrial fibrillation in the 6 months prior to enrollment and had no previous antiarrhythmic drug treatment were recruited. Patients were excluded if they had structural heart disease or had a complete contraindication for the use of heparin, warfarin, or both.

Patients were randomized by variable block generated by computer to receive either antiarrhythmic drugs or RFA. All patients were followed up at 1, 3, 6, 12, and 24 months after randomization. Each patient received a transtelephonic monitor system and was trained to record and transmit symptomatic episodes of possible atrial fibrillation. Patients were also instructed to transmit biweekly recordings on a Friday, regardless of whether they had experienced symptoms. Blinded experienced electrophysiologists analyzed all recordings, which may also have included scheduled or unscheduled electrocardiogram, Holter, or rhythm strips.

Patients randomized to the antiarrhythmic drug group were administered medications chosen by the investigators. Drug dosages titrated during the 90-day blanking period were maintained throughout the study. Patients in the antiarrhythmic drug group were also allowed to cross over and undergo ablation after 90 days if medical treatment had failed.

Patients randomized to the RFA group underwent circumferential isolation of the pulmonary veins. Additional ablation lesions were also allowed at investigator’s choice. Furthermore, selections of the ablation catheter, power and irrigation settings, as well as the use of navigation systems were left to the discretion of the investigator. Following RFA, anticoagulation with warfarin was maintained for at least 3 months.

Main outcome measures. The primary outcome was time to first recurrence of symptomatic or asymptomatic atrial fibrillation, atrial flutter, or atrial tachycardia lasting more than 30 seconds. Secondary outcomes were symptomatic recurrences of atrial fibrillation, atrial flutter,
or atrial tachycardia during the study period and quality of life as measured by EQ-5D Tariff score. There was a 90-day blanking period (the time after randomization when an AF event is not counted).

Main results. The RFA group experienced a significantly lower rate of recurrence of atrial tachyarrhythmias at 2 years compared with the antiarrhythmic drug group (54.5% vs. 72.1%, hazard ratio [HR] 0.56 [95% CI, 0.35–0.90]; \( P = 0.02 \)). The difference was present but smaller for the rate of symptomatic arrhythmias (47% RFA group vs. 59% drug therapy group, HR 0.56 [95% CI, 0.33–0.95]; \( P = 0.03 \)). There were no differences among treatment groups in regard to quality of life at 1-year follow-up using the EQ-5D Tariff score. No deaths or strokes reported in either group; 4 cases (6%) of cardiac tamponade were reported in the RFA group.

Conclusion. The authors of this study conclude that for paroxysmal atrial fibrillation patients without previous antiarrhythmic drug treatment, RFA resulted in a lower rate of recurrence of atrial tachyarrhythmias at 2 years compared with standard antiarrhythmic drug treatment. However, recurrence was frequent in both groups after 2 years.

Commentary
Atrial fibrillation is a common arrhythmia associated with an increased risk of stroke and other adverse events. Current practice guidelines recommend antiarrhythmic drugs as the first-line therapy for patients with symptomatic paroxysmal atrial fibrillation. However, a significant proportion of patients are nonadherent with antiarrhythmic therapy. As a result, antiarrhythmic therapy is only 46% effective at 12 months in preventing the recurrence of atrial fibrillation [1].

The purpose of the current study (Radiofrequency Ablation vs. Antiarrhythmic Drugs for Atrial Fibrillation Treatment-2, or RAAFT-2) was to determine whether RFA is superior to antiarrhythmic drugs as first-line therapy in patients with paroxysmal atrial fibrillation who had not been exposed to antiarrhythmic treatment. Over the past decade, various single-center trials attempted to demonstrate the superiority of RAF. Evidence from these trials suggested that RFA resulted in lower burden of atrial fibrillation and more patients free from atrial fibrillation. However, RFA had a higher initial cost, higher rate of complications, and conferred no improvement in the quality of life [2–5].

Despite the statistically significant lower rate of recurrence of atrial tachyarrhythmias in the RFA group, there are many limitations with this multi-center, multi-country study. First, selection bias may have been present, as it took 42 months to recruit 127 patients in 16 centers and 5 countries for a very common disease. Second, the use of a transtelephonic monitor was unique. When the investigators excluded transtelephonic monitor results and used electrocardiogram and Holter monitor results, similar to previous trials, the primary outcomes were no longer different. Third, biases in the study design favor RFA. For example, investigators permitted substantial variation in the RFA procedures but restricted dosage changes in the antiarrhythmic drugs group. Finally, 26 of the 61 patients (42.6%) assigned to the antiarrhythmic drug group crossed over to undergo RFA, and the intention-to-treat basis became invalid.

