Efficacy of Colchicine When Added to Traditional Anti-inflammatory Therapy in the Treatment of Pericarditis

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Efficacy of Colchicine When Added to Traditional Anti-inflammatory Therapy in the Treatment of Pericarditis

Abstract

Background: Pericarditis is the most common disease affecting the pericardium of the heart. It is inflammation of the fibrous pericardial sac surrounding the heart. Five percent of emergency department visits with chest pain not relating to myocardial infarction are attributed to pericarditis. Evidence shows 80% of cases in developed nations are idiopathic or post-viral in nature. Treatment has consisted of NSAIDS and glucocorticoids as first line therapy. Colchicine is an anti-inflammatory medication that has long been used in the therapy of gout arthritis and other rheumatologic complaints worldwide. It has been proposed that the anti-inflammatory profile occurring within joints can apply to the pericardium of the heart. The purpose of this study is to evaluate how efficacious colchicine is when added to traditional therapy in the treatment of pericarditis.

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, and Pub-Med using keywords: pericarditis and colchicine. Articles with primary data evaluating the use of colchicine in treating pericarditis were included. These relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Results: Three studies met the inclusion criteria for this systematic review. A randomized, double blind, placebo-controlled study investigating colchicine and the treatment of pericarditis demonstrated a reduction in recurrence rate, symptom persistence, and the need for hospitalization. A second randomized, double blind, placebo-controlled study demonstrated a reduction in disease recurrence, symptom persistence, and hospitalization related to the disease. Another randomized, open-label trial evaluating colchicine therapy in treating acute pericarditis demonstrated a decrease in recurrence rate and symptom persistence.

Conclusion: Colchicine when treating pericarditis was demonstrated to reduce disease recurrence, lessen symptom persistence, and limit the need for hospitalization. The safety and efficacy has been evaluated through multiple trials and deemed superior to standard therapy alone. The overall quality of the studies reviewed is moderate based on the GRADE criteria. A weak recommendation for the off-label use of colchicine in the treatment plan of pericarditis can be given at this time based on the available data.

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Efficacy of Colchicine When Added to Traditional Anti-inflammatory Therapy in the Treatment of Pericarditis

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A Clinical Graduate Project Submitted to the Faculty of the

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Faculty Advisor: Mark Pedemonte, MD
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Biography

Ryan Gilbreth is a native of Spokane Washington. He received a Bachelor of Science degree in Kinesiology from Washington State University in 2009. Prior to PA school, he worked for 3 years in Radiology as a patient care associate. He takes passion in the outdoors including hiking or walking 18 holes on the golf course. Ryan is interested in pursuing a medical career as a PA in Emergency Medicine, Orthopedics, or Family practice once he finishes the program.
Abstract

**Background:** Pericarditis is the most common disease affecting the pericardium of the heart. It is inflammation of the fibrous pericardial sac surrounding the heart. Five percent of emergency department visits with chest pain not relating to myocardial infarction are attributed to pericarditis. Evidence shows 80% of cases in developed nations are idiopathic or post-viral in nature. Treatment has consisted of NSAIDS and glucocorticoids as first line therapy. Colchicine is an anti-inflammatory medication that has long been used in the therapy of gout arthritis and other rheumatologic complaints worldwide. It has been proposed that the anti-inflammatory profile occurring within joints can apply to the pericardium of the heart. The purpose of this study is to evaluate how efficacious colchicine is when added to traditional therapy in the treatment of pericarditis.

