

2018

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Recommended Citation

Peeples, Haley T., "Are oral steroids as effective as NSAIDS in relieving patient pain from gout?" (2018). *PCOM Physician Assistant Studies Student Scholarship*. 373.

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**Are oral steroids as effective as NSAIDS in relieving patient pain
from gout?**

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A SELECTIVE EVIDENCE BASED MEDICAL REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Atlanta, Georgia

December 15, 2018

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not, “oral steroids are as effective as NSAIDS in relieving patient pain from gout?”

STUDY DESIGN: Review of three English language primary studies, published between 2008 and 2016.

DATA SOURCES: Three randomized controlled trials (RCTs) were found using PubMed and Embase database. These studies analyzed the effectiveness of steroids in relieving patient pain from gout.

OUTCOMES MEASURED: The major outcomes measured were improvements in joint tenderness on palpation, joint erythema, joint swelling, and joint activity measured on a 5-point Likert scale. (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, 4=extreme pain). Analgesic effectiveness was measured as changes in pain on a 100-mm visual analogue scale. With 1 being the least pain the patient has ever experienced and 100 being the worst.

RESULTS: All three studies showed comparable efficacy between prednisolone and NSAIDS in treating gout. The Xu et al study concluded similar results between NSAIDS and Prednisolone in improving pain, tenderness, and joint activity. Furthermore, the study also stated Prednisolone may be more effective in reducing inflammation and was better tolerated. The Rainer et al and Janssen et al study found prednisolone and indomethacin have similar analgesic effectiveness, and prednisolone is a safe, and effective first line option for gout treatment.

CONCLUSION: The results of all three RCT's which compared the efficacy between prednisolone and NSAIDS in the treatment of gout concluded similar results between the two groups. Therefore, proving steroids as an effective treatment option for patients diagnosed with gout.

KEY WORDS: Gout, Steroids, and NSAIDS.

INTRODUCTION

Gout is a metabolic disease associated with abnormal amounts of urates which manifests as recurrent acute arthritis.⁵ The disease will most commonly present in the first metatarsal phalangeal joint of the great toe also known as “podagra”.⁵ Areas such as the feet, ankles, and knees, are also commonly affected.⁵ The attacks are characterized by intense pain with swollen, warm, and tender joints, dusky red skin overlying the joint space, and fever.⁵ In some cases tophi can be found on the feet, ears, and hands as a result of accumulation of uric acid crystallization years after the initial gout attack.⁵ Purine rich foods are proven to potentiate attacks such as alcohol, seafood, and thiazide diuretics.⁵ Patients may be asymptomatic for months or even years after their first attack. However, if left untreated patients can develop chronic gout.⁵ This paper discusses the results of three randomized control trials to determine if steroids are indeed as effective as NSAIDS in treating patients diagnosed with gout.

This topic is relevant to both patients and the PA practice because gout is the most common form of inflammatory arthritis.⁵ Gout most commonly effects men over the age of 30 years old.⁵ When gout manifests in women it most commonly appears after the woman is postmenopausal.⁵ It is crucial as medical professionals we accurately diagnose and treat gout, because if left untreated patients can develop chronic gout which can lead to deformation of the joint spaces mimicking the effects of rheumatoid arthritis.⁵ As a result, these patients are at an increased risk for joint replacements and corrective surgeries.¹

Due to the rising frequency and widespread occurrence of gout there is an increased cost burden associated with the disease.¹ For patients who suffer six or more gout flares per year, direct gout-related health care costs top \$12,020.⁴ Furthermore, according to a 2016 study, gout hospitalization expenses have increased by 68% from 34,456 to 58,000.⁴ There is an increasing

number of patients who visit their healthcare provider due to gout attacks each year.⁴ According to the “National Ambulatory Survey” between the years of 2008 and 2016, there were 7 million ambulatory visits due to gout.¹ Therefore, there is an overwhelming need in the medical community to correctly diagnose, treat, and care for patients diagnosed with gout to decrease the economic burden surrounding the disease.⁴

Gout is widely understood throughout the medical community as uric acid deposition in the soft tissue as well as bone and joints.⁵ However, the amount of uric acid present in the serum does not depict the severity of the disease.⁵ Furthermore, the precise relationship between hyperuricemia and gouty arthritis is still unknown.⁵ This is because chronic hyperuricemia is found in those who have never before experienced a gout attack.⁵ Instead, medical professionals rely on arthrocentesis, as the test of choice when diagnosing patients with acute gout.⁵ The fluid will show negatively birefringent needle shaped crystals under a light microscopy which differentiate gout from pseudogout.⁵