One might ask, what is the worth of this trial? This trial provides additional evidence about about the risks of RFA. While no deaths or strokes were reported in this trial, 6 of the 66 patients (9.1%) in the RFA group had a serious adverse event, with 4 patients (6%) experiencing pericardial effusion with tamponade. The 6% tamponade rate is similar to that found in previous trials [2]. On the other hand, only 3 of the 61 patients (4.9%) in the antiarrhythmic drugs group experienced a serious adverse event (1 had atrial flutter with 1:1 atrioventricular conduction, 2 had syncope).

Applications for Clinical Practice
This trial of radiofrequency ablation vs. antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation provides further evidence of the risks and benefits of each of these options. The current guidelines should be followed. However, given the high level of medical therapy noncompliance, selected patients should also be given the option of using RFA as primary treatment. Patients who are offered the procedure should be made aware of the risks, and providers should incorporate patient’s risk perceptions and preferences in treatment planning.

—Ka Ming Gordon Ngai, MD, MPH

References


Declining Adverse Event Rates Among Patients With Cardiac Conditions But Not With Pneumonia or Surgical Conditions


Study Overview

Objective. To examine changes in adverse event rates among Medicare patients with common medical conditions and conditions requiring surgery hospitalized in acute care hospitals.

Design. Retrospective review utilizing the Medicare Patient Safety Monitoring System (MPSMS) [1], a large database of information abstracted from medical records of a random sample of hospitalized patients in the United States. The database was established in by the Centers for Medicare and Medicaid Services in 2001 to track adverse events in hospitals among Medicare patients, with data collected from every year thereafter except for 2008. The MPSMS tracks 21 indicators of safety that can be reliably abstracted from medical records. Among these are inpatients falls, hospital-acquired pressure ulcers, catheter-associated urinary tract infections, selected hospital-acquired infections, selected adverse events related to high-risk medications, operative events and postoperative events for certain conditions.

Setting and participants. Medicare patients aged 65 and older who had been hospitalized for acute myocardial infarction, congestive heart failure, pneumonia, or conditions requiring surgery from 2005 to 2007 and 2009 to 2011. A total of 61,523 patients were included in the final study sample—11,399 with acute myocardial infarction, 15,374 with congestive heart failure, 18,269 with pneumonia, and 16,481 with conditions requiring surgery from a total of 4372 hospitals.

Main outcome measures. The rate of occurrence of adverse events for which patients were at risk, the proportion of patients with 1 or more adverse events, and the number of adverse events per 1000 hospitalizations.

Statistical analysis. Outcome rates were described and reported in 2-year intervals: 2005–2006, 2007–2009, and 2010–2011. Trends in the number of adverse events per 1000 hospitalizations were modeled using a linear mixed-effects model with Poisson link function. Other composite outcomes were also modeled using linear mixed models for trend analysis.

Main results. Adverse event rates among patients with myocardial infarction and congestive heart failure declined significantly. Among patients with myocardial infarction, rate of adverse event among patients at risk for events declined from 5% to 3.7% (rate difference 1.3%; 95% confidence interval [CI], 0.7 to 1.9) and among patients with congestive heart failure, the rate declined from 3.7% to 2.7% (rate difference 1%; 95% CI, 0.5 to 1.4). Proportion of patients with 1 or more adverse events declined by 6.6% (95% CI, 3.3 to 10.2) among patients with myocardial infarction, and 3.3% (95% CI, 1.0 to 5.5) among patients with congestive heart failure. Number of adverse events per 1000 hospitalizations also declined by 139.7 among
patients with myocardial infarction and by 68.3 among patients with congestive heart failure. On the other hand, among patients admitted for pneumonia or for conditions requiring surgery, adverse event rates remained the same. Rate of adverse events among patients admitted for pneumonia remained the same at 3.4% in 2005–2006 and 3.5% in 2010–2011; and for patients admitted for conditions requiring surgery, rate of adverse events remained the same at 3.2% in 2005–2006 and 3.3% in 2010–2011. Similarly, proportion of patients with 1 or more events in the hospital also remained the same in patients with pneumonia (a proportion of 17.1% in 2005–2006 and 17.5% in 2010–11) and conditions requiring surgery (a proportion of 21.6% in 2005–2006 and 22.7% in 2010–2011). Number of events per 1000 hospitalizations also did not change over time. When accounting for patient characteristics and geographic differences in the models, the results also did not substantially change.