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List of Abbreviations

RCT          Random Control Trial
NNT          Number needed to treat
NIH          National Institute of Health
ECG          Electrocardiogram
GRADE        Grading of Recommendations, Assessment, Development and Evaluations
PPI          Proton Pump Inhibitor
ASA          Aspirin
NSAID        Non-steroidal anti-inflammatory Drug
CYP          Cytochrome P450 system
BID          Twice daily
CK           Creatinine Kinase
CBC          Complete blood count
FMF          Familial Mediterranean Fever
Efficacy of Colchicine When Added to Traditional Anti-inflammatory Therapy in the Treatment of Pericarditis

BACKGROUND

Pericarditis is the most common disease affecting the pericardium of the heart.\textsuperscript{1} The pericardium, a fibrous sac surrounding the myocardium of the heart, can become inflamed and irritated by various processes. These include idiopathic, tuberculous, neoplastic, or post-traumatic in nature. Greater than 80\% of these are of post-viral or idiopathic etiology in developed countries.\textsuperscript{2}

Pericarditis is said to be recorded 1 out of every 1000 hospitalized patients and 5\% of patients admitted to the emergency department for chest pain not attributed to myocardial infarction.\textsuperscript{3} Males under the age of 50 have demonstrated an increased incidence of acquiring pericarditis.\textsuperscript{4}

Pericarditis is typically a benign disease process overall but necessitates treatment to prevent dangerous sequela. Pericardial effusion or fluid surrounding the heart tissue within the pericardial sac can lead to cardiac tamponade. Cardiac tamponade and the restrictive nature placed on the myocardium results in reduced blood pressure and cardiac output requiring emergency action to prevent mortality.\textsuperscript{2}

Diagnosis is made on the basis of established criteria in previous studies,\textsuperscript{5} which include two of the following: Typical pleuritic chest pain improved with leaning forward, pericardial friction rub on auscultation, ST-segment changes on ECG, and new or worsening pericardial effusion seen on echocardiogram. Inflammatory markers such as elevated white blood cell count, elevated C-reactive protein, or elevated erythrocyte
sedimentation rate can help follow progression of the disease but are not solely used for diagnostic purposes.\(^6\)

The treatment of pericarditis has been tailored towards idiopathic causation which accounts for greater than 80% of cases in developed nations and has long been empirical in nature. The first line approach has been aspirin and other NSAIDS such as ibuprofen or indomethacin. Glucocorticoid use for patients who are unable to tolerate typical NSAIDS has been initiated but proven to increase risk of relapse once the drug is tapered.\(^7\) Pericardectomy is an option for severe cases of relapsing pericarditis and subsequent effusions. This invasive procedure is reserved for those resistant to pharmacological treatment including the topic of choice, colchicine.\(^8\)

Colchicine has long been used in the treatment and prevention of gout arthritis and related rheumatologic complaints. Originally extracted from the plant *Autumn Crocus*, it was initially described by Ebers Papyrus in 1500 BC. It has since been used in medicine over many centuries including today’s label indications for gout and familial mediterranean fever.\(^6\) Colchicine’s mechanism of action is not fully understood but is stated to actively concentrate in WBCs, especially granulocytes, blocking tubulin polymerization and microtubules generation. This interferes with several functions of these cells including migration, phagocytosis, and degranulation.\(^9\) The end result of this process is a limitation of a major player in the body’s inflammatory process, cytokine interleukin 1-beta.\(^6\)

The medication’s impact on pericardial disease has been pushed to the forefront since the mid 90’s and early 2000’s. Currently, a recommendation is made by The Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society
of Cardiology (level of evidence B, class IIa indication) but as such still remains off label. The purpose of this study is to explore the therapeutic potential of colchicine in treating pericarditis. This review will be primarily looking at outcomes associated with symptom duration, recurrence of disease, and hospitalization rate secondary to pericarditis.

METHODS

A comprehensive search of available medical literature was conducted using CINAHL, Medline-Ovid, and PubMed using the following keywords: pericarditis and colchicine. The search was then narrowed to studies in the English language, on human participants, and conducted as random control trials. The bibliographies of these articles were further researched for background information and relevant sources. The relevant articles were then assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation. (GRADE) Lastly, a search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to the use of colchicine in the treatment of pericarditis.

