

Use of Pentoxifylline combined with captopril/losartan in hypertensive or diabetic patients: An integrative review of randomized clinical trials

Uso de Pentoxifilina associada a captopril/losartana em pacientes hipertensos ou diabéticos: Uma revisão integrativa de ensaios clínicos

Uso de pentoxifilina combinada con captopril/losartán en pacientes hipertensos o diabéticos: Una revisión integradora de ensayos clínicos aleatorizados

Received: 11/26/2023 | Revised: 12/09/2023 | Accepted: 12/12/2023 | Published: 12/15/2023

Yan Santiago Nascimento

ORCID: <https://orcid.org/0000-0001-8435-8955>
Universidade de Pernambuco, Brasil
E-mail: yan.nascimento@upe.br

Yago Santiago Nascimento

ORCID: <https://orcid.org/0000-0003-0662-0780>
Universidade de Pernambuco, Brasil
E-mail: yago.santiagonascimento@upe.br

Leticia Maria Rendall Ferreira

ORCID: <https://orcid.org/0000-0001-7903-7049>
Universidade de Pernambuco, Brasil
E-mail: leticia.rendall@upe.br

Ricardo Ferreira dos Santos Júnior

ORCID: <https://orcid.org/0000-0002-6606-2760>
Universidade de Pernambuco, Brasil
E-mail: dr.ricjunior80@gmail.com.br

Abstract

Objective: To perform an integrative literature review to analyze the effects of the use of Pentoxifylline (PTX) combined and/or compared to captopril or losartan. **Methodology:** An integrative literature review was performed analyzing randomized clinical trials in Portuguese, English and Spanish in the following databases: MEDLINE via PubMed and Cochrane. The descriptors used were "Pentoxifylline", "Losartan", "Captopril", "Arterial Pressure" and "Hypertension, Malignant" according to the DeCS, with 6 randomized studies at the end. **Results:** Several studies point to the positive effects of PTX when associated with captopril or losartan with regard to renal function in hypertensive and/or diabetic patients. The literature is still uncertain and the data contradict each other regarding the effects on the blood pressure of patients when receiving the addition of PTX or in comparison of PTX versus losartan or captopril. **Conclusion:** The literature and clinical trials are still divergent regarding the effects on blood pressure, although there is a consensus regarding its positive effects on proteinuria. Randomized clinical trials analyzing the direct comparative effect between drugs are needed. Meta-analyses are necessary to make quantitative analysis of the studies already available.

Keywords: Pentoxifylline; Hypertension, malignant; Arterial pressure.

Resumo

Objetivo: Realizar uma revisão integrativa da literatura para analisar os efeitos do uso da Pentoxifilina (PTX) combinada e/ou comparada ao captopril ou losartana. **Metodologia:** Foi realizada uma revisão integrativa da literatura analisando ensaios clínicos randomizados em Português, Inglês e Espanhol nas seguintes bases de dados: MEDLINE via PubMed e Cochrane. Os descritores utilizados foram "Pentoxifilina", "Losartana", "Captopril", "Pressão Arterial" e "Hipertensão maligna" segundo o DeCS, com 6 estudos randomizados ao final. **Resultados:** Vários estudos apontam para os efeitos positivos da PTX quando associada ao captopril ou losartana na função renal em pacientes hipertensos e/ou diabéticos. A literatura ainda é incerta e os dados se contradizem quanto aos efeitos na pressão arterial dos pacientes quando recebem a adição de PTX ou na comparação de PTX versus losartana ou captopril. **Conclusão:** A literatura e os ensaios clínicos ainda divergem quanto aos efeitos na pressão arterial, embora haja consenso quanto aos seus efeitos positivos na proteinúria. São necessários ensaios clínicos randomizados que analisem o efeito comparativo direto entre os medicamentos. Metanálises são necessárias para análises quantitativas dos estudos já disponíveis.

Palavras-chave: Pentoxifilina; Hipertensão maligna; Pressão arterial.

