Safety and Efficacy of Colchicine in the Treatment of Recurrent Aphthous Stomatitis

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Recommended Citation
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Abstract
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Method: An exhaustive search of available medical literature was conducted, from 2000 to present, using CINHAL, Cochrane Systematic Reviews, PubMed, Medline-OVID, and MD Consult database. Quality of evidence in each article was assessed using GRADE.

Results: Three studies met criteria for this systematic review. A double blind, randomized-controlled trial, demonstrated reduction in pain and burning sensation from baseline score ± SD in colchicine (7.92 ± 2.39 score, p

Conclusion: Based on this systematic review of literature and use of GRADE, there is moderate evidence showing colchicine is a safe and effective treatment in pain reduction and relapse prevention for patients with recurrent aphthous stomatitis. However, further research is likely to have an impact on estimate of benefit and risk.

Keywords: Colchicine, recurrent aphthous stomatitis.
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Safety and Efficacy of Colchicine in the Treatment of Recurrent Aphthous Stomatitis

Cameron Hardy

A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

Pacific University School of Physician Assistant Studies
April, 2011
Faculty Advisor: Annjanette Sommers
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Biography

Cameron Hardy is a native of Utah where he grew up working on his family’s dairy farm. He grew up racing motorcycles and snowboarding. After graduating high school and serving two years as a missionary in Brazil for his church, he majored in Exercise Science at Utah State University. During completion of his undergraduate degree, he worked as a medical assistant at the Brigham City Medical Arts Clinic in pursuit of a career in medicine. In 2009, Cameron was accepted into the Pacific University School of Physician Assistant Studies. He looks forward to serving others in rural health, and spending time with his family.

Acknowledgements

To the faculty at Pacific University: Thank you for all your hard work and dedication to the program and its students. Your personalities and humor were most appreciated, even if we didn’t always laugh.

To my family: Thank you for your love and support. I could not have ever done this without you.

To my parents: Thank you for teaching me how to work hard even though I complained every second and used my money unwisely.
ABSTRACT

Background: Recurrent aphthous stomatitis is among the most common oral lesions observed by physicians. Definitive treatment has been difficult considering its unknown etiology; however, proposed immunologic factors have led to the use of immunosuppressive agents. Colchicine has been shown to have an effect on all types of RAS through its anti-inflammatory action by way of suppressing phagocytosis and migration of leukocytes, but its safety and efficacy have only been addressed in a few small studies.

Method: An exhaustive search of available medical literature was conducted, from 2000 to present, using CINHAL, Cochrane Systematic Reviews, PubMed, Medline-OVID, and MD Consult database. Quality of evidence in each article was assessed using GRADE.

Results: Three studies met criteria for this systematic review. A double blind, randomized-controlled trial, demonstrated reduction in pain and burning sensation from baseline score ± SD in colchicine (7.92 ± 2.39 score, p<0.001) and number of aphthous ulcers (2.77 ± 1.49, p<0.001). An open-label trial demonstrated excellent response to colchicine in 40% of ten patients, and moderate response in 50%. A retrospective study demonstrated 60% excellent therapeutic success in 50 patients using colchicine.

Conclusion: Based on this systematic review of literature and use of GRADE, there is moderate evidence showing colchicine is a safe and effective treatment in pain reduction and relapse prevention for patients with recurrent aphthous stomatitis. However, further research is likely to have an impact on estimate of benefit and risk.

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INTRODUCTION

Background

Recurrent Aphthous Stomatitis (RAS) is a pathologic condition characterized by recurring, painful, ulcers of the oral mucosa with outbreaks occurring three to four times per year or continuously. It is the most common cause of oral ulcers observed by physicians, affecting 20% of the US population and 2-66% of the international population (Axéll & Henricsson, 1985). It is a rather common affliction during childhood and adolescence, with a higher occurrence in females. (Crivelli, Aguas, Alder, Quarracino, & Bazerque, 1988). The three clinical presentations of RAS comprise of, minor, major and herpetiform.