Conclusions. In a large nationally representative sample of older adults aged 65 and above, adverse event rates declined among patients admitted for cardiac conditions, including myocardial infarction and congestive heart failure, but did not decline among patients admitted for other medical (pneumonia) or surgical conditions.

Commentary

Patient safety in inpatient hospital care is of paramount importance, and the Affordable Care Act has placed significant emphasis on improving patient safety by aligning incentives and disincentives with patient outcomes on the hospital level [2,3]. These measures, including adverse event rates, are reported publicly in reports such as Hospital Compare [3–5]. The current study reports on the recent national trends in safety and adverse events using data abstracted from medical records among older Medicare patients with 4 common conditions. The demonstration of the trends in adverse events represent an important first step towards understanding the current environment and trends in patient safety. The finding that in-hospital adverse event rates have improved in patients admitted for cardiac conditions is reassuring given that there were substantial nationwide efforts in promoting patient safety in hospitals, but the lack of progress in other conditions both medical and surgical is rather disappointing.

There is good quality evidence suggesting how hospitals may make changes to improve patient safety; these steps may include adopting care practices and protocols such as pressure ulcer monitoring and prevention protocols, fall prevention protocols, safety checklists, models for older adults inpatient care such as Mobile Acute Care of Elderly teams [6] and Acute Care for the Elderly models [7], quality improvement initiatives, and incorporation of information systems for data tracking and reporting, to name a few. How hospitals adopt different practices for the care of patients with different conditions may explain the study findings. The challenge is to figure out why noncardiac conditions do not have improving trends in patient safety and to demonstrate what works (and what doesn’t) on the hospital level. Understanding how care is delivered on the hospital level and correlating hospital level practices with patient outcomes from databases such as MPSMS may yield clues as to what specific steps hospitals have taken that have yielded changes in patient safety.

Applications for Clinical Practice

This study highlights trends in adverse events among hospitalized older adults that demonstrated improvements for patients with cardiac conditions but not for others. Future studies need to focus on understanding what works and what doesn’t so that hospitals can adopt safety practices that improve outcomes for older hospitalized patients.

—William Hung, MD, MPH

References

7. Landefeld CS, Palmer RM, Kresvic DM, Fortinsky RH,

Does Exercise Help Reduce Cancer-Related Fatigue?


Study Overview

Objective. To systematically review randomized controlled trials (RCTs) examining the effects of exercise interventions on cancer-related fatigue (CRF) in patients during and after treatment to determine differential effects.

Design. Meta-analysis.

Data. 70 RCTs with a combined sample of 4881 oncology patients during active treatment (eg, chemotherapy, radiation therapy, hormone therapy) or after completion of treatment published before August 2011 that analyzed the effect on CRF of an exercise program compared with a non-exercise control. Excluded from analysis were RCTs that compared exercise with other types of interventions (ie, education, pharmacotherapy, different methods of exercise). 43 studies examined exercise during treatment while 27 studied the effects after treatment.

Measurement. Effect size was calculated to determine the magnitude of the effect of exercise on improving CRF.

Main results. The effect size ($\Delta = 0.34$, $P < 0.001$) for the total sample of 70 RCTs indicated that exercise has a moderate effect on CRF regardless of treatment status. When effect sizes were calculated for the 43 RCTs that examined patients during treatment, exercise was found to significantly decrease CRF ($\Delta = 0.32$, $P < 0.001$). Based on calculated effect size for the 27 RCTs that examined exercise after treatment completion, exercise continues to significantly decrease CRF ($\Delta = 0.38$, $P < 0.001$). The effect of exercise on CRF was consistent not only during or after treatment, but also across cancer diagnosis, patient age, and sex.

Exercise reduces CRF both during and after treatment. In patients who exercise, CRF severity decreases by 4.9% compared to a 29.1% increase in CRF in patients who do not exercise. After treatment, exercise decreases CRF by 20.5% compared to a decrease of 1.3% in patients who do not exercise.

Both during and after treatment, patients with higher exercise adherence experienced the most improvement ($P < 0.001$). Patients in active treatment with less severe baseline CRF demonstrated greater adherence to the exercise program and saw greater improvements in CRF. Patients who were further from active treatment saw greater CRF severity reduction than patients closer to active treatment. After treatment, the longer the exercise program, the more effective it was in decreasing CRF. No specific type of exercise program (eg, home-based, supervised, vigorous, moderate) was shown to be more effective than another.