Resumen

Objetivo: Realizar una revisión integrativa de la literatura para analizar los efectos del uso de Pentoxifilina (PTX) combinada y/o comparada con captopril o losartán. **Metodología:** Se realizó una revisión integrativa de la literatura analizando ensayos clínicos aleatorizados en Portugués, Inglés y Español en las siguientes bases de datos: MEDLINE vía PubMed y Cochrane. Los descriptores utilizados fueron “Pentoxifilina”, “Losartana”, “Captopril”, “Presión Arterial” e “Hipertensión Maligna” según el DeCS, quedando al final 6 estudios aleatorizados. **Resultados:** Varios estudios señalan los efectos positivos del PTX cuando se asocia con captopril o losartán sobre la función renal en pacientes hipertensos y/o diabéticos. La literatura aún es incierta y los datos se contradicen entre sí con respecto a los efectos sobre la presión arterial de los pacientes cuando reciben la adición de PTX o en comparación de PTX versus losartán o captopril. **Conclusión:** La literatura y los ensayos clínicos aún son divergentes respecto a los efectos sobre la presión arterial, aunque existe consenso respecto a sus efectos positivos sobre la proteinuria. Se necesitan ensayos clínicos aleatorizados que analicen el efecto comparativo directo entre fármacos. Las metanálisis son necesarias para realizar análisis cuantitativas de los estudios ya disponibles.

Palabras clave: Pentoxifilina; Hipertensión maligna; Presión arterial.

1. Introduction

The relationship between blood pressure (BP) and cardiovascular, renal and endocrinological events is continuous, constantly based on pre-established BP values. In medical practice, blood pressure cutoff values are used pragmatically to simplify diagnoses and treatment decisions (Williams et al., 2018). Several observational studies have already demonstrated the association between high systolic and diastolic pressure with increased cardiovascular risk (Rapsomaniki et al., 2014). In a meta-analysis of 61 prospective studies, cardiovascular risk doubled for every 20mmHg increase in systolic pressure and every 10mmHg increase in diastolic pressure (Lewington et al., 2002).

Systemic arterial hypertension is a chronic non-communicable disease characterized by elevated blood pressure levels, in which the benefits of treatment (both non-drug and medication) outweigh the associated risks. This condition is influenced by several factors, including genetic/epigenetic, environmental and social aspects, making it a multifactorial condition. Hypertension is defined as systolic pressure values > 140mmHg and/or diastolic pressure > 90mmHg, defined based on several randomized clinical trials that have proven that treatment from this value is beneficial (Williams et al., 2018).

Hypertension, in turn, rarely occurs in isolation, and is usually associated with other cardiovascular risk factors such as dyslipidemia and diabetes (Bhatt et al., 2006). These risk factors added together have great importance, since they add up to a higher cardiovascular risk. High blood pressure was the leading cause of morbidity and mortality in 2010, being present in cardiovascular deaths more than any other modifier (Whelton et al., 2018). The treatment of systemic arterial hypertension depends on a number of factors, and changes in lifestyle habits are fundamental. Some changes that were shown to be beneficial were reduced sodium intake (~5/6mmHg), moderation in alcohol consumption (~4mmHg), high consumption of fruits and vegetables, adopting the DASH diet (~11mmHg), weight loss and maintenance of ideal weight (~5mmHg) and regular physical activity (~5/8mmHg) (Williams et al., 2018; Whelton et al., 2018).

The pharmacological treatment is done in addition to the non-pharmacological treatment, seeking to optimize and control the values of blood pressure. 4 major classes of drugs are used for the treatment of hypertension, namely: Angiotensin-converting enzyme (ACE) inhibitor, Blockers of the renin-angiotensin system (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like diuretics such as chlortalidone and indapamide). All are proven to be effective in lowering blood pressure and decreasing morbidity and mortality, as well as often having beneficial effects on other markers (dyslipidemia, diabetes, etc.), as has been proven in previous meta-analyses (Thomopoulos, et al., 2017; Rabi et al., 2020)

ACE inhibitors and ARBs are the most used classes in the treatment of arterial hypertension, having similar efficiency. ARBs are generally associated with significantly lower rates of discontinuation of treatment for adverse events than all other drug therapies, their primary representative being Losartan. ACE inhibitors are also widely used, the best-known

being Captopril, which should not be used in combination with ARBs as there is no benefit in outcomes and can cause several adverse renal effects (Williams et al., 2018). Both ACE inhibitors and ARBs reduce albuminuria more than any other antihypertensive drug and are effective in slowing the progress of CKD in diabetic and non-diabetic patients. In a meta-analysis it was proven that the use of ARBs can reduce the risk of end-stage chronic kidney disease. (Thomopoulos, et al., 2017).

