LA TUNISIE MEDICALE

Special issue: Septembre 2025

Heart Connections

Integrating Organ, Environmental, and Mental Health Impacts

Meta-analysis & systematic reviews

- Continuing versus withholding renin angiotensin aldosterone system antagonists before noncardiac surgery: A systematic review and meta-analysis
- The effect of Ambient heat exposure early in pregnancy on the frequency of congenital heart defects: A systematic review and meta-analysis
- The Effect of Inotropes in Patients with Advanced Heart Failure: A Meta-Analysis of Randomized Trials
- Effect of Paracetamol on Blood Pressure: A Systematic Review
- Effects of Heated Tobacco Products compared to Conventional Cigarettes on Cardiovascular System: A Systematic Review
- Efficacy and Safety of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) in Cardiac Amyloidosis: A Systematic Review
- Cardiovascular risk and JAK inhibitor for the treatment of spondyloarthritis: A systematic review
- Long working hours and the risk of ischemic cardiac death: A systematic review and meta-analysis
- Cardiovascular and pulmonary response in Internet gaming disorder: A systematic review
- Cardiac Phenotypes and Endophenotypes in Schizophrenia : A systematic Review
- The Effects of TNF-alpha Inhibitors on Subclinical Atherosclerosis and Endothelial Function in Patients with Psoriatic Arthritis: A Systematic Review

Effect of Paracetamol on Blood Pressure: A Systematic Review

Effet du paracétamol sur la pression artérielle : Revue systématique

Saoussen Miladi[1], Leila Rouached[2], Selma Bouden[2], Hiba Boussaa[1], Yasmine Makhlouf[1], Aicha Ben Tekaya[2], Siwar Ben Dhia[2], Ines Mahmoud[2], Raoudha Tekaya[2], Olfa Saidane[2], Kawther Ben Abdelghani[1], Alia Fazaa[1], Leila Abdelmoula[2], Ahmed Laatar[1]

1. University of Tunis El Manar, Faculty of Medicine of Tunis, Mongi Slim Hospital, Rheumatology department, Tunis, Tunisia
2. University of Tunis El Manar, Faculty of Medicine of Tunis, Charles Nicolle Hospital, Rheumatology department, Tunis, Tunisia

Abstract

Background: Paracetamol is widely used as a first-line analgesic for chronic pain, primarily due to its presumed safety profile. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol has been for long time considered free of significant cardiovascular effects, particularly on blood pressure (BP). However, emerging evidence suggests that long terme paracetamol use may be associated with elevated BP, challenging its status as a risk-free alternative to NSAIDs.

This systematic review aimed to investigate the association between paracetamol intake and changes in BP by screening existing clinical and epidemiological data to clarify its potential hypertensive effects.

Methods: A comprehensive search of Medline, Cochrane Library, and Embase databases was conducted. Eligible studies included randomized clinical trials, interventional and longitudinal observational studi involving adults receiving standard doses of oral paracetamol. Exclusion criteria were studies on pregnant women, patients with preeclampsia/eclampsia, and those using supratherapeutic doses. The primary outcome was variation in systolic and diastolic BP.

Results: A total of 10 studies was included comprinzing observational studies (n = 4) and randomized controlled trials (n = 6). Two observational studies reported a significant association between regular paracetamol use and an increased risk of hypertension particularly with high-dose (> 3 g/day) or prolonged use (> 30 days). The remaining two studies found no significant association, though one noted a trend toward elevated BP in older adults. Four RCTs demonstrated a small but consistent increase in systolic blood pressure (SBP), ranging from +0.2 to +4.0 mmHg. The effect appeared dose-dependent, with higher doses (> 2 g/day) linked to greater BP elevation.

Conclusion: Paracetamol may cause slight elevations in BP, with potential clinical implications in high- risk patients. Caution is warranted, and further prospective studies using ambulatory BP monitoring are needed to clarify this relationship.

Key words: acetaminophen, hypertension, review, cardiovascular events, side effects

Résumé

Introduction: Le paracétamol est largement utilisé comme traitement de première intention pour les douleurs chroniques en raison de sa présumée innocuité. Contrairement aux anti- inflammatoires non stéroïdiens (AINS), le paracétamol a longtemps été considéré comme dépourvu d'effets cardiovasculaires, notamment sur la tension artérielle (TA). Cependant, des études récentes suggèrent un effet potentiellement hypertensif. Cette revue systématique visait à étudier l'association entre la consommation de paracétamol et les variations de la TA.