Treatment of gout begins with lifestyle modifications such as a decrease in intake of purine rich food such as alcohol, seafood, and red meat.⁵ It is also crucial to consider medications such as loop and thiazide diuretics which can potentially increase serum uric acid levels and provoke gout attacks.⁵ NSAIDS such as Indomethacin are currently used as the drug of choice in acute gout attacks.⁵ Colchicine is considered 2nd line if the patient presents within 36 hours of onset or are refractory to the use of NSAIDS.⁵ Steroids are then considered if the patient is unresponsive to both NSAIDS and Colchicine.⁵ It is important to treat episodes of acute gout and chronic gout differently as medications to treat chronic gout can potentiate or worsen gout symptoms if given during an acute gouty episode.⁵ Drugs such as Allopurinol which reduces uric acid production or Probenecid which promote renal uric acid secretion are available

to treat patients with recurrent or chronic gout.⁵ Each treatment listed above has shown to be beneficial for patients suffering from gout. Treatment is based on patient presentation, time-period, and past medical history. In addition, based on the three articles, steroids are proven to be just as effective as NSAIDS as first line treatment for gouty arthritis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not, “oral steroids are as effective as NSAIDS in relieving patient pain from gout?”

METHODS

The population analyzed in this review includes patients diagnosed with gout. One group was given Prednisone in comparison to the other group which received a trial of NSAIDS. The outcome studied in these reviews is pain relief, and the patients rated their amount of pain through a Likert or visual analogue scale. All three studies are randomized controlled trials which studied the effectiveness of Prednisolone in comparison to NSAIDS.

All three studies were published in peer reviewed English articles. The key words used to locate the articles included “gout”, “steroids”, and “NSAIDS”, and were searched on the Pubmed and Embase databases. The articles were chosen based on relevance to the clinical question, and due to importance to the patient population in order to create a POEM. A POEM stands for patient-oriented evidence that matters. Inclusion criteria included all randomized controlled trials published after 2001. Exclusion criteria included patients who used NSAIDS or steroids 24-72 hours prior, had progressed to the chronic gouty arthritis stage, or had been diagnosed with gastrointestinal disease. The statistics reported in all three studies included confidence interval, p-value and mean change from baseline. Each of the three studies demographics and characteristics can be found on Table 1.

Results: Table of demographics and characteristics of included studies (Table 1)

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Janssens, 2008 (1)	RCT	120	All ages	Pts with monoarticular gout confirmed by arthrocentesis. Pts were required to give consent.	Pts with comorbidities such as renal failure or heart attack. Pts with history of GI disease. Pts were not allowed to have NSAIDs or other pain meds 24 hours prior.	1	Prednisolone
Rainer, 2016 (2)	RCT	416	Pts aged 18 years or older	Pts who presented to the ER within 3 days of symptom onset. Pts were evaluated by a physician to be diagnosed with gout.	Pts were not allowed to receive steroids or NSAIDs within 24 hours. Pts with hx of comorbidities, suspected septic arthritis or history of bleeding disorders.	40	Prednisolone
Lingling Xu, 2015 (3)	RCT	132	Pts aged 18 years and older	Pts who presented with gout attacks within 72 hours of screening. The degree of pain on the Likert scale was at least moderate.	Pts were excluded if they had chronic gouty arthritis, clinical suspicion of joint disease, comorbidities, GI issues, NSAIDs or steroids within 72 hours.	19	Prednisolone

OUTCOMES MEASURED

All three studies measured the outcome of pain relief through either a 5-point Likert scale or visual analog scale. The Xu et al study primarily focused on the reduction of pain as experienced by the patient.⁷ The degree of joint pain was represented by a 5-point Likert scale (0=no pain, 2=moderate pain, 3=severe pain, 4=extreme pain).⁷ The number was then recorded by the patient on day 1 before the start of treatment and on day 2 and 4 approximately 4 hours after the dose of drug was administered.⁷ The physician also measured the patient's overall response to treatment on a 5-point Likert scale (0=very good, 1=good, 2=fair, 3=poor, 4=very poor) at day 4 at the end of the study.⁷ Although the study also analyzed joint tenderness to palpation, joint erythema, joint swelling, and joint activity, for the purpose of study only pain scores were analyzed.⁷ The remaining two studies measured analgesic effectiveness as changes in pain on a visual analogue scale with 1 being the least amount of pain the patient has ever experienced to 100 being the worst.

RESULTS

All three studies included in this paper are randomized control trials studying the effectiveness of Prednisolone in comparison to NSAIDS in the treatment of gout. Although each study implemented different participant age requirements, all patients were included if they were diagnosed with acute gouty arthritis. All studies presented data in continuous format and no dichotomous data was converted. Changes in mean score, confidence interval, and p-value with a significance of ≤ 0.05 was analyzed.