A disorder of uncertain etiology, various local, systemic, immunologic, nutritional, and genetic factors have been proposed for RAS. Irregularity in cellular immunity has been shown to play the main role in its pathogenesis Pakfetrat et al. (2010). It can also be associated with systemic diseases such as Behcet’s syndrome, systemic lupus erythematosus, Crohn’s disease, celiac disease, and ulcerative colitis (Crispian, Gorsky, & Lazada-Nur, 2003).

Current systemic therapies in the treatment of RAS include diverse agents, including corticosteroids, pentoxifylline, dapsone, and more recently thalidomide. All of these current therapies, however, have varying degrees of effectiveness and have the potential for serious adverse effects. These factors exhibit the need for an improved treatment option of RAS.

In the past two decades, the plant alkaloid colchicine has been shown to have a positive effect on all types of RAS due to its anti-inflammatory actions (Altenburg, Abdel-
Naser, Seeber, Abdallah, & Zouboulis, 2007). These actions are caused by colchicine’s binding to microtubular protein, which suppress the mobility of granulocytes and phagocytosis of leukocytes Altenburg et al. (2007). The most common side effects occurring with the use of colchicine include nausea, vomiting, diarrhea and in rare cases of long-term use, myopathy, neutropenia, and aplastic anemia (Finkel, Cubeddu, & Clark, 2009). These recent discoveries have drawn increased interest in colchicine as a safe and effective treatment for patients with RAS.

Purpose of the Study

The purpose of this paper is to perform a systematic review of literature on the treatment of recurrent aphthous stomatitis with colchicine in comparison to other systemic therapies with regard to clinical response and side effects. Review of each article was done using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool developed by the GRADE Working Group. Accordingly, the clinical question asks: In adult patients with recurrent aphthous stomatitis, is colchicine safe and effective in pain reduction and relapse prevention?

METHOD

Using the search terms “colchicine”, “aphthous stomatitis”, and “treatment”, an exhaustive literature search was performed using the following databases: CINHAL, Cochrane Systematic Reviews, PubMed, Medline-OVID, and MD Consult. These databases were accessed through the Pacific University Library system. Only articles in English were considered. The initial results included nine articles. Articles older than the year 2000 were excluded. This resulted in three studies to review and use in the final analysis.
RESULTS

Comparison of Colchicine Versus Prednisolone in Recurrent Apthous Stomatitis:
A Double-Blind Randomized Clinical Trial by Pakfetrat et al. (2010)

The first study reviewed compared the therapeutic effects of prednisolone to colchicine in the treatment of RAS. In this randomized double blind clinical trial, 34 patients with frequent RAS (at least three episodes each month), were unresponsive to conventional topical treatments, and had not taken any medication for treatment of RAS in two weeks prior to beginning the study, were included in the study. Inclusion criteria was restricted to patients 18 years of age or older, who had normal results of biological screening (cell blood count, fasting plasma glucose, hepatic transaminases, serum levels of ferritin, iron, zinc, vitamin B12, B6, and folate). Subjects were excluded if they had previous medical history of systemic disease (diabetes mellitus, liver disease, inflammatory bowel disease, renal insufficiency, and Behcet’s disease), or who had taken any medicine that might have an effect on the immune system.

Patients were randomly divided into two treatment groups with a daily dose of 5mg/d prednisolone or 0.5 mg/d colchicine. Both groups took the medicine for three months. To guarantee blinding, a random number was generated for each participant using the Statistical Package for the Social Sciences (SPSS) software, after which, patients were referred to the pharmacist to obtain their assigned medication according to their number. Patients were instructed to report immediately any side effects at any time of the study until six months after treatment. Clinical findings of both study groups were evaluated every two weeks. Researchers assessed number of lesions, recurrence, intensity of pain (on a scale of 1-10 using visual analogue scale), and any side effects.
The mean age of the patients was 31.5 ± 11.9 years. Baseline characteristics of patients were as follows, pain and burning sensation (33.11 ± 11.83 for colchicine group and 29.82 ± 12.09; p=0.428 for the prednisolone group), and number of aphthous ulcers per case (3.06 ± 1.39 for colchicine group and 4.18 ± 2.16 for prednisolone group).