RESULTS

The initial search produced 354 articles for review. After screening these relevant articles for primary data using the above eligibility criteria, a total of three articles remained. These articles included three randomized controlled trials that were conducted in Italy by the same researchers. (see Table 1).
ICAP Trial

The Investigation on Colchicine for Acute Pericarditis trial,\textsuperscript{11} described by its authors is a prospective double blind, placebo-controlled trial. The purpose of the study was to investigate the effects of adding colchicine to traditional anti-inflammatory therapy in treating acute pericarditis. The primary outcome to be measured was pericarditis recurrence. Secondary outcomes included symptom persistence beyond 72 hours, hospitalizations related to disease, remission rate at 1 week, and adverse effects of the therapy.\textsuperscript{11}

In this study a total of 240 patients were selected from five general hospitals in Northern Italy. Two groups were set forth and balanced for prognostic and diagnostic characteristics (see Table 2). Eligibility for enrollment was limited to subjects aged at least 18 and presenting with their first episode of acute pericarditis. The diagnosis of acute pericarditis was made with the following criteria: presentation of typical sharp and pleuritic chest pain improved by leaning forward, a pericardial friction rub, widespread ST-changes on ECG, or new or worsening pericardial effusion seen on echocardiogram. Patients were considered ineligible and therefore excluded if the etiology of pericarditis was tuberculous, neoplastic, or purulent. Additionally, they were omitted if subjects had known severe liver disease or transaminases >1.5 of normal limit, had CK above 2.5 mg/dL, had known blood dyscrasias or gastrointestinal disease, were pregnant or lactating females, who were women of childbearing age not protected by contraception.
methods, who are undergoing colchicine therapy for any other known reason, or who have known sensitivity to the drug.\textsuperscript{11}

Once proven to be eligible, patients were randomly assigned to one of two treatment groups by way of a central computer-based automated sequence. Randomization was based on permuted blocks of four. The random assignment was enacted with the use of sequentially numbered drug containers. All participants received conventional treatment for acute pericarditis which included 800mg of aspirin or 600mg of ibuprofen orally every 8 hours for 7-10 days; followed by tapering over 3-4 weeks. Glucocorticoids (prednisone 0.2-0.5mg/kg) were used in those with absolute contraindication to NSAIDS such as allergy, history of peptic ulcer disease or gastrointestinal bleed, and current oral anticoagulation whose bleeding risk was considered high. All patients received an undisclosed PPI for prophylaxis. Patients allocated to receive colchicine were given a dose of 0.5 mg to 1.0 mg day for 3 months. This dosing was previously established from safety measures in the COPE trial.\textsuperscript{12} The lower dose (0.5mg BID) was reserved for those weighing less than 70kg. The placebos were indistinguishable in color, shape, and taste as well as being scored so that it is identical to the colchicine tablets for lower dosing.\textsuperscript{11}

The enrollment period began in August 2005 and ended in December 2010. Follow-up continued through June 2012. Outcomes were measured for a minimum of 18 months, with an average of 22 months. Regular visits were established at 1 week, 1 month, 3 months, 6 months, 1 year, and 18 months. Each visit consisted of blood work (CBC, C-reactive protein, aminotransferase), ECG, and echocardiogram. A clinical
endpoint committee who was unaware of group assignment adjudicated each clinical endpoint.\textsuperscript{11}

Of the 120 patients who received colchicine as part of their therapy, the primary outcome of recurrent pericarditis occurred 11/120 vs 25/120 in the placebo group (RR: 0.43, NNT: 9, p=0.02). The secondary endpoints of symptom persistence greater than 72 hours occurred 23/120 patients who received colchicine and 48/120 in those who received traditional therapy plus placebo (RR: 0.40, NNT: 5, p=0.001). Lastly, the outcome of hospitalization occurred 6/120 in the colchicine group and 17/120 in the placebo group (RR: 0.35, NNT: 11, p=0.02). In the ICAP trial, there were 11 out of 120 subjects having gastrointestinal intolerances to colchicine compared to 10 out of 120 patients in the placebo group. Complete follow-up was accomplished in 106/120 patients in the colchicine group and 108/120 in the placebo group. The most frequent adverse effect to cause discontinuation being gastrointestinal intolerance.\textsuperscript{11}

The authors concluded colchicine reliably reduced the rate of recurrence in pericarditis, effectively lessened symptom persistence longer than 72 hours, and limited the need for disease-related hospitalization. It was proven to be a safe and reliable adjunctive therapy in the treatment of pericarditis.