In the Xu et al study, 132 inpatients aged 18 or older with acute gouty arthritis within 72 hours of onset were randomly assigned to trial treatments.⁷ These patients were diagnosed with gout according to the clinical criteria of the 1977 American College of Rheumatology

classification.⁷ The participants were chosen based on the inclusion and exclusion criteria listed in Table 1. The patients were randomly assigned using computer-generated tables and prepared by an independent party.⁷ The participants received either Prednisolone 35 mg qd, Etoricoxib 120 mg qd, or Indomethacin 50 mg tid.⁷ The patients were only studied for 4 days due to the self-limiting nature of acute gouty arthritis.⁷ The participants pain levels were measured using a 5-point Likert scale and the same physician observed and studied each patient throughout the 4 days.⁷ Of the 132 patients who were randomized, 113 participants were ultimately analyzed. Of the 113 studied, 33 were given Prednisolone, 44 were given Etoricoxib, and 36 were given Indomethacin.⁷ Adverse effects noted during the trial mainly included gastric or abdominal pain, dizziness, edema, fatigue, drowsiness, and dry mouth.⁷

The results demonstrate both Indomethacin and Prednisolone significantly decrease the severity and pain of acute gouty arthritis. The mean difference between the two groups is 0.11 with a p value of 0.416.⁷ The treatment effect is small. This is because the reduction in pain when comparing Prednisolone to Indomethacin is 0.11. The confidence interval is wide at 95% (-0.16 to 0.39).⁷ This is due to the small sample size.⁷ The p-value is 0.415.⁷ Therefore, because the $p > 0.005$ there is no significant difference between the groups. The efficacy of Prednisone in reducing pain was comparable to Indomethacin after 4 days. Furthermore, there is no significant difference between the groups and Prednisolone can be used just as effectively to treat gout.

Results: Indomethacin vs Prednisolone (Table 2)

Group	Value Measured	LS Mean Difference	Confidence Interval	P Value
Prednisolone vs Indomethacin	Pain	0.11 (.0138)	-0.16 to 0.39	0.415

In the Rainer et al double-blind randomized trial, 416 patients aged 18 years or older with a clinical diagnosis of acute gout were enrolled in the study.³ Of the 416 enrolled, 376 completed the study.³ The patients were chosen based on the inclusion and exclusion criteria listed in table 1. Patients were randomly assigned using a 1:1 ratio to receive either Indomethacin or Prednisolone for 5 days.³ The physicians and patients were unaware of which drug they were to receive. In the Indomethacin group (n=208), patients initially received 50mg (two 25mg tablets) of oral Indomethacin 3 times daily.³ Patients were also given 6 tablets of oral placebo Prednisolone to take once daily for 2 days.³ This was followed by 25 mg of Indomethacin 3 times a day and the placebo Prednisolone to take once per day for 3 days.³ In the Prednisolone group (n=208), patients initially took 30 mg (three 10mg tablets) of oral Prednisolone once a day, and 2 tablets of placebo Indomethacin 3 times a day for 2 days.³ This was followed by 30mg (three 10 mg tablets) of Prednisolone once a day and 1 tablet of placebo Indomethacin 3 times a day for 3 days.³ Patients were required to take the first dose in the presence of one of the investigators and all patients were given the analgesic Acetaminophen to use as needed.³ The results were measured using a 100mm visual analogue scale.³

When comparing the effectiveness of Indomethacin to Prednisolone in this study, there was a small difference between the two groups. While measuring decrease in pain scores on days 1-14 while the patient was at rest, demonstrated a reduction of 1.67 mm for Indomethacin and 1.52 mm for Prednisolone.³ As a result, the difference in mean pain score between the two groups is 0.15 mm.³ Furthermore, the number of patients which demonstrated a significant change in their pain score was calculated.³ Among the patients who received Indomethacin, 111 patients illustrated a significant change, and in the Prednisolone group 101 patients demonstrated a change in pain score.³ Therefore, the average difference between the two

groups are 10 (4.8%).³ Ultimately, when analyzing the small mean difference and p-value of 0.92, which is clinically insignificant, indicates Prednisolone can be used as effectively as NSAIDS in the treatment of gout.

Results: Indomethacin vs Prednisolone (Table 3)

Day 1-14 At Rest	Indomethacin N=208	Prednisolone N=208	Difference	P Value
Mean Decrease in Pain Score (95% CI)	1.67 (1.36 to 1.98)	1.52 (1.25 to 1.79)	0.15	0.92
Patients with significant change in Pain Score	N=111	N=101	10	

In the Janssens et al study, 120 patients were randomly assigned to trial treatments.²

Between the months of March 24, 2004 and July 14th, 2006, family doctors were asked to send all patients with monoarthritis to the trial center.² These patients were sent even if gout was not the primary diagnosis, to minimize the risk of missing potential study participants.² Patients were then assessed in the trial center for inclusion eligibility within day 1 after they visited their family doctor.² Patients were separated randomly into two groups by computer generated randomization, and 60 patients were in each group.² Both the patients and the physicians were unaware which group received Naproxen or Prednisolone.² The first group received one 35 mg tablet of Prednisolone, and the other group received 500 mg of Naproxen which was taken twice a day.² The trial period lasted for 5 days.² The results were measured on a 100mm visual analogue scale.² The adverse effects recorded were similar to the Rainer study, and resolved within 3 weeks.²