Méthodes: Une recherche exhaustive a été réalisée dans les bases de données PubMed, Cochrane Library et Scopus. Les études éligibles comprenaient des essais cliniques randomisés, des études interventionnelles et observationnelles impliquant des adultes recevant des doses standards de paracétamol par voie orale. Les critères d'exclusion concernaient les études sur les femmes enceintes, les patientes atteintes de prééclampsie/éclampsie et les personnes utilisant des doses supra thérapeutiques. Le critère principal était la variation de la TA systolique et diastolique.

Résultats: Un total de 10 études a été inclus, incluant des études observationnelles (n = 4) et des essais contrôlés randomisés (ECR, n=6). Deux études observationnelles ont rapporté une association significative entre l'utilisation régulière de paracétamol et un risque accru d'hypertension, en particulier à dose élevée (> 3 g/jour) ou lors d'une utilisation prolongée (> 30 jours). Les deux autres études n'ont trouvé aucune association significative, avec toutefois, une tendance à une augmentation de la TA chez les personnes âgées sous paracétamol.

Quatre ECR ont montré une augmentation faible mais constante de la TA systolique, allant de +0,2 à +4,0 mmHg. L'effet semblait dépendant de la dose. Une élévation plus marquée de la TA été notée avec des doses plus élevées de paracétamol (> 2 g/jour).

Conclusion : Le paracétamol pourrait provoquer une légère élévation de la PA, avec des implications cliniques potentielles chez les patients à haut risque. Des études prospectives supplémentaires utilisant la mesure ambulatoire de la TA sont nécessaires pour clarifier cette relation.

Mots-clés : Acetaminophen, hypertension, revue, effets cardiovasculaires, effects indésirables

Correspondance
Leila Rouached
University of Tunis El Manar, Faculty of Medicine of Tunis, Charles Nicolle Hospital, Rheumatology department, Tunis, Tunisia
Email: leila.rouached@gmail.com

LA TUNISIE MEDICALE-2025; Vol 103 (09): 1175-1182 DOI: 10.62438/tunismed.v103i9.6243

Introduction

Paracetamol is widely used for managing mild to moderate pain. In the UK, its consumption increased significantly from 1,500 million tablets per year in 1967 to 3,500 million in 2000 [1]. This rise may be attributed to its availability in various formulations both, as a single-agent drug and in combination with other analgesics, such as codeine or tramadol, as well as its widely accessibility, cheapness and perceived safety. Additionally, its efficacy in treating common conditions like headaches, osteoarthritis, and post- operative pain has contributed to its widespread use [2]. Despite its prevalence, the exact mechanism of paracetamol's analgesic action remains unclear, though some evidence suggests it may involve central inhibition of prostaglandin synthesis without significant peripheral anti-inflammatory effects [3].

Often considered a safer alternative to non-steroidal anti-inflammatory drugs (NSAIDs), particularly in patients with cardiovascular comorbidities, paracetamol is generally associated with mild side effects, including nausea, headache, abdominal pain, and rash [4]. Unlike NSAIDs, it does not increase gastrointestinal bleeding risk, making it preferable for long-term use in certain populations [5]. However, its most serious adverse effect—hepatotoxicity—typically occurs only with excessive intake, often due to unintentional overdose or prolonged high-dose therapy [6]. Unlike NSAIDs, which are known to elevate blood pressure (BP) and increase cardiovascular risk [7], paracetamol has traditionally been perceived as having a neutral effect on BP. Nevertheless, recent studies have challenged this assumption, suggesting that regular or high-dose paracetamol use may have hypertensive effects, possibly through oxidative stress or endothelial dysfunction.

This systematic review aimed to investigate the association between paracetamol intake and changes in BP by screening existing clinical and epidemiological data to clarify its potential hypertensive effects.

Methods

This review is based on previously published studies; no ethical approval was required. All the search strategy, literature selection and data extraction were conducted by two investigators (RL and BS) independently, then discussed. They screened titles, abstracts, and full texts. Disagreements were resolved with a third reviewer (MS).

Search strategy

Before starting the literature of relevant studies, we used the PICO framework: P: adults receiving paracetamol, I: paracetamol use, C: controls receiving placebo or not O: blood pressure changes.