The authors acknowledged limitations within the study. First, the study may not be generalized to other clinical conditions or populations secondary to the extensive exclusion criteria. Second, the use of colchicine is currently off label and not approved for the prevention of recurrent pericarditis in North America or Europe. Finally, they note a small sample size that may preclude certain adverse effects. The researchers recommend further research into proper colchicine duration of therapy.\textsuperscript{11}
COPE Trial

The Colchicine for Acute Pericarditis (COPE) trial\textsuperscript{12} is described by its authors as a prospective, randomized, open label design. The intent of the study was to evaluate the efficacy of colchicine when added to conventional anti-inflammatory therapy in the treatment of acute pericarditis. The primary outcome measured was recurrence rate of pericarditis after treatment. Secondary outcomes included symptom persistence and adverse effects of therapy. The study was approved by the institutional review board.\textsuperscript{12}

In this study, a total of 120 patients selected from two Italian medical centers were randomly assigned to one of two groups. They were balanced for prognostic and demographic quality (see Table 3). Eligibility for enrollment was limited to patients with a first episode of acute pericarditis defined by at least two of the following: typical chest pain, pericardial friction rub, and widespread ST- segment changes on ECG. In addition, subjects were limited to those of ages 18 or older, pericarditis of (idiopathic, viral, autoimmune causes, PPS, connective tissue disease), and those who gave informed consent. Patients were excluded if the etiology of pericarditis was tuberculous, neoplastic, or purulent. Additionally, they were omitted if subjects had known severe liver disease or transaminases >1.5 of normal limit, had CK above 2.5 mg/dL, had known blood dyscrasias or gastrointestinal disease, were pregnant or lactating females, who were women of childbearing age not protected by contraception methods, those who are undergoing colchicine therapy for any other known reason, or who have a known sensitivity to the drug.\textsuperscript{12}
The two randomly assigned treatment groups were to receive conventional therapy with aspirin 800mg orally every 6-8 hours for 7 to 10 days with tapering over 3-4 weeks alone (group 1) or combined with colchicine 1.0-2.0 mg on day 1 and then maintenance dosing of 0.5-1.0 mg daily for 3 months.(group 2). The lower maintenance dose of 0.5 mg was reserved for those <70kg in the study. Both groups received omeprazole 20mg/day for gastrointestinal prophylaxis. Prednisone replaced aspirin at a dose of 1.0-1.5 mg/kg/day for 2-4 weeks for those with absolute contraindication to aspirin such as allergy or elevated bleeding risk.\textsuperscript{12}

Between the enrollment period of January 2002 and August 2004, 120 patients were entered into the study. After randomization was complete using permuted blocks of four, follow-up visits were conducted at the following intervals: 48 hrs, 72 hrs, 10 days, 1 month, 3 months, 6 months, 1 year, and yearly for cases of uncomplicated nature. The average time for follow up was 23.7 months for the control group and 24.2 months in the colchicine group. Complete follow-up was accomplished in 55/60 patients in the colchicine group with five patients lost secondary to discontinuation due to diarrhea. No subjects within the control group were lost to follow-up. Each clinical event was ensured by an ad-hoc committee of expert cardiologist blinded to patient’s treatment assignment. The data analyses were performed by external committee which was blinded to treatment subgroups.\textsuperscript{12}