Pentoxifylline (PTX) is a methylated xanthine derivative that offers various cardiovascular advantages. It functions by inhibiting phosphodiesterase, which leads to reduced platelet aggregation and improved blood viscosity. Additionally, it exhibits anti-inflammatory properties by reducing the levels of inflammatory cytokines like tumor necrosis factor α (TNF- α). Moreover, PTX has demonstrated the ability to significantly decrease red blood cell (RBC) aggregation. Another advantage is that it is an affordable medication with a low incidence of adverse effects (Zhang, et al., 2004). In a study it was shown that the addition of (PTX) in hypertensive rats could improve captopril activity, improving the rheological features of blood at the early stage of hypertension (Plotnikov MB et al., 2017). In addition, the effects of Pentoxifylline in addition or replacement to ARBs and ACE in improving proteinuria and glomerular filtration rate in diabetic patients have been described in the literature (Aminorroaya, 2005; Rabizadeh et al., 2017).

Considering the wide variety of beneficial effects that the addition of PTX can provide to individuals with hypertension or diabetes, both as a complement and as a substitute for Losartan or Captopril, in the cardiovascular, endocrinological and renal aspects, this integrative review becomes important by providing guidance and organization in the understanding of this drug from data published in randomized clinical trials, through the analysis of the effects of the use of Pentoxifylline (PTX) combined and/or compared to captopril or losartan.

2. Methodology

This study is an Integrative Literature Review (RIL) that seeks to comprehensively analyze and synthesize the existing literature on a specific topic, using a rigorous methodology. To accomplish this, several steps were followed during the preparation of the article: (1) Definition of the scope of the theme and formulation of the central question of the research; (2) Evaluation of the feasibility of the objectives and establishment of criteria for inclusion/exclusion of the studies; (3) Development of a search strategy that determines the platforms and databases to be consulted, as well as the relevant prospective records; (4) Screening of studies identified during the initial search; (5) Analysis of the data contained in the selected literature; (6) Classification and analysis of the information found in each included study; (7) Presentation of the results obtained in the literature review; (8) Inclusion, critical analysis of the findings and synthesis of the results found in the review (Souza et al., 2010).

To elaborate the guiding question of this study, we used the PICO strategy (P – population, I - intervention, C – comparison and O – *outcome*) which in Portuguese means population, intervention, comparison and expected results respectively. This approach aims to provide concrete support to define exactly what the research question will focus on, with the aim of formulating a clear and objective question as an essential element for the implementation of the research project. (RIVA et al., 2012). Thus, using the PICO strategy, which aims to determine the population, the intervention group, the control group and the outcomes, it was delineated as follows: P - Hypertensive and/or diabetic patients, I - Use of Pentoxifylline, C - Use of captopril or losartan, O - Analyze effects on patients' blood pressure and renal tissue. The methodological support for this research was based on the “Manual revisão bibliográfica sistemática integrativa: a pesquisa baseada em evidência” (Educação, 2014).

The time frame used to research was from 2010-2023, although the articles used were expanded based on the reference list of those initially researched, using relevant articles from literature from other years, for example: Solerte, et al.

(1987), Aminorroaya et al. (2005) and Lewington et al. (2003). Therefore, this integrative literature review was based on the following guiding question: "What are the cardiological, endocrinological and renal benefits of the use of Pentoxifylline with losartan or captopril, two amply used antihypertensive drugs?" (Pigott & Polanin, 2020).

Then, for the construction of this study, the languages Portuguese, English and Spanish were used in the search of the following databases: *Cochrane library* and *Medical Literature Analysis and Retrieval System Online* (MEDLINE via PubMed). To complement the research, the reference lists of the selected articles were used as an additional source of information, in addition to seeking the guidance of professionals specialized in the area.

The studies were located from the advanced search, applying as a filter the need to be a "randomized clinical trial" throughout the search, with no limit of publication date, however. Thus, we chose to include publications that included Pentoxifylline in comparison or in conjunction with losartan or captopril in hypertensive and/or diabetic patients. European and American hypertension guidelines were also used for contextualization and comparison purposes, as well as meta-analyses referenced in these guidelines. In addition, the reference list of articles was used to expand the research.

