

The ICAP Trial: Investigation on Colchicine for Acute Pericarditis

Rachel Kile, PharmD
PGY1 Pharmacy Resident
Memorial Health Care System
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Journal

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Overview

■ Study Goal

- To evaluate the efficacy and safety of colchicine in reducing incessant or recurrent pericarditis after a first acute attack

■ Study Support

- Azienda Sanitaria Locale 3 of Turin
- Acarpia grant (provided study drug and placebo)
- Trial designed by primary author; approved by steering and ethics committees

Pericarditis

- Pericardium of heart
 - Fibrous
 - Visceral and parietal layers separated by pericardial cavity
- Acute inflammation of the pericardium
- 90% of cases are idiopathic or viral
 - See Table 1, Causes of Acute Pericarditis

TABLE 1. Causes of Acute Pericarditis

Idiopathic

Infections (viral, tuberculosis, fungal)

Uremia

Acute myocardial infarction (acute, delayed)

Neoplasm

Post–cardiac injury syndrome (trauma, cardiothoracic surgery)

Systemic autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosing periarteritis nodosa, Reiter's syndrome)

After mediastinal radiation

Acute Pericarditis

- Clinical Manifestations
 - Sharp, retro-sternal chest pain
 - Must be differentiated from myocardial infarction/ischemia, pulmonary embolism
 - See Table 2, Differentiation of Pericarditis from MI/PE
- Sequelae
 - Cardiac tamponade
 - Recurrent pericarditis (15-30%)
 - Pericardial constriction

TABLE 2. Differentiation of Pericarditis From Myocardial Ischemia/Infarction and Pulmonary Embolism

	Myocardial Ischemia or Infarction	Pericarditis	Pulmonary Embolism
Chest pain			
Character	Pressure-like, heavy, squeezing	Sharp, stabbing, occasionally dull	Sharp, stabbing
Change with respiration	No	Worsened with inspiration	In phase with respiration (absent when the patient is apneic)
Change with position	No	Worse when supine; improved when sitting up or leaning forward	No
Duration	Minutes (ischemia); hours (infarction)	Hours to days	Hours to days
Response to nitroglycerin	Improved	No change	No change
Physical examination			
Friction rub	Absent (unless pericarditis is present)	Present in 85% of patients	Rare; a pleural friction rub is present in 3% of patients
ECG			
ST-segment elevation	Localized convex	Widespread concave	Limited to lead III, aVF, and V ₁
PR-segment depression	Rare	Frequent	None
Q waves	May be present	Absent	May be present in lead III or aVF or both
T waves	Inverted when ST segments are still elevated	Inverted after ST segments have normalized	Inverted in lead II, aVF, or V ₁ to V ₄ while ST segments are elevated

Pericarditis Treatment

- Aspirin
 - High dose
 - Ex: 650-975 mg every 6-8 hours for ~4 weeks
- NSAIDs (ibuprofen)
 - High dose
- Glucocorticoids
 - Less favorable to aspirin and NSAIDs
- Colchicine

Colchicine

- Isolated centuries ago
- Mainstay of prevention/treatment for acute gout flare
- Substrate of CYP3A4 and P-gp (drug interactions)
- US availability
 - Colcrys 0.6 mg PO tablet only

Colchicine

■ Indications

■ Approved

- Prevention and treatment of acute gout flares
- Treatment of familial Mediterranean fever

■ Unlabeled

- Primary biliary cirrhosis
- Pericarditis

■ Theoretical Mechanism of Action: Pericarditis

- Concentrate in leukocytes (granulocytes)
- Disrupt microtubules
- 16x greater concentration than plasma

Hypothesis

- “Our study, called the Investigation on Colchicine for Acute Pericarditis (ICAP), was a randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the efficacy and safety of colchicine to treat a first attack of acute pericarditis and to prevent recurrences.”