Following the PRISMA 2020 guidelines [8], we performed a systematic search in Medline, Cochrane Library, and Embase. Besides, a search on ongoing protocols was addressed on Prospero and Cochrane Library (Protocols). The literature search was be supplemented by a manual search on Google scholar, grey literature, congresses abstract books and theses and dissertations presented at the faculty of medicine of Tunis. On Medline, we used a search equation associating Mesh (Medical Subject Headings) and free words. Our equation is represented in the table 1 and published in the protocol of the review [9].

Table 1. Search equation for Medline search

Equation	
("Acetaminophen"[Mesh] OR "Arylsulfotransferase"[Mesh] OR "Acetamidophenol" OR "Acetominophen" OR "APAP" OR "Paracetamol" OR "Algotropyl" OR "Acamol" OR "Panadol" OR "Tylenol" OR "Acephen")	("Cardiovascular Diseases"[Mesh] OR "Blood Pressure Determination"[Mesh] OR "Blood OR Pressure"[Mesh] "Hypotension"[Mesh] OR "Hypertension"[Mesh] OR "Cardiovascular Disease" OR "Cardiac Events" OR "Cardiac Event" OR "Pressure, Pulse" OR "Diastolic Pressure" OR "Pressure, Diastolic" OR "Systolic Pressure" OR "Pressure, Systolic" OR "Arterial Pressures" OR "Arterial Blood Pressure" OR "Arterial Tension" OR "Blood Pressure, Arterial" OR "Mean Arterial Pressure" OR "Monitor, Blood Pressure" OR "Pressure Monitor, Blood" OR "Hypotension, Vascular" OR "Low Blood Pressure" OR "High Blood Pressure")

Selection criteria

Our research strategy for this systematic review was based on the following inclusion and exclusion criteria

Inclusion Criteria

We included studies that enrolled adult participants aged 18 years and older, with or without a history of hypertension or cardiovascular disease. Eligible studies investigated the use of paracetamol for chronic pain, administered orally at a standard therapeutic dose of 0.5–1 g every 4–6 hours, up to a maximum of 4 g/day, compared with placebo or non-use. Only studies published in English or French were considered.

Exclusion Criteria

We excluded studies conducted in women of childbearing age or in those with preeclampsia/eclampsia. Studies using supratherapeutic doses of paracetamol were also excluded. In addition, meta-analyses, reviews, editorials, letters, comments, and studies with insufficient data were not considered for inclusion.

Data Extraction

Data were extracted using Covidence on a (free version). Information collected was: characteristics of the studies

(year of publication, design and follow-up period), patients (total number of patients, age and gender), paracetamol intake (dose, duration), blood pressure (blood pressure variation before and after paracetamol intake, systolic blood pressure, diastolic blood pressure). Extracted data from each study were scrutinized by both investigators independently (BS and RL)

Risk of bias and quality assessment

The risk of bias in the included studies was evaluated independently by two authors, following the Cochrane RoB2 Tool for randomized studies (Figure 1), and the Newcastle Ottawa Scale (NOS) (Table 2) and Joanna Bridge Institute (JBI) for non-randomized studies.

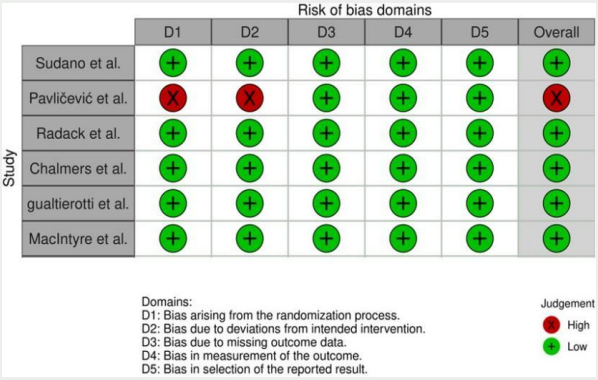

Figure 1. Evaluation of the risk of bias in RCTs using Cochrane RoB 2 tool

Table 2. Evaluation of the risk of bias in cohort studies using Newcastel Ottawa Scale

	Selection				Comparability	Outcome			Quality
	1	2	3	4	1	1	2	3	
Kurth et al. [7]	*	*	-	*	*	-	*	*	Good
Dawson et al. [9]	*	*	*	*	*	*	*	*	Good
Forman et al. [8]	*	*	*	*	*	*	*	-	Good
Curhan et al. [6]	*	*	*	*	*	-	*	-	Good

For quality assessment, we used JADAD tool for randomized studies and Minors for non- randomized studies [10] (Table 3 and 4).
The MINORS scale includes 12 items (maximum score: 16 for non-comparative and 24 for comparative studies). Scores <50% indicate low quality, 50–75% moderate quality, and >75% high quality.