With regards to the primary outcome, recurrence rate of pericarditis at 18 months, colchicine was shown to be superior to the control group of ASA/Glucocorticoid therapy alone. Recurrence of pericarditis occurred in 7/60 patients within the colchicine therapy group vs. 20/60 patients in the control group (RR 0.35, NNT 5, p=0.004).\textsuperscript{12} The secondary
outcome of symptom persistence of 72 hours in duration was similarly lessened in the colchicine group. Symptoms persisted in 7/60 patients within the colchicine group and 22/60 in the control group (RR 0.32, NNT 4, p=0.003). According to the researchers of this study, therapy was generally well tolerated in both groups. There were five reported cases of diarrhea within the colchicine therapy group; causing discontinuation of the drug and prompt reversal of symptoms. There were no participants who acquired gastrointestinal intolerance leading to the withdrawal from the control group. The authors concluded that colchicine in combination with traditional therapy such as aspirin was efficacious and safe in the treatment of pericarditis. They noted, however, the limitations of the study center around the open label design, which allows for bias to enter into the equation by both the prescribing doctor and the patient. There was an attempt to minimize the effect with a blinded ad hoc committee overseeing outcome events and an independent data analyses committee blinded to assignment. Never the less, a double-blind study would eliminate all cause for concern.

CORP Trial

The Colchicine for Recurrent Pericarditis (CORP) trial is described by the authors as a prospective, randomized, double-blind, placebo-controlled multicenter design. The intent of this study was to evaluate the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis. The primary outcome set forth was recurrence rate at 18 months. Secondary endpoints included symptom persistence at 72 hours, disease-related hospitalization, remission rate at 1 week, number of recurrences, time to first recurrence, and cardiac tamponade.
In the study, a total of 120 patients were selected from four general hospitals in Italy (Maria Vittoria Hospital, Ospedali Riuniti, San Maurizio Regional Hospital, and Ospedale SS Annunziata). They were balanced for prognostic and diagnostic quality (see Table 4). Eligibility for enrollment was limited to patients with a first recurrence of pericarditis. Pericarditis was established by having two of the following criteria: typical pericardial chest pain, pericardial friction rub, widespread ST changes on ECG, and new or worsening pericardial effusion seen on echocardiogram. Participants in additional needed to be 18 years of age or older and provide informed consent. Patients were excluded if they were having first episode of acute pericarditis, pericarditis with etiology that was tuberculous, neoplastic, or purulent. Subjects were additionally precluded with known severe liver disease or transaminases >1.5 of normal limit, had CK above 2.5 mg/dL, had known blood dyscrasias or gastrointestinal disease, were pregnant or lactating females, who were women of childbearing age not protected by contraception methods, and those who are undergoing colchicine therapy for any other indication.

Participants were randomly assigned to one of two groups by a central computer-based automated sequence based on permuted block sizes of four. Random allocation sequence was implemented by using sequentially numbered containers. All participants and investigators were blinded to assignment. Unblinded data was made available to an independent data and safety and monitoring board in the event of side effects. The data was collected by using case report and clinical events adjudication forms which were managed by a blinded committee. An end point committee oversaw clinical endpoints and was blinded to assignment as well.
All patients in both the control and experimental group received conventional therapy in the form of aspirin 800-1000 mg (or ibuprofen 600 mg) orally every 8 hours for 7-10 days with a gradual taper of 3-4 weeks. Prednisone in a dosing of 0.2-0.5 mg/kg/day for four weeks followed by a similar taper was given to those with absolute contraindication to NSAIDS such as allergy, history of peptic ulcer, gastrointestinal bleed, or high risk of bleeding due to oral anticoagulation. Every patient who received either aspirin or ibuprofen received a PPI for prophylaxis.  

The experimental group was additionally given colchicine 1.0-2.0 mg on day one, followed by maintenance of 0.5-1.0 mg/day for six months. All doses were given every 12 hours. The lower dosing of 0.5 mg/day was implemented for those who weighed less than 70 kg or were unable to tolerate the higher dose of 1.0 mg/day. Placebo tablets were identical in shape, color, and taste.  