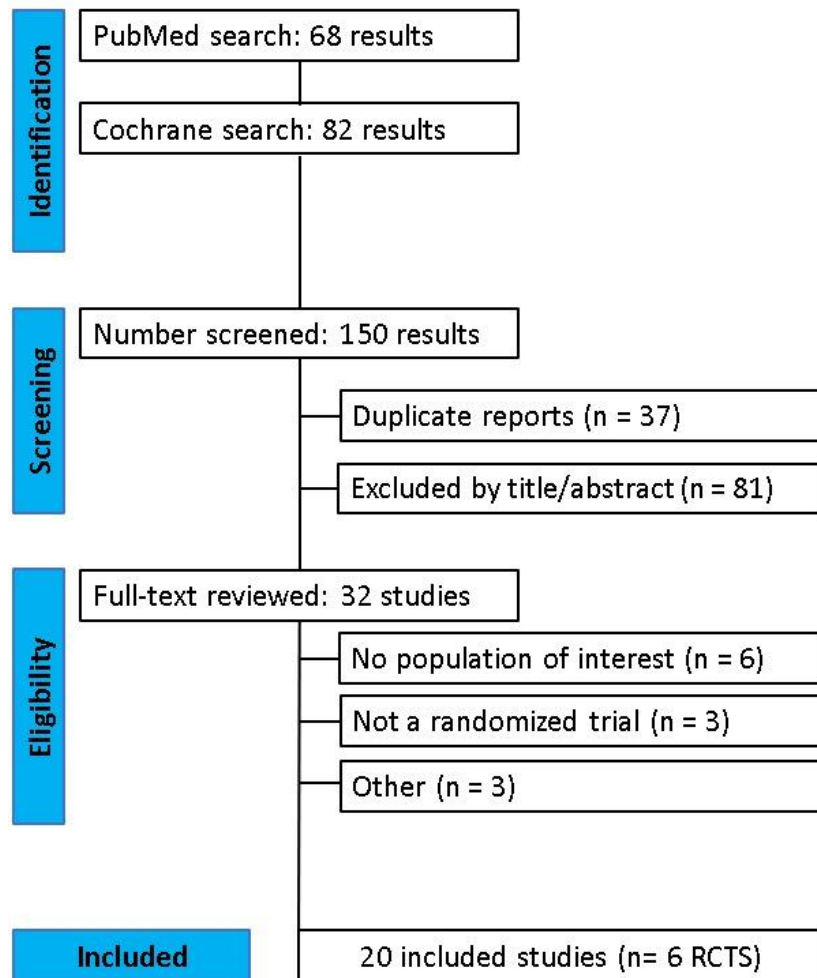
To search for the scientific studies corresponding to the objectives of this RIL, the following search terms were used: ("Pentoxifylline" AND "losartan" / "Pentoxifylline" AND "captopril" / "Pentoxifylline" AND "hypertension" / "Pentoxifylline" AND "blood pressure"). The descriptors were selected according to the Health Sciences Descriptors (DeCS) and *Medical Subject Headings* (MeSH/PubMed), namely: "Pentoxifylline", "Losartan", "Captopril", "Hypertension" and "blood pressure." All were combined with each other by the Boolean operators AND and OR. As inclusion criteria, we considered articles available in previously defined databases and approved by the scientific community. We included articles with a publication time between 2010 and 2023, written in Portuguese, English, and Spanish. Complementary information was obtained using the journal 'Research, Society and Development,' and references from articles were used to expand the research, as mentioned earlier, to address the guiding question. We reviewed randomized clinical trials related to Pentoxifylline in conjunction with losartan or captopril, in hypertensive and/or diabetic patients. As exclusion criteria, we excluded manuscripts that did not align with the study's objective and the guiding question. Additionally, results from publications in the gray literature (publications not cataloged in printed and electronic formats), those with a small sample size, and those lacking a description of the methodology were excluded.

Full articles available in the defined databases and approved by the scientific community in the languages Portuguese, English and Spanish were used as inclusion method; complementary information was included using the European and American guidelines on hypertension. Only randomized controlled trials were included. Manuscripts that did not respect the objective of the study and the guiding question were excluded; as well as those that were in the gray literature (publications not cataloged in print and electronic format, those that did not describe the methodology and those that did not use the population of interest) (Çalis & Aslan, 2020).