This study further indicated the similar efficacy of Prednisolone in comparison to NSAIDS.² Pain score was measured at baseline and at 90 hours. Pain score at baseline for

Prednisolone was 61.5 mm, and 58.9 mm for Naproxen.² After 90 hours, pain score for Prednisolone was 16.8 mm, and 12.9 mm for Naproxen.² Therefore, patients who took Prednisolone had a pain decrease of 44.7mm, and those who took Naproxen had a decrease of 46.0 mm.² This equals a 1.3 mm overall difference between the two medications.² The confidence interval is (-9.8 to 7.1).² The confidence interval is wide due to small sample size, however the small change in mean from baseline proves there is no significant difference between the groups.² Adverse side effects included nausea, dizziness, and sleepiness. No major side effects were reported.²

Results: Naproxen vs Prednisolone (Table 4)

Prednisolone (n=59)	Naproxen (n=59)
Baseline: 61.5	Baseline: 58.9
After 90 hr: 16.8	After 90 hr: 12.9
Score Reduction: 44.7	Score Reduction: 46.0

DISCUSSION

Due to the statistics presented above it is evident Prednisolone is as effective as NSAIDS in the treatment of acute gout. All three studies found a similar reduction in pain score between the steroid and NSAID group. Furthermore, the p-values calculated in the studies were clinically insignificant indicating both drugs can be used interchangeably. The Xu et al RCT claimed efficacy was comparable among Prednisolone, Etoricoxib, and Indomethacin in treating acute gout.⁷ However, Prednisolone might be more effective in reducing inflammation and was better tolerated.⁷ Furthermore, the Xu et al study found that patients experienced more total adverse events with Indomethacin compared to Prednisolone.⁷ The Rainer et al study claimed Prednisolone is a safe, effective first line treatment for acute gout.³ Per current medication

guidelines, NSAIDS are the first line treatment option for patients presenting with acute gout. However, due to the data presented above it is reasonable to consider Prednisolone as an alternative first line treatment to NSAIDs in treating gouty arthritis.

After reviewing the different methods and study designs it is apparent there were some limitations. Firstly, it is important to note the definitive diagnoses for acute gout is arthrocentesis where the fluid is analyzed to determine the diagnosis.⁵ However, only the Janssens et al study diagnosed patient gout with arthrocentesis. The other two studies only used clinical judgment to make a diagnosis. Therefore, it is uncertain that all patients in the studies without arthrocentesis had gout. This diagnostic uncertainty could have resulted in inaccurate data. Secondly, the sample sizes in each study were small. The Janssens et al and Xu et al both studied around 130 patients, and the Rainer et al, analyzed around 400. Therefore, it is difficult to make large scale predictions on the data due to the small amount of the population represented in the studies. Thirdly, the time-period to which the patients were studied was relatively short. The Rainer et al RCT was the only study to analyze patients for over a week. The presentation of acute gout is limited and may only last for hours to a few short days.⁵ Therefore, due to the limited nature of acute gout it is difficult to study it for a significant amount of time.

Prednisolone is a good and convenient treatment option due to its affordability, and accessibility.⁸ It is also crucial to provide patient education about the medication prescribed, and encourage each patient to finish their prescription to avoid relapses and unwanted medical costs.¹ Furthermore, most patients will be familiar with steroid medications and will feel comfortable taking their prescription.⁸ However, physicians do have their hesitations about steroids due to Cushing's syndrome, diabetes mellitus, hypertension, and osteoporosis.⁷ However, side effects

associated with NSAID use include gastrointestinal stomach pain, bleeding and peptic ulcers.⁷ Furthermore, all medications will present potential risks and benefits.

CONCLUSION

The results of all three RCT indicate Prednisolone is just as effective as NSAIDS in the treatment of patients diagnosed with acute gout. Due to the increasing number of patients diagnosed with gout each year, it is important to consider different treatment options other than NSAIDS to treat patient symptoms.¹ It is also crucial to provide patient education about the medication prescribed, and encourage each patient to finish their prescription to avoid relapses and unwanted medical costs.¹ If patients are not taking their medications as prescribed it is impossible to determine the efficacy of the medication. Furthermore, it is important all future studies consider and ensure patient compliance. It is imperative studies use arthrocentesis as a diagnosis requirement, as well as implement larger sample sizes to study different medication options. This would improve accuracy and credibility of each study. Lastly, it is important scientists and physicians continue to expand on treatment options for all patients, to successfully care and treat each individual patient diagnosed with acute gouty arthritis.

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