After three months follow up, no significant differences were found between the two groups in regard to degree of pain (p=0.209), and number of aphthous ulcers per patient (p=0.673). Both groups showed a significant reduction in pain and burning sensation (7.92 ± 2.39, p<0.001 for colchicine and 8.21 ± 2.01, p<0.001 for prednisolone group) and number of aphthous ulcers (2.77 ± 1.49, p<0.001 for colchicine and 3.79 ± 2.49, p<0.001 for prednisolone group). During the follow up period, 9.1% of the patients displayed no recurrences, while in 36.4% of the patients a one-time recurrence was seen, and in 45.5% of the patients two recurrences were seen. Number of recurrences (p=0.171) and the duration of pain-free periods (p= 0.571) were not significantly different between the two groups.

In the study, 67.6% of the patients showed no side effects. Side effects of the colchicine (52.9%) group were significantly higher compared to the prednisolone (11.8%) group (p=0.027). These side effects included gastric disorders (n=8, 47.1%), head-ache (n=1, 5.9%), and vertigo (n=3, 17.6%).

The authors concluded that that both colchicine and prednisolone were equally effective in reducing pain, recurrences, and number of lesions in patients with RAS. Due to the higher incidence of side effects in colchicine, they preferred the use of prednisolone for patients with RAS.
Systematic Treatment in Severe Cases of Recurrent Aphthous Stomatitis: An Open Trial by (Mimura, Hirota, Sugaya, Sanches, & Migliari, 2009)

The second study reviewed was an open-label, four-year clinical trial of twenty-one consecutive patients with severe RAS, to evaluate the efficacy of the systemic drugs thalidomide, dapsone, colchicine, and pentoxifylline in the treatment of severe RAS. Patients were selected for the study based on a severe clinical course of RAS, such as multiple episodes of lesions monthly. Patients were excluded if they had any hematologic disease, Behcet’s syndrome, Crohn’s disease, HIV infection or Reiter’s syndrome, either initially or as a later development. Thirty-two patients were originally enrolled in the study after diagnosis of RAS, of which five participants were found to have the aforementioned systemic diseases and were excluded from the study. Twenty-seven patients were enrolled in the treatment protocol.

Before entering the study, patients were informed of the medications and their possible side effects. A clinical history was recorded concerning the aphthae type, size, number, recurrence, healing time, and symptoms. Initially, patients were given 0.5mg/kg/day of prednisone for a two-week period, decreased to half the initial dose after one week. Simultaneously, one of the four test drugs was assigned to each patient without blinding, keeping the proportion of assignments as equal as possible. After withdrawing the prednisone, the assigned drug was maintained for six months, unless adverse side effects or unsatisfactory results occurred. In either of these cases, the patient was switched to one of the other three drugs. Dosages given were, 100mg/ day of thalidomide, 25mg/day of dapsone that was increased 25mg every three days until 100mg/day maintenance dose, 0.5mg/d of colchicine that was increased 0.5mg every
seven days until 1.5mg/day maintenance dose, and 400mg three times a day of pentoxifylline.

In the study, patients were evaluated at fifteen day intervals, during which clinical status (benefits and side effects) was recorded, as well as compliance. Efficacy of each drug was determined by its potential to prevent relapse and/or reduce symptoms, number of ulcers, and healing time. Efficacy was classified as excellent (no relapses), moderate (patient showing relapses but with decreasing frequency, less lesions per cycle, and alleviated symptoms), mild (relief of symptoms only), or no response. Patients were followed for a period ranging from six to twelve months.

Of the twenty seven patients, six stopped showing up for treatment, and data for these patients was omitted. The study was effectively conducted in twenty one (n=21) patients with a mean age of 35.5 years. Eleven patients were switched to alternative drugs during the study.

