Multicenter InSync Randomized Clinical Evaluation - MIRACLE (Pacing Study)

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Description:

The goal of the MIRACLE trial was to compare the effect of cardiac resynchronization therapy (CRT) versus no CRT on the quality of life and functional capacity in patients with chronic heart failure (CHF) and ventricular dysynchrony, as well as to assess the safety of CRT using the Medtronic InSync® System in patients with CHF.

Hypothesis:

Multisite ventricular pacing resynchronizes contraction of the failing left ventricle (LV) and improves cardiac performance.

Study Design:
Patients Enrolled: 453
NYHA Class: III, IV
Mean Follow Up: Minimum 6 months
Mean Patient Age: Mean age 64 years
Female: 32
Mean Ejection Fraction: Mean LVEF 22%

Patient Populations:
1. NYHA class III or IV heart failure
2. QRS of at least 130 ms (mean 165 ms)
3. LV systolic dysfunction with an LVEF ≤35%
4. LV end-diastolic dimension at least 55 mm (mean 69 mm)
5. Six-minute walking distance of ≤450 m

Exclusions:
1. Baseline six-minute walk >450 m
2. Unstable angina, acute myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the past three months
3. Cerebrovascular accident or transient ischemic event within the past three months
4. Existing implantable cardioverter defibrillator (ICD) or indications for an ICD
5. Existing pacing system or contraindications for standard cardiac pacing
6. Systolic blood pressure <80 mm Hg or >170 mm Hg

7. Resting heart rate >140
8. Creatinine >3 mg/dl
9. Hepatic function >3 x upper limit of normal
10. Primary valvular disease
11. Severe primary pulmonary disease
12. Chronic atrial arrhythmia within past month
13. Post heart transplant
14. Life expectancy from noncardiac disease <6 months
15. Mechanical heart valves
16. Ventricular tachycardia associated with reversible causes
17. More than two infusions per week of positive inotrope

Primary Endpoints:
1. Minnesota Living With Heart Failure Questionnaire Quality of Life (QOL) Measure
2. NYHA functional class
3. Six-minute hall walk

Secondary Endpoints:
Peak oxygen consumption; time on a treadmill; LV ejection fraction (LVEF) and end-diastolic dimension; severity of mitral regurgitation; duration of QRS interval; and a clinical composite response, which assigns patients to one of three response groups: improved, worsened, or unchanged

Drug/Procedures Used:
Following baseline assessment, patients underwent implant attempt within one week. Following successful lead placement (93%), patients underwent a predischarge randomization to the control group (no CRT, n=225) or CRT group (n=228), then underwent a six-month period of double-blinded study with follow-up at one, three, and six months. The electrophysiologist served as an unblinded third party, and the heart failure specialist, the managing physician, and the patient were kept blinded to study assignment during the six-month period of pivotal study.

Control arm patients could then go into the resynchronization mode. These patients were then followed up at nine months, and all patients continue to be followed at six-month intervals following the double-blind period of the controlled study.

Concomitant Medications:
All patients were required to be on stable medications for one month, including an angiotensin-converting enzyme (ACE) inhibitor or ACE inhibitor substitute. Patients who had been prescribed beta-blockers were required to be on a stable regimen for three months. Changes in the background medical therapy were discouraged during the six-month period of randomized controlled study.

Principal Findings:

Device implantation was unsuccessful in 8% of patients, and was complicated by refractory hypotension, bradycardia, or asystole in four patients (two that died) and by perforation of the coronary sinus requiring pericardiocentesis in two patients.

Compared with placebo, CRT was associated with a significantly improved six-minute walk distance

(+39 vs. +10 m, p=0.005), improved New York Heart Association (NYHA) class by at least one class (68% vs. 38%, p<0.001), quality of life (-18.0 vs. -9.0 points, p=0.001), time on the treadmill during exercise testing (+81 vs. +19 seconds, p=0.001), and ejection fraction (+4.6% vs. -0.2%, p<0.001). CRT was also associated with a significantly improved peak oxygen consumption (+1.1 vs. +0.2 ml/kg/min, p=0.009).

The QRS duration was significantly lower in CRT patients compared with control (-20 vs. 0 ms, p<0.001). Need for hospital admission (8% vs. 15%, p=0.02) and intravenous medication (7% vs. 15%, p=0.004) were lower in CRT patients compared to controls.

Using the Heart Failure Clinical Composite Outcome Measure, a significantly higher percentage of CRT patients were classified as improved (67% vs. 39%, p<0.001) and fewer CRT patients were classified as worsened (16% vs. 27%). Death or worsening heart failure requiring hospitalization occurred less frequently in the CRT arm (28% vs. 44%, hazard ratio 0.60, 95% confidence interval 0.37–0.96; p=0.03).

Interpretation:
Among patients with CHF and ventricular dysynchrony, biventricular pacing was associated with improved functional class, increased six-minute walk distance and maximal oxygen uptake, and improved quality of life.

Recently, CRT, or biventricular pacing, has emerged as a potential treatment option for patients with severe heart failure. Patients thought to benefit include those with intraventricular conduction delay who are refractory to medical therapy.

The optimal performance of biventricular pacing devices has yet to be determined. Lead placement remains problematic, and reliable predictors of response have yet to be identified.

The MIRACLE trial is one of the largest clinical trials of CRT in CHF reported to date. The results are encouraging, with 67% of CRT patients showing improvement in the clinical composite endpoint that included NYHA functional class and global assessment compared with 39% of placebo patients. This difference in clinical improvement is striking compared to other heart failure trials that have applied this same composite clinical endpoint.

The MIRACLE data suggest that CRT is safe and well tolerated, with no serious adverse events among those patients receiving active therapy.

References:

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Clinical Topics: Arrhythmias and Clinical EP, Cardiac Surgery, Diabetes and Cardiometabolic Disease, Heart Failure and Cardiomyopathies, Invasive Cardiovascular Angiography and Intervention, Pericardial Disease, Prevention, Implantable Devices, SCD/Ventricular Arrhythmias, Cardiac Surgery and Arrhythmias, Cardiac Surgery and Heart Failure, Acute Heart Failure, Exercise

Keywords: Follow-Up Studies, Coronary Sinus, Hypotension, Heart Arrest, Pericardiocentesis, Cardiac Resynchronization Therapy, Walking, Oxygen Consumption, Quality of Life, Heart Failure, Bradycardia, Confidence Intervals, Heart Ventricles