The enrollment period proceeded from August 2005 to April 2009 with the trial completed in October 2010, which was at the 18 month follow up for the last enrolled patient. Once each subject was allocated to the treatment or control group, follow-up visits were conducted at the following intervals: 1 week, 1 month, 3 months, 6 months, 12 months, and 18 months. Each visit consisted of echocardiogram, blood chemistry, complete blood count, C-reactive protein, creatinine, and aminotransferase levels. During the follow up, adverse events were monitored by the above mentioned independent safety committee. Lost to follow-up but not analysis were 5/60 in the colchicine group and 4/60 in the placebo group. This was reportedly due to gastrointestinal discomfort (see Table 5).
The primary outcome of pericarditis recurrence rate at 18 months was demonstrated to be superiorly improved with the addition of colchicine to the traditional therapy of NSAIDS or glucocorticoids. The recurrence rate within the colchicine group was effectively 14/60 and the placebo group was 33/60 (RR: 0.42, NNT: 4, p=<0.001). Additionally, colchicine showed to benefit symptom persistence beyond 72 hours at a rate of 13/60 vs. the placebo group’s 33/60 (RR: 0.42, NNT: 4, p=0.001). Hospitalization related to disease was lessened as well with the colchicine group having 3/60 and the placebo group attaining 8/60 hospitalized subjects (RR: 0.38, NNT: 12, p=0.20). The most frequently adverse effect was GI discomfort (see Table 5). This was reversed promptly with lowering the dose of colchicine or ultimately withdrawing the medication by the investigators. Overall, 4 out of 60 patients reported gastrointestinal side effects in the colchicine group and 3 out of 60 patients obtained gastrointestinal intolerance issues.13

The authors concluded colchicine halved the recurrence rate at 18 months, hastened symptom resolution, and limited hospitalization while maintaining a high level of tolerability. The addition of colchicine to traditional anti-inflammatory regiment was safe and efficacious.13

The authors did acknowledge study limitations as such the exclusion criteria were extensive and were only applicable to adults. A significant road block echoed by the authors is that, currently, the use of colchicine in the treatment of pericarditis is not approved in North America or Europe, and that the use is off-label.13
DISCUSSION

Clinical Relevance

The general approach in the treatment of pericarditis has been well established in literature. NSAIDs and glucocorticoids are still the mainstay of therapy and recommended in the only guidelines available on the treatment pericarditis. However, a consideration for colchicine administered as adjunctive therapy should be considered due to the above research.

Colchicine has proven to be both safe and efficacious when added to conventional therapy in the treatment of pericarditis. To date, the reviewed RCTs\textsuperscript{11-13} have produced promising results regarding the benefit of treating patients with colchicine in addition to traditional pericardial anti-inflammatory therapy. All three clinical trials conducted by Imazio et al\textsuperscript{11-13} determined that the use of colchicine was superior in minimizing symptom persistence, stalling recurrence of disease, and limiting hospitalizations due to pericarditis. While classified officially as an “off-label” indication in the therapy of pericarditis, evidence is being brought to the forefront for the safety and effectiveness when added to traditional treatment regiments.

Efficacy and safety profiles in addition to developing a standardized dosing of colchicine have given the taskforce for European Society of Cardiology confidence to include it in their guidelines.\textsuperscript{7} However, there is still some question as to the duration of therapy. The above studies treated patients for 3-6 months. Moreover, one must take into consideration the patient at hand and the specific etiology of pericarditis.

When specifically addressing the safety of colchicine in patients with acute pericarditis, research is lacking. A brief overview of adverse events in each of the three...
trials is available found in Table 5. However, the safety profile is well established in patients with gout. It is well known that gastrointestinal upset including diarrhea, vomiting and nausea, are the main side effects of colchicine. This has been effectively reduced by lowering the effective dose or adding prophylaxis with a proton pump inhibitor.

The individual circumstance of your patient including renal and liver function must meet requirements in order to be considered safe for therapy. Colchicine is eliminated primarily via hepatic metabolism by the Cytochrome P450 (CYP) system. It is interference with this system that potentially causes toxicity from colchicine. Any medications that interact with the CYP system or those that inhibit P-glycoprotein have the potential to increase colchicine’s exposure by slowing down elimination. Some of these commonly prescribed medications include digoxin and macrolide antibiotics. Colchicine's half-life is doubled in patients with renal failure and by 10 times in the presence of liver cirrhosis. These facts contributed to the exclusion criteria focused on liver and renal disease noted in all three trials.