Conclusion. Exercise decreases CRF in patients during and after treatment. The type of exercise does not change the positive effect of exercise, so it is important to encourage patients to be active.

Commentary

Cancer-related fatigue (CRF) is the most disturbing symptom associated with cancer diagnosis and its treatment [1]. Defined as a persistent, subjective sense of tiredness that is not proportional to activity and not relieved by rest, CRF is reported in over 80% of oncology patients during active treatment [1]. This symptom is not limited to the active treatment phase, with over 30% of cancer survivors reporting CRF lasting at least 5 years [2]. CRF is associated with decreased quality of life (QOL), decreased functional status, and decreased participation in social activities [1]. The pathogenesis of CRF is not fully understood [3,4]. Disruptions in biochemical pathways [5], genome expression [6] chemotherapy or radiation...
treatments [7,8], cancer pathogenesis [4], or a combination of factors [9] are hypothesized as contributing to the development and severity of CRF. The complexity of CRF pathogenesis makes clinical management difficult.

The current meta-analysis suggests that exercise is an effective nonpharmacologic intervention to ameliorate the impact of this devastating symptom and improve patients’ QOL [10–12]. The meta-analysis demonstrated strong rigor using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. Multiple electronic databases were accessed and additional evidence was obtained by review of the retrieved article reference lists. No language limitations were placed on the search, adding to the potential generalizability of the results. The procedures to extract data and evaluate the quality of each retrieved article are detailed providing evidence of the rigor of the authors’ methodology.

The limitations of the meta-analysis are related to the difficulties extracting data from multiple studies without consistent reporting of exercise mode, duration or evaluation methods. Inconsistent CRF assessment methods across studies limits the validity of the results quantifying the magnitude of CRF change identified. Despite the limitations, this is the first known meta-analysis of the effect of exercise on CRF during and after treatment synthesizing current research to provide clinical recommendations.

As with all exercise prescriptions for any patient, the patient’s level of adherence is a moderating factor for its effectiveness. A recent study describes an interesting exercise intervention that utilizes a resource some cancer patients may already have in their homes. Seven patients with early-stage non-small cell lung cancer performed light-intensity walking and balance exercises in a virtual reality environment with the Nintendo Wii Fit Plus for 6 weeks after thoracotomy [14]. Exercise started the first week after hospitalization and continued for 6 weeks. Outcomes seen included a decrease in CRF severity, a high level of satisfaction, high adherence rate, and an increase in self-efficacy for managing their CRF [14]. While the small sample size and homogeneous cancer diagnosis and stage limit generalizability, the study describes a promising approach to supporting patient adherence to exercise.

Applications for Clinical Practice

The results of this meta-analysis support exercise as an effective intervention to decrease CRF in oncology patients during and after treatment. Based on the results, exercise should be prescribed as a nonpharmacologic intervention to decrease CRF. Patients’ adherence to the exercise intervention is needed for effective CRF reduction. Thus, exercise prescription should be tailored to patients’ individual preferences, abilities, and available resources.

—Fay Wright, MSN, APRN, and Allison Squires, PhD, RN

References

Sequential and Concomitant Therapies for Helicobacter pylori Eradication


Study Overview

Objective. To compare the effectiveness and safety of “sequential” and “concomitant” regimens for H. pylori eradication in a setting with increased rates of clarithromycin resistance.

Design. Prospective, multi-center, randomized controlled trial using an intention-to-treat and a per-protocol analysis (patients who adhered to study protocol and had a medication compliance of ≥ 90%).

Settings and participants. Patients from 11 Spanish hospitals with confirmed H. pylori infection were invited to participate from December 2010 to May 2012. Participants were at least 18 years old with either non-investigated/functional dyspepsia or gastric/duodenal ulcer. Exclusion criteria included patients with prior H. pylori eradication treatment, the use of bismuth salts or antibiotics for 4 weeks prior to study inclusion, advanced chronic disease that would preclude study completion or follow-up visits, pregnant or breastfeeding patients, as well as patients with prior gastric surgery or alcohol or drug abuse. Participants were allocated using computerized randomization. Study physicians obtained informed consent in the outpatient clinic setting as well as disclosed study arm assignment and dispersed study drugs to participants. The study was unblinded since the number of study drugs and dosing regimens differed between treatment arms.

Intervention. The sequential treatment group received 5 days of dual therapy with omeprazole 20 mg and amoxicillin 1 g every 12 hours, followed by 5 days of triple therapy with omeprazole 20 mg, clarithromycin 500 mg, and metronidazole 500 mg every 12 hours. The concomitant treatment group received 10 days of quadruple therapy with omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg every 12 hours. All drugs were of generic branding.

