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Pentoxifylline vs. Prednisolone: A Comparison of Efficacy in the Treatment of Severe Alcoholic Hepatitis in Adult Patients

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Abstract

Background:

Alcoholic hepatitis is a chronic, inflammatory liver disease that is on the rise in the United States. Traditionally, the progression of severe alcoholic hepatitis has been slowed with a 28-day course of prednisolone. However, since corticosteroids such as prednisolone have been associated with increased risk of infection and multiple unpleasant side effects, newer research is aimed at using pentoxifylline (PTX) as an alternative treatment. PTX has been shown to have a better safety profile than prednisolone, but its effectiveness in the treatment of severe alcoholic hepatitis is in question. Therefore, the aim of this systematic review is to further evaluate the efficacy of PTX as compared to prednisolone in the treatment of severe alcoholic hepatitis in adult patients.

Methods:

An exhaustive search using MEDLINE-Ovid, MEDLINE-Pub-Med, Web of Science, and Up-To-Date was performed using the terms: pentoxifylline, corticosteroids, and alcoholic hepatitis. Animal studies, articles published over ten years ago, and articles written in non-English languages were excluded from the search. Only randomized-controlled trials were considered for review. All articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Results:

Three studies met criteria and were used in this systematic review. The STOPAH trial, an RCT by Thursz et al found that PTX is less effective than Prednisolone at treating severe alcoholic hepatitis in adults in the prevention of mortality at 28 days ($P < 0.06$). In a small, RCT by Park et al, it was found that PTX is not inferior nor superior to prednisolone in the treatment of severe alcoholic hepatitis. A third RCT by De et al indicated that PTX was superior to prednisolone in the regards to survival at 3 months ($P<0.05$).

Conclusion:

The overall quality of evidence supporting the use of PTX rather than prednisolone in the treatment of severe alcoholic hepatitis in adult patients is low. Although there is indication that PTX may be a safer alternative or perhaps equivalent to prednisolone in select patients, there is a lack of evidence from good RCTs to support this theory. Based on the results discussed in this systematic review, further investigation with larger, longer RCTs is warranted.

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Faculty Advisor: Annjanette Sommers, PA-C, MS

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Biography

Ashley Hilliker grew up in Swanton, Vermont. She attended North Country Community College in upstate New York where she earned an associate degree in applied sciences, radiology. She also attended Kaplan University where she earned a Bachelor degree in Health Science and a Nutrition minor. She later attended the University of Vermont for pre-medical studies. During her undergraduate years, Ashley worked full time as a radiologic and CAT scan technologist at Northwestern Medical center and per diem as a radiologic technologist at the University of Vermont Medical Center. She had a total of 10 years experience in radiology prior to starting the Physician Assistant program in 2014.

Abstract

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The overall quality of evidence supporting the use of PTX rather than prednisolone in the treatment of severe alcoholic hepatitis in adult patients is low. Although there is indication that PTX may be a safer alternative or perhaps equivalent to prednisolone in select patients, there is a lack of evidence from good RCTs to support this theory. Based on the results discussed in this systematic review, further investigation with larger, longer RCTs is warranted.

Keywords: *Pentoxifylline, corticosteroids, treatment, alcoholic hepatitis*

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List of Abbreviations

PTX…….....Pentoxifylline
TNF…….Tissue Necrosis Factor
STOPAH.....Steroids Or Pentoxifylline for Alcoholic Hepatitis

Pentoxifylline vs. Prednisolone: A Comparison of Efficacy in the Treatment of Severe Alcoholic Hepatitis in Adult Patients

BACKGROUND

Alcoholic hepatitis is a chronic, inflammatory liver disease that is on the rise in the United States.[1] Associated with the toxic effects of excessive alcohol consumption, alcoholic hepatitis leads to irreversible liver pathologies including fatty liver disease, cirrhosis, and eventually hepatocellular necrosis. Traditionally, the progression of severe alcoholic hepatitis has been slowed with a 28-day course of prednisolone. However, since corticosteroids such as prednisolone have been associated with increased risk of infection, newer research is aimed at using pentoxifylline (PTX) as an alternative treatment.[2] PTX works to improve erythrocyte flexibility by lowering blood viscosity, achieving healthier blood flow.[3] PTX is also an inhibitor of tissue necrosis factor (TNF) synthesis and since TNF is increased in patients with alcoholic hepatitis,[4] the drug is being considered as an off-label treatment for this disease.