3. Results and Discussion

The search resulted in the following distribution among the publications found in each database: MEDLINE via PubMed (n=68), Cochrane (n=82), totaling 150 publications on the subject, respectively. Subsequently, manuscripts duplicated by title and abstract (n=37) and those whose title or abstract were not of interest (n=81) were excluded, leaving the number of articles read and reviewed in full (n=32). After reading and final evaluation of the studies, 20 manuscripts included in the literature review were selected. To systematize the process of selecting articles, the methodology used by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (Sarkis-Onofre et al., 2021) was used. The steps in this process are described in the form of a flowchart (Figure 1).

Figure 1 - PRISMA flow diagram of study screening and selection.



Source: Own autorship (2023).

Chart 1 was made from the analysis and review of the 6 randomized clinical trials selected and used throughout the work, selecting them based on their main findings, using a virtual spreadsheet as a method for computing and organizing the data.

Chart 1 - Main findings of the selected randomized clinical trials.

Article, year	Proposal	Main findings
NAMDAR, Hossein et al. (2020)	Stage 1 hypertensive patients of the study (n=62) divided into an intervention group (n=30) using 1200mg PTX + 75mg captopril versus the control group (n=32) using only 75mg captopril	After adding PTX to captopril, there was no evidence of a significant reduction in blood pressure in patients with stage 1 hypertension
RABIZADEH, Soghra et al. (2018)	Diabetic patients with daily use of losartan (n=59) divided into an intervention group (n=30) using PTX 400mg + losartan 50mg versus control group (n=29) receiving only losartan 50 mg for 12 weeks	The value of urinary excretion of albumin and serum C-reactive protein showed a significant reduction in the PTX group, while the losartan alone group showed a greater decrease in systolic and diastolic pressure
GHORBANI, Ali et al. (2012)	Patients with diabetic nephropathy (n=100) were randomized into a control group (n=50) using losartan or enalapril and an intervention group (n=50) using the same therapy with the addition of PTX	In patients with type 2 diabetes and diabetic nephropathy with residual proteinuria, the use of PTX may be beneficial. The PTX group, however, showed no decrease in blood pressure.
ROOZBEH, Jamshid et al. (2010)	Patients with type II diabetes and nephropathy with controlled blood pressure (n=74) were divided into a control group (n=37) using captopril 25mg and intervention group (n=37) using captopril 25mg and PTX 400mg	Systolic pressure was lower in the group (p=0.041). Urinary protein excretion was significantly lower in group 2.
Solerte SB et al. (1987)	Type 1 diabetic patients with nephropathy (n=21) were randomized to antihypertensive therapy or PTX (400).	There was a decrease in blood pressure associated with a reduction in proteinuria in the PTX group, but in a similar way to patients on antihypertensive treatment.
AMINORROAYA, Ashraf et al. (2005)	To compare patients with type 2 diabetes (n=39) in a control group (n=19) that used captopril 25mg and intervention group (n=20) that used PTX 400mg	Captopril proved equivalent in efficiency and safety to PTX. Both groups showed decreased proteinuria. PTX and captopril have been shown to have a similar decrease in diastolic and mean blood pressure, although they did not change systolic pressure. PTX proved to be a good drug to be used in normotensive diabetic patients.

Source: Own autorship (2023).

The main study that we can have as a basis for discussion in this review is the study by Namdar Hossein et al., 2020, which directly analyzed the effects of adding PTX to captopril on primary hypertension and its effects. This randomized clinical trial included patients with a diagnosis of stage 1 hypertension, based on the definitions of the Eighth Joint National Committee, between 18 and 80 years of age. Patients with secondary hypertension, White coat syndrome, liver and renal failure (clearance of creatinine under 30ml/min), among others, were excluded from the study. The control group was composed of 32 patients, this being the group that would receive 75mg of captopril divided into 3 doses for 2 months. The intervention group was composed of 30 patients using 1200mg of PTX added to 75mg of captopril. The primary endpoint of the study was to assess the change in blood pressure value, with all measurements being taken according to the American Heart Association (AHA). After 1-month, systolic blood pressure and diastolic blood pressure showed no significant difference between groups (p=0.20 to SBP and p= 0.31 to BPD). Although other studies have indirectly evaluated the blood pressure value of patients from the use of PTX, this was the first study to evaluate in direct comparison, only in stage 1 hypertensive patients. The final conclusion of this study was that the addition of PTX to captopril did not help lower blood pressure levels in patients. However, the study lacked some limitations, such as: population size, study time, and was not a double-blinded and placebo-controlled (which would reduce bias) study.