Colchicine was administered to a total of ten patients for a time period of two to six months and resulted in four patients (40%) with excellent results showing complete remission, five patients (50%) with moderate to mild results showing relief of symptoms, and one patient (10%) with no response to treatment. Side effects of diarrhea occurred in three patients (30%), which improved after dosage adjustment.

In conclusion, authors specified that significant relief occurred with most drugs, but relapse eventuated in all patients after medication was discontinued. They also determined that thalidomide provided the best results in the trial, although, the drug has problems in regard to accessibility and is highly contraindicated in fertile women. Colchicine demonstrated good results and was well tolerated by patients.
Successful Treatment of Complex Aphthosis with Colchicine and Dapsone
by Lynde and Rogers III (2009)

The final article reviewed was a retrospective study of 55 subjects with complex aphthosis, collected from medical records at the Department of Dermatology, Mayo Clinic, between the years 1998 and 2007 to investigate the effectiveness of colchicine and dapsone in the treatment of complex aphthosis. The study included only patients who received colchicine, dapsone, or both, and were available for follow-up.

Patients included in the study received treatment according to a therapeutic ladder with colchicine being the initial drug. Dapsone was added for those who did not have a substantial response to colchicine (>75% improvement of symptoms) at twelve weeks, or who could not continue due to adverse effects.

Colchicine was initiated at 0.6mg each evening for one week. If there were no gastrointestinal symptoms, the dose was increased to 1.2mg in the evening. Again, if the dose was tolerated, it was increased to 1.8mg. Dapsone was administered in a stepwise manner with the initial dose started at 25mg daily for 3 days and increased 25mg every 3 days until 125-150mg was achieved. Patients were evaluated objectively and subjectively according to the frequency, intensity, and severity of aphthosis events.

All patients included in this study had tried multiple topical therapies, and short course corticosteroids, resulting in failure. Colchicine was initially started in 52 of the 55 patients (95%), two of which received dapsone simultaneously due to severity of disease, and had treatment success. Of the 50 patients who received colchicine alone, 30 (60%) achieved therapeutic success and no longer needed further treatment. In this subset of patients with success, 29 (97%) had at least 75% improvement, and one
patient (3%) had complete resolution of symptoms. Of the 50 patients initially receiving colchicine alone, thirteen (26%) had no response to the medication and seven (14%) had adverse effects leading to their discontinuation of therapy. The most common adverse effect with colchicine was diarrhea (31%; 16 of 52), causing four (8%) to stop therapy. Other adverse effects occurred in five patients. These included a burning sensation in the feet and transient thrombocytopenia, which did not require therapy discontinuation, although occurrence of rash with elevated liver enzyme levels, easy bruising, and vomiting required discontinuation.

The authors determined that these results offer promise for colchicine as an effective first-line non-steroidal therapy for complex aphthosis, concluding that colchicine therapy can be maintained long-term since it is safe and well tolerated with regular follow-up and monitoring.

DISCUSSION

Treatment of RAS has proven to be difficult considering its unknown etiology, but over the years several factors have been proposed in which therapy has been directed. Colchicine, along with other systemic medications, has been used in attempt to relieve pain and prevent relapse, yet remain safe to the patient. The key points to discuss in this section are the general safety and efficacy of colchicine in the treatment of RAS, and the overall strength and limitations of the literature reviewed.

All three studies reviewed found colchicine to be effective in the treatment of RAS in regards to the clinical outcomes of pain reduction, aphthae size and number, and prevention of relapse. Pakfetrat et al. (2010) demonstrated colchicine’s effectiveness, in comparison to prednisolone, in pain reduction, number and size of
aphthae, and recurrence of RAS. Patients in the colchicine group exhibited significant pain reduction by more than 85% during the twelve week period of therapy. Pain reduced rapidly in the first two weeks, then gradually thereafter. During follow-up, relapse did occur once in 41% of the patients and twice in 59% of the patients, which was similar to the prednisolone group.