Main outcome measures. The primary outcome measure was eradication of H. pylori infection confirmed by C-urea breath test or histology a minimum of 4 weeks after ending treatment; secondary outcome was treatment regimen compliance of at least 90% with each study drug.

Main results. 338 patients were randomized, 170 to sequential treatment and 168 to concomitant treatment. There was no significant difference between the 2 arms in relation to age or gender. The average age of participants was similar (47.5 vs 47.3 years in the sequential and concomitant groups, respectively). Women comprised 58.8% of the sequential treatment population and 62.5% of the concomitant population. 95% of both study arms finished treatment.

There was no difference in the primary outcome of eradication of H. pylori infection between the 2 treatment groups in the intention-to-treat analysis as well as in the per-protocol analysis (81.2% vs 86.9%, P = 0.15, and 85.6% vs 91.2%, P = 0.14, in the sequential and concomitant treatment groups, respectively). No statistically significant differences were found between treatment groups based on type of underlying disease. Treatment regimen compliance was also not statistically different between treatment regimens (82.4% sequential vs 82.7% concomitant).

The 2 treatment regimens did not differ significantly in terms of rate and severity of adverse events (P = 0.09). Overall, adverse reactions were reported in 58.6% of the study patients (54.1% in the sequential treatment arm and 63.1% in the concomitant treatment arm). The most common adverse reactions were taste distortions (35.9%), diarrhea (20.1%), and nausea (10.8%). Overall these adverse reactions were characterized as mild (59.2%), moderate (36.2%), and severe (5%).

Conclusion. There was no significant difference between treatment outcomes. Both treatments arms
were found to have acceptable compliance and safety profiles.

**Commentary**

Gastric cancer is the fifth most common malignancy in the world and the third leading cause of cancer death, with estimates of almost 1 million new cases for the year 2012 leading to over 720,000 deaths [1]. On a national level, gastric cancer is less common, with estimates of 21,600 new cases for the year 2013 (1.3% of new cancer cases), leading to an estimated 10,990 deaths (1.9% of all cancer deaths) [2]. Infection with *H. pylori* is the major risk factor for noncardia gastric cancer (cancer in all areas of the stomach, except for the top portion near where it joins the esophagus) and has been implicated in the development of peptic ulcer disease, chronic gastritis, gastric B-cell mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma [3].

The American College of Gastroenterology [4] and the European Consensus guidelines [5] provide evidence-based recommendations for *H. pylori* treatment. Standard triple therapy with a proton-pump inhibitor (PPI), clarithromycin, and amoxicillin remains the most widely prescribed regimen, although increasing rates of clarithromycin resistance as well as decreasing rates of *H. pylori* eradication have prompted investigations of alternative medication and dosing regimens [6].

The present study assesses the efficacy of concomitant therapy for 10 days compared with sequential therapy (omeprazole plus amoxicillin for 5 days, followed by omeprazole, clarithromycin and metronidazole for 5 days). The authors found similar compliance and safety profile rates between the 2 groups, and no significant differences in terms of *H. pylori* eradication rates. In multivariate analysis, eradication was not associated with patient age, sex, treatment hospital, type of treatment, smoking habit, or presence of ulcer, but was associated with compliance. A strength of this study is the prospective, randomized design, with 11 Spanish hospitals participating. Another strength is the high retention rate, with 95% of subjects completing the trial. A limitation of the trial, as noted by the authors, was not assessing antibiotic resistance in the study patients. This is a relevant omission due to clarithromycin resistance rates in Spain of approximately 14%, which could influence the efficacy of *H. pylori* eradication when using clarithromycin. Lastly, this study assessed eradication of *H. pylori* at an interval of at least 4 weeks post-treatment, whereas other investigations have used longer time intervals. Future efforts could assess for *H. pylori* at an interval of at least 8 weeks post-treatment in order to further validate efficacy of eradication treatment.

**Applications for Clinical Practice**

Non-bismuth, quadruple concomitant therapy appears to be an effective, safe, well-tolerated and less complex alternative than sequential therapy for *H. pylori* eradication. Therefore, this regimen appears well suited for use in settings where efficacy of triple therapy is unacceptably low, either due to increasing rates of clarithromycin resistance and/or decreasing rates of *H. pylori* eradication.

—Kristen R. Weaver, ACNP-BC, ANP-BC and Allison Squires, PhD, RN

**References**