The study by Rabizadeh et al., 2018, demonstrated, in a sample of 68 patients with type 2 diabetes, aged between 30 and 80 years and urinary albumin excretion >150, that these markers, when associated with the use of PTX with losartan, suffered a great reduction. In this study there was a division between an intervention group (n=30) using PTX 400mg + losartan 50mg versus a control group (n=29) receiving only losartan 50 mg for 12 weeks. It is said in this study that the circulating value of NT-proBNP decreased equally in the PTX group and in the losartan group, however there was a considerable decrease in the excreted value of albumin and at the highly sensitive C-reactive protein in the PTX group, while the values of systolic and diastolic pressure reduced more in the losartan alone group. Finally, this study brings good evidence of the anti-proteinuric and anti-inflammatory effects of PTX, concluding that it is possible to affirm that the addition of PTX to losartan may be a more effective approach in reducing residual albuminuria and inflammation, compared to increasing the dose of losartan in the treatment of patients with diabetic nephropathy.

In the study by Ghorbani et al. (2012), 100 patients with diabetic nephropathy who had recorded proteinuria (>150mg/24h) were randomized into a control group (n=50) using losartan or enalapril and an intervention group (n=50) using the same therapy with the addition of PTX. This study showed that patients with diabetic nephropathy and residual proteinuria, despite being on ARB or ACEI therapy, could benefit from the use of PTX to provide an antiproteinuric effect and decrease urinary protein excretion. In addition, it is said that the beneficial antiproteinuric effect of PTX was not associated with lowering blood pressure. It is also brought up that there is a slow increase in the glomerular filtration rate in these patients. In the study by Roozbeth et al., 2010, patients with type 2 diabetes and proteinuria >500mg/24h, with medication-controlled blood pressure were divided into control group (n=37) using captopril 25mg and intervention group (n=37) using captopril 25mg and PTX 400mg. The proteinuria of group 2 was significantly lower. The systolic pressure value was lower in group 2, although there was no relationship between the decrease in systolic pressure and changes in proteinuria (p=0.903). This study concludes by showing that PTX has an additive effect when paired with captopril alone in proteinuria, starting after 2 months of drug administration and with greater evidence after 6 months.

In the study by Solerte et al. (1987), we have the first RCTs to seek to bring the effects of PTX on urinary protein excretion and blood pressure in insulin-dependent type 1 diabetic patients with nephropathy. Two groups were divided in this study, one group (n=11) with the use of antihypertensive drugs typical of the time and the other with the use of PTX 400mg. Although this study does not bring the direct comparison between losartan or captopril and pentoxifylline, it is of great importance in the literature for showing the improvement in blood rheology pattern with contribution of renal hemodynamics, i.e., glomerular filtration rate and renal plasma flow. However, it is brought that the reduction in proteinuria and blood pressure was similar between the groups, showing a non-superiority in the group with PTX. In the study by Aminorroaya et al, 2005, patients with type 2 diabetes (n=39) were compared in a control group (n=19) that used captopril 25mg and intervention group (n=20) that used PTX 400mg, in a form of direct comparison between groups. Once again it is brought up that both treatments were sufficient to reduce proteinuria. It is also said that PTX and captopril made a difference in blood pressure, although they had no effect on systolic pressure. It is said that creatinine clearance was better in patients with PTX. It is concluded in the study that PTX is a suitable medication in the treatment of macroproteinuria in diabetic nephropathic patients and it is logical to administer PTX instead of ACE inhibitor in normotensive diabetic patients or in those who do not respond or cannot tolerate it because of its side effects.