Methods

Study Design

- Prospective, randomized, double-blind, placebo controlled study of efficacy and safety
- Multicenter trial: 5 general hospitals in Northern Italy

Treatment

- Each patient received colchicine or placebo for 3 months, plus conventional therapy and PPI
 - Colchicine 0.5 mg twice daily (1 mg total) if > 70 kg
 - Colchicine 0.5 mg once daily if ≤ 70 kg OR with side effects at 0.5 mg twice daily
 - No loading dose
 - Colchicine and placebo tablets identical

Treatment

- Conventional Therapy
 - Aspirin 800 mg or ibuprofen 600 mg
 - Every 8 hours for 7-10 days, followed by a tapering period of 3-4 weeks
 - Prednisone 0.2-0.5 mg/kg
 - Daily for 2 weeks with gradual tapering
 - **Only** for patients with contraindications to aspirin or ibuprofen OR patients with a history of side effects
- Proton-pump inhibitor daily, unnamed

Objectives

- Establish the efficacy and safety of colchicine for treatment of an initial attack of acute pericarditis
- Confirm preliminary findings of colchicine's effectiveness in acute pericarditis

Criteria

■ Inclusion

- 18 years of age or older
- First episode of acute pericarditis
 - Idiopathic
 - Viral
 - Post-cardiac injury
 - Associated with connective-tissue disease

Criteria

- Inclusion, continued.
 - Acute Pericarditis diagnosis criteria:
 - At least TWO of the following:
 - Typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward)
 - Pericardial friction rub
 - Suggestive changes on ECG
 - New or worsening pericardial effusion
 - Informed consent provided by all participants

Criteria

■ Exclusion

- Tuberculosis pericarditis
- Neoplastic pericarditis
- Purulent pericarditis
- Severe liver disease or current aminotransferase levels $> 1.5x$ ULN
- SCr > 2.5 mg/dL
- Skeletal myopathy or CK $> ULN$
- Blood dyscrasia
- Inflammatory bowel disease

Criteria

- Exclusion, continued.
 - Hypersensitivity to colchicine or other contraindication to its use
 - Current treatment with colchicine
 - Life expectancy \leq 18 months
 - Pregnant or lactating women
 - Women of childbearing potential not protected by a contraception method
 - Myocarditis, evidenced by elevated troponin level

Protocol

- Random assignment to colchicine or placebo in a 1:1 ratio based on permuted blocks of 4
- Regular follow up visits planned at 1 week, 1 month, 3 months, 6 months, 12 months, and every 6 months thereafter until study completion
 - All patients followed for at least 18 months
 - Average follow up = 22 months

Protocol

- Follow-up visits
 - Blood testing
 - CRP
 - Aminotransferases
 - CK
 - CBC
 - ECG
 - Echocardiogram

Endpoints

- Primary
 - Incessant or recurrent pericarditis
- Incessant = Persistent pericarditis or symptom-free interval < 6 weeks
- Recurrent = Documented first attack, plus symptom-free interval ≥ 6 weeks, plus evidence of subsequent recurrence of pericarditis

Endpoints

- Secondary
 - Symptom persistence at 72 hours
 - Remission within 1 week
 - Number of recurrences
 - Time to first recurrence
 - Disease-related hospitalization
 - Cardiac tamponade
 - Constrictive pericarditis

Statistical Analysis

- Assumed rate of incessant or recurrent pericarditis of 30% in placebo group at 18 months
 - Estimated that colchicine could reduce this rate by 50%
- Two-sided alpha of 0.05 required enrollment of 240 patients for a power of 80%
- Detection of ARR of 15 percentage points in incessant or recurrent pericarditis

Statistical Analysis

- Intention-to-treat analyses
- Mann-Whitney test for continuous variables
- Chi-square test for categorical variables
- Kaplan-Meier, Log-rank tests
 - Time-to-event data

Results

Patient Enrollment

- 280 patients assessed for eligibility
- 240 randomized (85.7%)
- 240 included in analysis
 - 120 colchicine group (14 discontinued)
 - 120 placebo group (10 discontinued)

Compliance

- $> 95\%$ compliance with colchicine *before* the primary outcome was reached or study completed
 - Placebo compliance rate not significantly different, yet unreported
- Target compliance $\geq 80\%$
 - Count of pills in dispensed boxes