The last concern is cost. The cost of colchicine is currently at $4.85 a tablet (0.6 mg tablet) since 2009 when the FDA granted sole exclusivity to URL-Pharma. Prior to this change it was 9 cents per pill as a generic medication. Factoring in these considerations while meeting criteria laid down through prior research, we can treat safely and appropriately with colchicine for pericarditis.

Limitations of studies

While every study demonstrated an added benefit and minimal harm in the addition of colchicine as seen in the summary of findings table (see Table 1) the
studies are not without limitations. The ICAP trial\textsuperscript{11} showed us that while specific causes of pericarditis can successfully be treated with colchicine, it excluded various other etiologies of the disease including bacterial and neoplastic. The applicability to a more general population contracting this disease is minimized as evidence shows us that outside of developed countries, tuberculous and bacterial etiology is of common occurrence.\textsuperscript{15} The COPE trial\textsuperscript{12} lacked concealment or blinding allowing each participant and investigator knowledge of who was receiving colchicine therapy. This damages the validity of the results in any study and can be easily remedied with appropriate study design adjustments. The CORP trial,\textsuperscript{13} while again proving that colchicine has its place amongst the therapy of pericarditis, demonstrated flaws. Similar to those before it, a cross application to bacterial pericarditis cannot be achieved. Research to further apply colchicine in this arena is needed and recommended by its authors.

Overall, the lack of experimental trials conducted by others practicing outside of the Italian Cardiology community is disconcerting. Dr. Immazio has been well established as a leading expert in the field of pericardiology, but further diverse investigations need to be obtained. The geographical limitations set forth by selection of participants in the Italian Health System show mild cause for concern in the true effectiveness of colchicine. The Mediterranean part of the world is privy to isolated familial disease including familial mediterranean fever. FMF is treated with colchicine as well.\textsuperscript{16} The possibility that each study’s sampling location skews the results secondary to a perceived advantage when colchicine is used.

Currently there is a systematic review\textsuperscript{17} conducted by Dr. Imazio regarding his own work including the COPE and CORP trials as well as study by Finkelstein regarding
pericarditis.\textsuperscript{18} The objectivity of a systematic review on one’s own studies seems a difficult task to maintain. The question needed addressing and an independent review of whether the included trials\textsuperscript{12, 13} were of high quality was initiated. This review in addition, included Dr. Imazio’s newest trial\textsuperscript{11} published in the New England Journal of Medicine which was not originally incorporated in his systematic review.

To fully assess for bias or limitations in design, all three RCTs were evaluated using the GRADE protocol. The outcomes of pericarditis recurrence and symptom persistence were investigated by all three studies,\textsuperscript{11-13} while only two of the three examined hospitalization rate.\textsuperscript{11, 13} All three studies being RCTs began with a GRADE of high. With regards to all three primary outcomes, the overall GRADE was moderate, related to the high risk of publication bias.

CONCLUSION

Colchicine has been demonstrated to be a valuable adjunctive therapeutic option when treating pericarditis. More specifically is has shown to reduce the rate of recurrent pericarditis, limit symptom persistence, and lower hospitalization rate secondary to the disease. It has been used for decades in medicine but only recent has been making a case for being included in the therapy for pericarditis. The overall qualities of the studies reviewed were moderate based on the GRADE criteria. A weak recommendation for the use of colchicine in the therapy of pericarditis can be made based on quality of evidence. Further research and randomized control studies evaluating colchicine as mono-therapy for pericarditis are needed to determine independent efficacy and work towards achieving on-label approval for pericarditis management.
References


Table 1 GRADE evidence profile: Colchicine and the treatment of pericarditis

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
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<tr>
<td>Downgrade Criteria</td>
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<tr>
<td>No. of Studies</td>
<td>Design</td>
</tr>
<tr>
<td>3</td>
<td>3 RCT</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recurrence of Pericarditis

<table>
<thead>
<tr>
<th>Symptom persistence &gt;72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 RCT</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Hospitalization related to disease

| 2 RCT                         | No serious limitation | No serious indirectness | No serious imprecision | No serious inconsistencies | Publication bias is likely | ICAP\textsuperscript{11} | 6/120 | 17/120 | 0.35 | NNT 11 |
|                               |                      |                       |                       |                         |                       | CORP\textsuperscript{13} | 3/60 | 8/60 | 0.38 | NNT 12 |

\textsuperscript{a}COPE Trial: The COPE trial was an open label study however the other two studies had strong allocation concealment therefore no downgrade necessary.