While PTX has been associated with arrhythmias, dyspepsia, and nausea, prolonged treatment with prednisolone has been shown to cause several serious adverse drug reactions including, but not limited to adrenal insufficiency, diabetes mellitus, hypertension, congestive heart failure, pancreatitis, and growth suppression.[3,5] Although PTX has a better safety profile than prednisolone, there are arguments that it may not be as effective in the treatment of severe alcoholic hepatitis. However, with comparable costs[3,6] and fewer side effects, it is an alternative treatment worth consideration. Therefore, the aim of this systematic review is to further evaluate the efficacy of PTX as compared to prednisolone in the treatment of severe alcoholic hepatitis in adult patients.

METHODS

An exhaustive literature search using MEDLINE-Ovid, MEDLINE-Pub-Med, Web of Science, and Up-To-Date was performed using the terms: pentoxifylline, corticosteroids, and alcoholic hepatitis. Exclusion criteria included animal studies and non-English articles. All studies considered for this review were randomized controlled trials published within the past 10 years. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria was used to assess all articles considered for the review.[7]

RESULTS

The above search resulted in 38 total articles, which were then screened for relevance. Of the 38 articles, three met the inclusion criteria and were used for this systematic review.[4,8,9] As previously stated, all articles included in this review are RCTs and were evaluated using the GRADE criteria (see Table I).

Thursz et al

This double-blind, randomized control trial[8] known as the STOPAH trial, was constructed to evaluate the effects of PTX in comparison to prednisolone in the treatment of severe alcoholic hepatitis in adult patients. Its primary endpoint was mortality at 28 days. Secondary endpoints included liver transplant or death at 90 days and 1 year. However, funding was limited for the trial and therefore, these secondary endpoints could not be evaluated for all enrolled patients. The STOPAH trial consisted of 1103 patients with clinical diagnoses of severe alcoholic hepatitis, randomly divided into one of four groups: 276 were selected for the placebo group, 277 for the prednisolone group, 276 for the PTX group, and 274 for the prednisolone/PTX group. While those in the prednisolone group received 40mg of prednisolone and a PTX dose-equivalent placebo per day, those in the PTX group received 400mg of PTX three times daily

(TID) with a prednisolone-dose equivalent placebo. Those in the prednisolone/PTX group received 40mg of prednisolone per day, as well as 400mg of PTX three times daily.[8]

The STOPAH trial's exclusion criteria included patients with jaundice > 3 months, other potential cause of the hepatitis, abstinence from alcohol for 2 months or longer prior to the trial, patients with aspartate transaminase (AST) > 500IU/L, patients with alanine transaminase (ALT) > 300IU/L, and anyone with prior entry into the study within the 6 months preceding randomization.[8]

A logistic regression analysis was used to compare the rates of mortality at 28 days between the treated and untreated groups of patients. In the placebo group, mortality at 28 days was 17%. Mortality at 28 days in the prednisolone group was 14% with an odds ratio of 0.72 ([95% CI] 0.52-1.01, P: 0.06). After adjustments were made for baseline categories (age, encephalopathy, WBC, PT, serum bilirubin, blood creatinine, and blood urea) and factorial design, this odds ratio improved to 0.61 ([95% CI] 0.41-0.91, P: 0.02). In the PTX group, mortality at 28 days was 19% with an odds ratio of 1.07 ([95% CI] 0.77-1.49, P: 0.69). No adjustments were made for this group. The prednisolone/PTX group had 13% mortality at 28 days. For the participants who were evaluated for secondary endpoints, the effects of prednisolone vs. PTX were nonsignificant.[8]

Park et al

In this randomized non-inferiority RCT,[4] 121 patients were divided into two treatment groups to evaluate the effectiveness of PTX as compared to prednisolone in the treatment of severe alcoholic hepatitis in adult patients. While 59 patients received 40mg of prednisolone daily, 62 received 400mg of PTX three times daily. Survival at 1 month of treatment was the primary outcome of this study.[4]

The criteria eligibility of this study was closely matched to that of prior studies. Inclusion criteria required the clinical diagnosis of severe alcoholic hepatitis, a minimum consumption of 40mg of alcohol per day within the 3 months preceding the study, and adult patients aged 20-75 years. Patients were not considered for this study if they had recent history of bacterial infection, pancreatitis, GI bleeding, renal impairment, or other causes of liver disease.[4]