Table 1. Characteristics of the Patients at Baseline.*

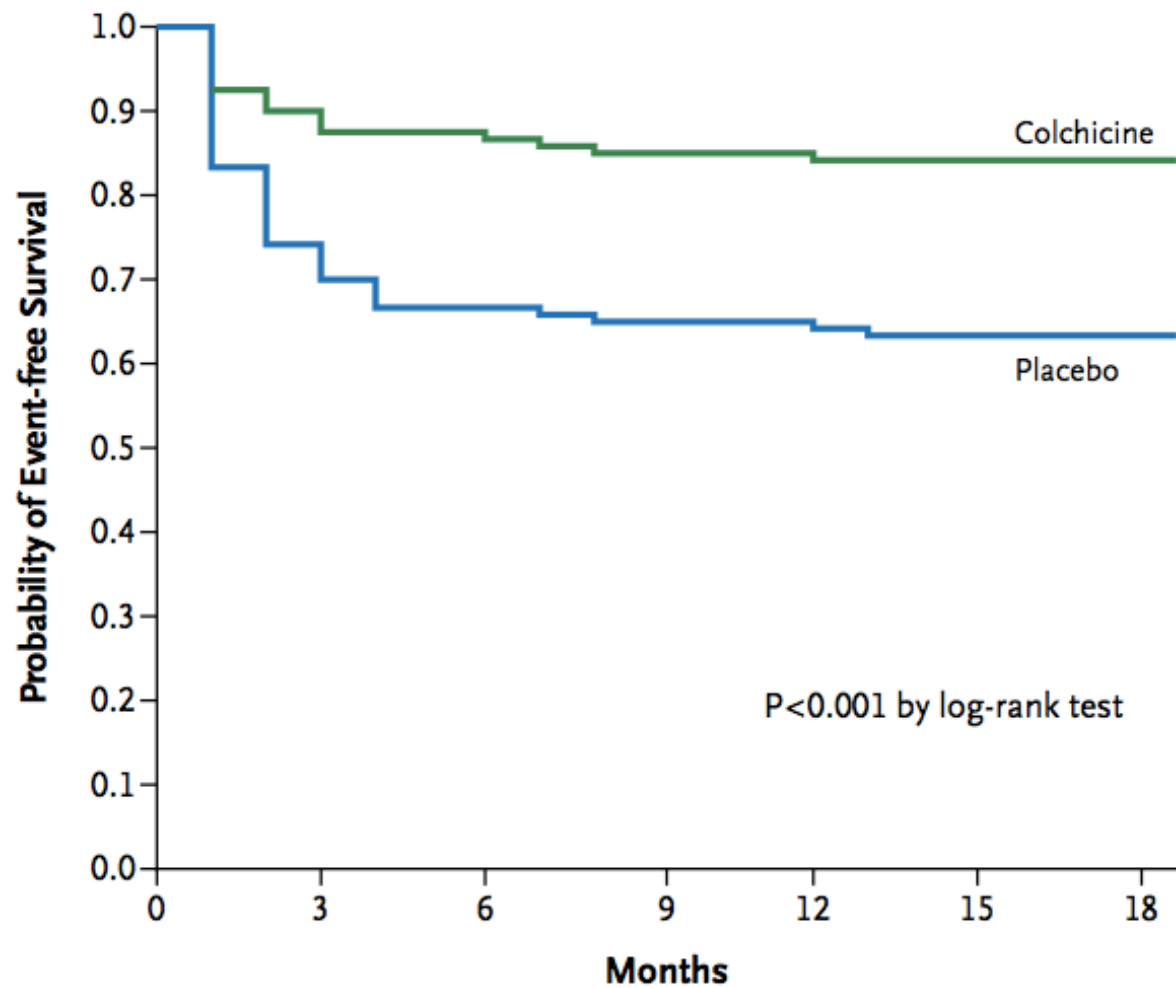
Characteristic	Placebo (N = 120)	Colchicine (N = 120)
Age — yr	50.7±17.5	53.5±16.2
Male sex — no. (%)	74 (61.7)	71 (59.2)
Cause of pericarditis — no. (%)		
Idiopathic	93 (77.5)	92 (76.7)
Post-cardiac injury syndrome	23 (19.2)	25 (20.8)
Connective-tissue disease†	4 (3.3)	3 (2.5)
Clinical findings — no. (%)		
Pericarditic chest pain	119 (99.2)	120 (100.0)
Pericardial rub	38 (31.7)	44 (36.7)
ST-segment elevation	26 (21.7)	35 (29.2)
Pericardial effusion‡	82 (68.3)	76 (63.3)
Mild (<10 mm)	76 (63.3)	64 (53.3)
Moderate (10–20 mm)	2 (1.7)	9 (7.5)
Large (>20 mm)	4 (3.3)	3 (2.5)
Cardiac tamponade	2 (1.7)	2 (1.7)
Elevated C-reactive protein level	89 (74.2)	85 (70.8)
Medications — no. (%)		
Aspirin	96 (80.0)	86 (71.7)
Ibuprofen	18 (15.0)	24 (20.0)
Prednisone	6 (5.0)	10 (8.3)