Table 3. Effects of paracetamol on blood pressure: Cohort studies

Author(s)	Year	Study Design	Population	Sample Size	Follow-up Duration	Paracetamol Use (Frequency)	SBP / DBP Variation	Hypertension Cases	Relative Risk	MINORS evaluation
Curhan et al. [11]	2002	Prospective cohort	Nurses without prior hypertension	80,020	2 years	Days/month: 0 1–4 5–14 15–21 >22	Not reported	369 661 229 62 72	1.00 1.22 1.63 1.27 2.83 (p<0.001)	High quality 18/
Kurth et al. [12]	2005	Prospective cohort	Male physicians without prior hypertension	8,229	14 years	Cumulative tablets : <12 12-1499 1500-2499 ≥2500	Not reported	1204 607 87 97	1.00 0.87 1.20 1.01	High quality
Forman et al. [13]	2007	Prospective cohort	Male nurses without prior hypertension	16,031	2 years	Days/week: 0 1 2-3 4-5 6–7	Not reported	1743 47 69 36 50	1.00 1.01 1.01 1.64 1.36 (p=0.007)	High quality
Dawson et al. [14]	2013	Retrospective cohort	Hypertensive patients (mean age: 73.1)	8,876	1 year	Not specified	SBP : +3.1 mmHg (p = 0.05) DBP : +1.3 mmHg (p = 0.09)	Not specified	Not specified	Moderate quality

SBP = systolic blood pressure; **DBP** = diastolic blood pressure; **CI** = confidence interval; **RR** = relative risk; **NR** = not reported.

Table 4. Effects of paracetamol on blood pressure : randomised controlled trials

Author(s)	Year	Study Design	Population	N	Paracetamol Dose	Duration	Change in SBP (mmHg)	Quality evaluation JADAD
Chalmers et al. [15]	1984	RCT, double-blind, crossover, placebo-controlled	Hypertensive patients	22	1 g × 3/day	4 weeks	+4 mmHg (supine & standing; p < 0.05)	3
Radack et al. [16]	1987	RCT, double-blind, parallel	Mild/moderate hypertension (controlled)	29	1 g × 3/day	3 weeks	+0.2 (supine), - 1.7 (sitting); not significant	5
Pavlicevic et al. [17]	2008	RCT, single-blind, 3-phase, parallel	Hypertensive OA patients	49	1 g × 3/day	1 month	-5.4 to +1.2 mmHg (across different subgroups)	3
Sudano et al. [18]	2010	RCT, double-blind, crossover, placebo	CAD patients on cardiovascular therapy	33	1 g × 3/day	Several weeks	+3 mmHg (p < 0.02 vs placebo)	4
Gualtierotti et al. [19]	2013	RCT, double-blind, parallel + crossover	Hypertensive patients	174	2 g/day	Several weeks	+3.8 to +4.4 mmHg across treatment groups (p< 0.05)	4
MacIntyre et al. [20]	2022	RCT, double-blind, crossover, placebo	Hypertensive adults (≥18 years)	110	4 g/day	2 weeks	+3.8 mmHg vs placebo (-1.4 mmHg); p < 0.0001	5

RCT = randomized controlled trial; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **CAD** = coronary artery disease; **OA** = osteoarthritis; **NR** = not reported.

Result

A total of 10 studies were included, encompassing 6 randomized controlled trials and 4 cohort studies. Prisma flow diagram is illustrated in figure 2.

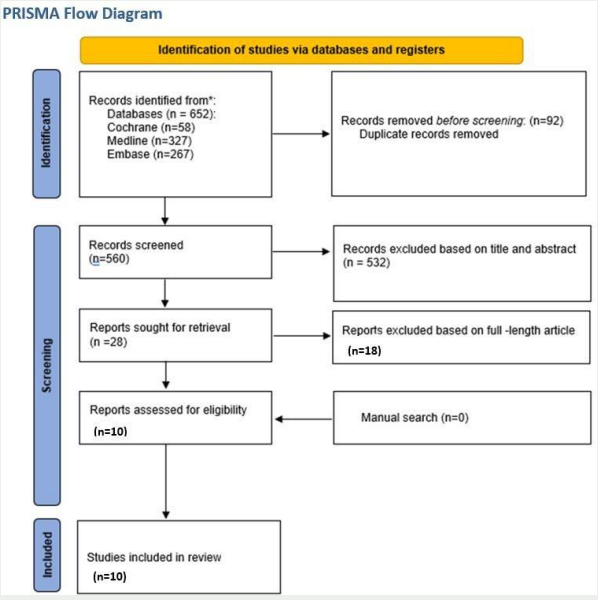

Figure 2. PRISMA 2020 flow diagram showing study selection process.