All quantitative variables were compared using the student t-test, whereas all qualitative variables were expressed in percentages based off of results from x^2 or Fisher exact tests. A pre-defined inferiority margin was set at 15%. The difference in probability of survival between patients treated with prednisolone vs. PTX ([95% CI] 4.2%-28.7%, P: 0.08) exceeded that of the pre-defined inferiority margin, indicating that the difference in survival was not significant and inconclusive. Therefore, this evidence from this study cannot establish PTX as non-inferior to prednisolone.[4]

De et al

This randomized, double-blinded RCT[9] consisted of 68 patients that were divided into two treatment groups: the prednisolone group and the PTX group. The primary purpose of this study was to evaluate the effectiveness of PTX as compared to prednisolone in the treatment of severe alcoholic hepatitis in adult patients. While 28 patients received 40mg of prednisolone daily, 34 received 400mg of PTX three times daily. Those taking prednisolone were given placebo tablets twice daily to maintain blinding. The primary outcome of this study was survival at 3 months.[9]

Candidates were carefully selected to participate in this study using strict criteria eligibility. Patients considered for the study were required to have a history of chronic alcohol intake with a minimum consumption of 50g/day, AST:ALT > 2:1, or AST > 500IU/L and ALT >

200IU/L. Exclusion criteria included patients who were abstinent from alcohol anytime within the month preceding the study and patients with other causes of liver disease, HIV, peritonitis, GI bleeding, pancreatitis, hypertension, diabetes, heart failure, pulmonary disease, or malignancy.[9]

Treatment with Prednisolone was discontinued prematurely in 13 patients and treatment with PTX was discontinued early in five patients due to life-threatening complications. All statistical data was analyzed using the student t-test, x^2 test, or Fisher exact test. At 3 months, 35.29% of patients in the prednisolone group and 14.71% of patients in the PTX group had died ($P < 0.05$). [9]

DISCUSSION

The three studies discussed in this review are inconsistent with their results. However, the De et al study[9] followed patients for 90 days and was able to demonstrate a 42% reduction in mortality in patients taking PTX. Therefore, PTX still has potential as an alternative to prednisolone but more research is necessary. Other considerations in managing severe alcoholic hepatitis is the safety and cost of each medication. Comparisons of the cost and safety of prednisolone versus PTX indicate that PTX is a safer option. Whereas PTX has been associated with arrhythmias and GI upset,[3] prednisolone has been linked to multiple serious side effects including adrenal insufficiency, diabetes mellitus, hypertension, congestive heart failure, pancreatitis, and growth suppression...etc.[3,5] In addition to the common reactions of dyspepsia and nausea associated with PTX, prolonged treatment with prednisolone is likely to result in fluid retention, hypokalemia, hirsutism, skin changes, and depression. Furthermore, because of its many adverse drug reactions, prednisolone should not be used in patients with recent infection, hypertension, recent myocardial infarction, diabetes mellitus, seizure disorders,

irritable bowel disease, osteoporosis, thyroid disorders, or any other form of immunosuppression.[5] Since adults with a history of chronic alcoholism and alcoholic hepatitis are likely to have one or more of these co-morbidities, an alternative treatment to prednisolone should be an important focus of future medical research.

While prednisolone costs about fifty dollars per month, the average monthly cost of PTX is sixty-four dollars. If PTX proves to be effective in the treatment of severe alcoholic hepatitis in adult patients, then the additional fourteen-dollar cost per month greatly outweighs the health risks and subsequent additional medical costs associated with prednisolone. Therefore, additional research in this area of medicine is of great significance.

Thursz et al

Although the STOPAH trial[8] is a strong RCT, it presents some weaknesses. The STOPAH trial is currently the largest RCT to evaluate and compare the effectiveness of prednisolone vs. PTX in the treatment of severe alcoholic hepatitis in adult patients. The blinding and randomization process utilized to conduct this trial allowed for a strong study with minimal concern for bias. Inclusion criteria ensured that all patients had similar clinical diagnoses and prognoses without additional causes of liver disease, making skewed results related to other health problems unlikely.