Table 2. Trial Outcomes.*

Outcome	Placebo (N=120)	Colchicine (N=120)	P Value
Incessant or recurrent pericarditis: primary end point — no. (%)‡	45 (37.5)	20 (16.7)	<0.001†
Symptom persistence at 72 hr — no. (%)	48 (40.0)	23 (19.2)	0.001
Remission at 1 wk — no. (%)	70 (58.3)	102 (85.0)	<0.001
Incessant course — no. (%)	20 (16.7)	9 (7.5)	0.046
Recurrent course — no. (%)	25 (20.8)	11 (9.2)	0.02
No. of recurrences per patient	0.52±0.81	0.21±0.52	0.001
Time to first recurrence — wk	17.7±9.0	24.7±11.0	<0.001
Cardiac tamponade — no. (%)	3 (2.5)	0	0.25
Constrictive pericarditis — no. (%)	1 (0.8)	0	1.00
Pericarditis-related hospitalization — no. (%)	17 (14.2)	6 (5.0)	0.02
Mean follow-up — mo	22.3±8.7	22.9±8.7	0.61

Result Analysis of Primary Endpoint?

	RR	RRR	ARR	NNT
Primary Endpoint	0.45	55%	20.8%	4.8



No. at Risk

Colchicine	120	105	105	102	102	98	89
Placebo	120	87	80	78	78	75	69

Figure 2. Kaplan–Meier Survival Curves for Freedom from Incessant or Recurrent Pericarditis (Primary Outcome).

Adverse Events

- No significant difference in overall rate
 - 11.7 % in colchicine group
 - 10 % in placebo group
 - P-value = 0.84
- No significant difference in individual rates
 - GI disturbance (diarrhea), p-value = 0.67
- Drug discontinuation rate not significant between both groups, p-value = 0.52

Discussion & Conclusions

Author's Conclusions

- “In patients with a first episode of acute pericarditis, the use of colchicine in addition to conventional anti-inflammatory therapy significantly reduced:
 - the *rate* of incessant or recurrent pericarditis
 - the *number* of recurrences of pericarditis
- In patients with a first episode of acute pericarditis, the use of colchicine in addition to conventional anti-inflammatory therapy significantly *prolonged* the time to recurrence.”

Study Validity

- Strong Internal Validity
 - Appropriate statistical analysis
 - Computer generated randomization
 - Sound methodology
- Questionable External Validity
 - Italian study, only 5 centers (sample size)
 - Extensive exclusion criteria
 - Similar baseline characteristics

Authors' Conclusions vs. Current Literature

- European Society of Cardiology
 - 2004 Guidelines on the Diagnosis and Management of Pericardial Diseases
 - Acute pericarditis treatment
 - NSAIDs Class IB recommendation
 - Addition of/monotherapy colchicine (0.5 mg BID) for initial attack and recurrence prevention, Class IIaB
- 2005 COPE Trial: Colchicine in Addition to Conventional Therapy for Acute Pericarditis
 - Same hypothesis as ICAP trial (same lead author)
 - Prospective, randomized, OPEN label, 120 patients
 - Reduced recurrence rate in patients with a *first episode* of acute pericarditis

Authors' Conclusions vs. Current Literature

- 2005 CORE Trial: Colchicine as First-Choice Therapy for Recurrent Pericarditis
 - Evaluate efficacy and safety of colchicine as adjunct to conventional therapy for the *first* episode of *recurrent* pericarditis (same lead author)
 - Prospective, randomized, OPEN label, 84 patients
 - Reduced recurrence rate in patients with a first episode of *recurrent* pericarditis
- 2011 CORP Trial: Colchicine for Recurrent Pericarditis
 - Evaluate the efficacy and safety of colchicine for the *secondary prevention of recurrent* pericarditis (same lead author)
 - Prospective, randomized, double-blind, placebo-controlled, multicenter trial, 120 patients
 - Colchicine is safe and effective for secondary prevention of recurrent pericarditis

Conclusions / Clinical Application

- Colchicine appears to be an effective and safe option for qualified patients with initial attacks of acute pericarditis, in addition to conventional therapy
- Care must be taken in patient selection prior to colchicine administration
- Consider drug interactions and always administer with an agent for ulcer prophylaxis

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Questions?