There were no serious adverse reactions in the colchicine group. The most common side effect was mainly gastrointestinal, occurring in less than 50% of the patients. The authors concluded that prednisolone and colchicine were nearly identical in results, but since more side effects occurred with the colchicine group they considered prednisolone the better choice. However, the long-term effects of prednisolone were not taken into consideration in the discussion of this study. Limitations found in the study were the relatively small sample size, determined appropriate via SPSS software before conducting the study, although, it necessitates caution when interpreting results. Also, the study was a retrospective in design and conducted in Iran, which may indicate a different effect of colchicine to that particular population, thus decreasing its external validity.

The study conducted by Mimura et al. (2009) showed colchicine effectively decreased pain in 90% of the patients to whom it was administered during a period of two to six months, and 40% of these patients never experienced a relapse of symptoms until the medication was discontinued. During treatment, 30% of the patients experienced gastrointestinal disturbance, mainly diarrhea, which was easily controlled by dosage adjustments. Limitations to this study included the likelihood of a strong selection bias, considering the absence of randomization in both selection and
allocation. Also, no blinding was done in this study as was understood when patients were informed about the trial, medications and their side effects, therefore leaving a strong possibility of measurement bias. These limitations decrease the validity of this study.

The last study reviewed was Lynde and Rogers III (2009). This observational study showed that 60% of the patient had therapeutic success with use of colchicine as monotherapy, and of these patients, 97% were said to have a substantial response in regard to frequency, intensity, and severity of RAS attacks. One patient experienced complete remission while using colchicine. No serious adverse effects were seen with the use of colchicine during the study and the most common side effect was diarrhea, occurring in 31% of the patients using colchicine. The study design was a retrospective review of medical records in patients with complex aphthosis, and as such, is likely limited by bias. The study was also limited in terms of the vagueness in response to therapy, which was evaluated subjectively and objectively by the patient and the physician.

Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE), each study was appraised to determine the quality of evidence and strength of recommendation. The first study, Pakfetrat et al. (2010), was the only randomized controlled trial used in this systematic review. As such, it was given a high grade initially and the limitations were reviewed. The study was double blinded and randomized with no serious limitations, inconsistencies, indirectness, imprecisions, or bias, and therefore, was not downgraded and remained a high quality of supporting
evidence (Appendix A, Table 1). As a result, the study shows strong evidence that colchicine is a safe and effective treatment for pain and relapse prevention of RAS.

The two other studies reviewed, Mimura et al (2009) and Lynde and Rogers III (2009), were both observational studies. These two studies achieved all their desired outcomes of pain reductions and relapse prevention. Since the studies were observational, and neither were blinded or randomized, an initial low grade was determined using GRADE. Neither study met requirements to upgrade their quality as demonstrated in Appendix A, Table one. With all studies achieving the desired outcomes of this review, all were evaluated using GRADE and subsequently given an overall moderate GRADE of evidence as shown in Appendix A, Table 1. A moderate overall GRADE for the evidence in the literature reviewed suggests that further research is likely to have an impact on estimate of benefit and risk, which may or may not change the clinical effect.

In summary, there is moderate evidence that supports the safety and efficacy of colchicine for the treatment of RAS. Colchicine proved to relieve pain and decrease relapse in the majority of patients in all three studies without the occurrence of severe adverse effects. A large prospective, double blind, randomized-controlled trial, with longer duration of treatment would likely benefit this proposition and further evaluate the superiority of colchicine in comparison to other systemic drugs for the treatment of RAS.
REFERENCES


## APPENDIX

### Table 1: Strength of evidence

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<th>Comparison</th>
<th>Outcome</th>
<th>Quantity and type of evidence</th>
<th>Findings</th>
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<th>Decrease GRADE</th>
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Notes: Small Magnitude; Medium Magnitude; Large Magnitude; Dose-Response; Confounders; Publication Bias; Precision; Directness; Consistency; Study Quality; Quantity and type of evidence; Findings; Starting grade; Decrease GRADE; Increase GRADE; Ending grade; Grade of Evidence for Outcome; Overall GRADE of Evidence.