The STOPAH trial's biggest limitation was its lack of funding, which resulted in the inability to evaluate mortality after 28 days in all patients enrolled in the study.[8] While baseline adjustments were made for the prednisolone group, there is no mention of baseline adjustments for the PTX group. However, despite these limitations, the results of the STOPAH trial in regards to mortality at 28 days remain significant.

The results of the STOPAH trial[8] indicate decreased mortality in adult patients with severe alcoholic hepatitis taking prednisolone vs. those taking PTX at 28 days of treatment ($P < 0.02$). However, since funding only allowed for 28 days of follow-up, mortality at later dates could not be effectively evaluated for either treatment group. Additionally, infection occurred in 13% of patients receiving prednisolone as compared to 7% of patients who did not receive this drug, indicating that PTX may be a safer option[8]. There is a chance that with this trial's early termination, long-term benefits of PTX vs. prednisolone may have been missed. This may prompt further research to evaluate PTX as a safer alternative in the chronic treatment of adult patients with severe alcoholic hepatitis.

Park et al

Although this is an RCT, there are significant limitations that make its results questionable. This was an open-trial, indicating that there was no blinding amongst the researchers or the patients. However, since this was a non-inferiority study and its results are objective, the lack of blinding is not likely to have significant effects on the outcome. Additionally, no placebo group was used for comparison. For this reason, the data from this study cannot conclude that the effects of PTX are inferior nor superior to those of prednisolone in the treatment of severe alcoholic hepatitis in adult patients. Furthermore, this study utilized a very small sample size, which makes skewed data more likely.[4]

Based on its limitations and low quality of evidence, the results of this study[4] were not significant. Therefore, solid conclusions cannot be drawn from the data provided. This study indicates the need for additional research to further evaluate the effectiveness of PTX as compared to prednisolone in the treatment of severe alcoholic hepatitis in adult patients. Perhaps future studies will include a larger sample size with blinding and a placebo group.

De et al

This RCT[9] also demonstrates several strengths and weaknesses. While it is a double-blinded RCT, the sample size is very small making inaccurate data more likely. In addition, the researchers involved in this study bring up a valid point that no patients underwent liver biopsies to assess for histological improvement and TNF-*a* was not evaluated in patients taking PTX. This would be an important factor to measure in the PTX group, since this treatment is aimed at reducing its synthesis.

Due to this study's limitations and low quality of evidence, the clinical decision to treat adult patients with severe alcoholic hepatitis with PTX rather than prednisolone should not be made without additional research. This area of medicine would benefit greatly from larger RCTs. Additionally, studies aimed at evaluating histological improvement and TNF-*a* factors could provide stronger evidence supporting the efficacy of prednisolone and PTX in the treatment of severe alcoholic hepatitis in adult patients.[9]

CONCLUSION

Alcoholic hepatitis is a chronic disease with significant mortality. Linked to excessive alcohol consumption, this debilitating disease has become a serious medical problem in the United States where the rates of chronic alcohol use remain high. Traditionally, this disease has been treated with a 28-day course of prednisolone. However, since the costs of prednisolone and PTX are comparable and prednisolone has been linked to many serious adverse drug reactions, newer research is aimed at treating severe alcoholic hepatitis with PTX.

The overall quality of evidence supporting the use of PTX rather than prednisolone in the treatment of severe alcoholic hepatitis in adult patients is low. However, there is indication that PTX may be a safer alternative to prednisolone in select patients. There is a lack of evidence and

good RCTs to support this theory, making it apparent that more research is needed to further evaluate the safety and efficacy of PTX and prednisolone in the treatment of severe alcoholic hepatitis in adult patients. Based on the results of this systematic review, further investigation with larger RCTs of longer duration is warranted to ensure patients are receiving the best treatment for alcoholic hepatitis with the least amount of risk.

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Table I: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Thursz et al[8]	RCT	Serious[a]	Not Serious	Serious[b]	Not serious	Not Likely	None	Low
Park et al[4]	RCT	Not Serious[c]	Not Serious	Serious[b]	Serious[d]	Not Likely	None	Low
De et al[9]	RCT	Not Serious	Not Serious	Serious[b]	Serious[d]	Not Likely	None	Low

[a] The study stopped early for some patients due to lack of funding, resulting in the inability to evaluate for secondary endpoints
[b] Results were inconsistent among all studies
[c] Lack of blinding; however, objective outcome measures were used
[d] Small sample size