\textsuperscript{b}All studies were conducted by the same researchers.
Table 2: ICAP trial patient characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N=120)</th>
<th>Colchicine (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>50.7 +/-17.5</td>
<td>53.5 +/-16.2</td>
</tr>
<tr>
<td>Male Gender #</td>
<td>74</td>
<td>71</td>
</tr>
</tbody>
</table>

**Causes of Pericarditis**

<table>
<thead>
<tr>
<th>Causes of Pericarditis</th>
<th>Placebo (N=120)</th>
<th>Colchicine (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Autoimmune(^{a})</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

**Clinical Findings**

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Placebo (N=120)</th>
<th>Colchicine (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial Chest pain</td>
<td>119</td>
<td>120</td>
</tr>
<tr>
<td>Pericardial Rub</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>ST Elevation on ECG</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>84</td>
<td>76</td>
</tr>
</tbody>
</table>

**Total Subjects in each group**

<table>
<thead>
<tr>
<th>Total Subjects in each group</th>
<th>N=120</th>
<th>N=120</th>
</tr>
</thead>
</table>

*Source: ICAP\(^{11}\)*

\(^{a}\)Autoimmune includes those with connective tissue etiology.
### Table 3: COPE trial patient characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Colchicine (N=60)</th>
<th>Colchicine (N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>57.2 +/- 19.6</td>
<td>56.5 +/- 18.2</td>
</tr>
<tr>
<td>Male Gender #</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td><strong>Causes of Pericarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Autoimmune^b</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td><strong>Clinical Findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial Chest pain</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Pericardial Rub</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>ST Elevation on ECG</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total Subjects in each group</strong></td>
<td>N=60</td>
<td>N=60</td>
</tr>
</tbody>
</table>

*Source: COPE^1*

^1Autoimmune includes those with connective tissue etiology

### Table 4: CORP trial patient characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>(N=60)</th>
<th>(N=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean)</td>
<td>47.3+/-14.4</td>
<td>47.9+/-15.4</td>
</tr>
<tr>
<td>Male Gender #</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td><strong>Causes of Pericarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Autoimmune&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td><strong>Clinical Findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericardial Chest pain</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Pericardial Rub</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>ST Elevation on ECG</td>
<td>Not Included</td>
<td>Not Included</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

**Total Subjects in each group**  
N=60  
N=60

*Source: CORP<sup>11</sup>*

<sup>c</sup>Autoimmune includes those with connective tissue etiology

**Table 5**: Subjects with adverse events
<table>
<thead>
<tr>
<th></th>
<th>ICAP</th>
<th>COPE</th>
<th>CORP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colchicine group</td>
<td>Placebo</td>
<td>Colchicine group</td>
</tr>
<tr>
<td>GI Intolerance(^a)</td>
<td>11 (9.2%)</td>
<td>10 (8.3%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>2 (1.6%)</td>
<td>1 (.83%)</td>
<td>NS</td>
</tr>
<tr>
<td>Subjects withdrawn from study</td>
<td>14 (11.7%)</td>
<td>10 (8.3%)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>Total participants analyzed</td>
<td>N=120</td>
<td>N=120</td>
<td>N=60</td>
</tr>
</tbody>
</table>

Source: ICAP, COPE, CORP trials\(^{11-13}\)
\(^a\) Includes diarrhea, nausea, vomiting, abdominal pain
\(^b\) One additional patient withdrew self from study without cause or adverse event