4. Final Considerations

After analyzing these studies, the literature still lacks direct comparative studies or additions between Pentoxifylline and other antihypertensive drugs, especially losartan and captopril. Its pro-renal effects are well described in the literature, especially in patients with diabetic nephropathy, with regard to proteinuria and glomerular filtration rates. However, the data

regarding the effect on blood pressure still need attention. None of the RCTs have a large enough sample size to completely rule out the hypothesis that adding PTX to antihypertensive treatment may be beneficial. The improvement in blood rheology pattern by PTX is already well described in the literature and its assumptions that it can improve blood pressure require further studies, with strong methodologies, to analyze and finally conclude this aspect. For now, the limitation of data leads us to believe that the association of PTX with captopril and losartan should be done individually, on a case-by-case basis among patients, bearing in mind its possible beneficial effects when associated with a diabetic nephropathy clinic, for example. Therefore, it is important to invest in new studies with a larger N, which shall make a direct comparison between this subject, in order to evaluate significant primary outcomes efficiently.

References

- Aminorroaya, A. et al. (2005). Comparison of the effect of pentoxifylline and captopril on proteinuria in patients with type 2 diabetes mellitus. *Nephron Clinical Practice*, 99(3), c73-c77.
- Bhatt, D. L. et al. (2006). International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama*, 295(2), 180-189.
- Çalış, H., & Aslan, A. (2020). What is gray literature and how to search for it?. *Acta Medica Alanya*, 4(2), 111-112.
- Educação, G. A. (2014). Manual Revisão Bibliográfica Sistemática Integrativa: a pesquisa baseada em evidências. *Belo Horizonte: Grupo Anima Educação*.
- Ghorbani, A. et al. (2012). The effect of pentoxifylline on reduction of proteinuria among patients with type 2 diabetes under blockade of angiotensin system: a double blind and randomized clinical trial. *Nephrology (English Edition)*, 32(6), 790-796.
- Lewington, S. et al. (2003). Age-specific relevance of usual blood pressure to vascular mortality. *The Lancet*, 361(9366), 1391-1392.
- Namdar, H. et al. (2020). Effects of adding pentoxifylline to captopril on primary hypertension: A pilot randomized clinical trial. *The Journal of Clinical Pharmacology*, 60(2), 181-187.
- Pigott, T. D., & Polanin, J. R. (2020). Methodological guidance paper: High-quality meta-analysis in a systematic review. *Review of Educational Research*, 90(1), 24-46.
- Plotnikov, M. B. et al. (2017). Pentoxifylline treatment enhances antihypertensive activity of captopril through hemorheological improvement in spontaneously hypertensive rats during development of arterial hypertension. *Journal of the American Society of Hypertension*, 11(11), 769-778.
- Rabi, D. M. et al. (2020). Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. *Canadian Journal of Cardiology*, 36(5), 596-624.
- Rabizadeh, S. et al. (2018). Beneficial effects of pentoxifylline plus losartan dual therapy in type 2 diabetes with nephropathy. *The American Journal of the Medical Sciences*, 355 (5), 442-448.
- Rapsomaniki, E. et al. (2014). Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 125 million people. *The Lancet*, 383(9932), 1899-1911.
- Riva, J. J. et al. (2012). What is your research question? An introduction to the PICOT format for clinicians. *The Journal of the Canadian Chiropractic Association*, 56 (3), 167.
- Roosbeh, J. et al. (2010). Captopril and combination therapy of captopril and pentoxifylline in reducing proteinuria in diabetic nephropathy. *Renal failure*, 32 (2), 172-178.
- Sarkis-Onofre, R. et al. (2021). How to properly use the PRISMA Statement. *Systematic Reviews*, 10(1), 1-3.
- Solerte, S. B. et al. (1987). Pentoxifylline, total urinary protein excretion rate and arterial blood pressure in long-term insulin-dependent diabetic patients with overt nephropathy. *Acta diabetologia latina*, 24, 229-239.
- Souza, M. T. D., Silva, M. D. D., & Carvalho, R. D. (2010). Revisão integrativa: o que é e como fazer. *Einstein*, 8, 102-106.
- Thomopoulos, C., Parati, G., & Zanchetti, A. (2017). Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *Journal of hypertension*, 35 (11), 2150-2160.
- Whelton, P. K. (2018). ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (vol 71, pg 2199, 2018). *Journal of the American College of Cardiology*, 71(19), 2273.
- Williams, B. et al. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Journal of Hypertension*, 36 (10), 1953-2041.