Observational Studies

Four cohort studies were included encompassing for 113 156 persons [11-14]. Two of them found a significant association between regular paracetamol use and the development or worsening of hypertension, particularly with prolonged use or higher doses [11,13] (Table3).

Curhan et al. (2002) [11], in the Nurses' Health Study, followed 80,020 women without a history of hypertension or chronic kidney disease to assess incident hypertension via self- reported physician diagnoses. Paracetamol use was associated with an increased risk of developing hypertension across all levels of use when compared to non-use (RR = 2.83 for paracetamol use on more than 22 days per month versus RR = 1 for non-use). A significant dose-response relationship was identified, with the risk of hypertension rising progressively with greater frequency of paracetamol use (RR = 1.22 for use on 1–4 days per month versus RR = 2.83 for use on more than 22 days per month).

However, a major limitation of this study was the absence of information regarding the indication for analgesic use. This raised concerns about potential confounding, such as headache-related paracetamol use in individuals with elevated blood pressure.

In contrast, the Physicians' Health Study conducted by

Kurth et al. (2005) [12] involved 8,229 men without prior hypertension and found no increased risk of hypertension associated with cumulative paracetamol use, regardless of dose.

Dawson et al. [14] compared BP changes in acetaminophen-exposed versus non-exposed patients. No significant differences were observed in systolic or diastolic BP between the two groups. Among patients not receiving antihypertensive therapy, systolic BP increased by 3.1 mmHg and diastolic BP by 1.3 mmHg ($p = 0.05$ and $p = 0.09$, respectively). There was no clear relationship between BP changes and either the dose or duration of acetaminophen exposure.

In conclusion, two observational studies out of four reported a significant association between regular paracetamol use and an increased risk of hypertension.

Randomized studies

Six randomized controlled trials (RCTs) have specifically assessed the impact of paracetamol on blood pressure (Table 4) [15-20]. Four RCT demonstrated a modest but statistically significant increase in systolic BP following short-term paracetamol use (2 to 4 weeks). Increases ranged from +0.2 mmHg to +4 mmHg.

The first study, conducted by Chalmers et al. in 1984,[15] was a randomized, double-blind, placebo-controlled crossover trial. It included 22 hypertensive patients previously treated with NSAIDs. Participants received sodium-free paracetamol (1 g every 8 hours) or placebo for 4 weeks. A significant 4 mmHg increase in both supine and standing systolic BP was observed with paracetamol use compared to placebo ($p < 0.05$).

In another RCT, Radack et al. (1987) [16] compared ibuprofen (400 mg), paracetamol (1 g), and placebo administered every 8 hours for 3 weeks. No significant changes in systolic BP were observed in the paracetamol group relative to baseline.

Pavlicevic et al. (2008) [17] conducted a single-blind, three-phase parallel study involving 49 hypertensive osteoarthritis patients and 39 hypertensive controls. The study compared ibuprofen, piroxicam, and subsequent paracetamol (1 g three times daily), each for one month. In patients treated with lisinopril/hydrochlorothiazide, systolic BP increased with ibuprofen (139 to 144.4 mmHg) and piroxicam (133.3 to 149.4 mmHg), but decreased with paracetamol (to 133.9 and 132.9 mmHg, respectively). However, a greater reduction was observed in the analgesia-free control group, suggesting a possible white coat effect. In the amlodipine subgroup, none of the three analgesics significantly altered BP, indicating that calcium channel blockers may be less affected by NSAIDs.

Sudano et al. (2010) [18] performed a double-blind crossover trial in 33 patients with coronary artery disease. Paracetamol (1 g, sodium-free) or placebo was administered three times daily for two weeks. Paracetamol significantly increased mean systolic BP (122.4 to 125.3 mmHg, $p < 0.02$), comparable to the hypertensive effects observed with NSAIDs.

Gualtierotti et al. (2013) [19] conducted a double-blind, placebo-controlled RCT with both parallel and crossover arms. Acetaminophen produced small but statistically significant increases in both clinic and ambulatory systolic/diastolic BP and heart rate (HR) across patients treated with ramipril, valsartan, or aliskiren. Increases were observed for 24-hour, daytime, and nighttime BP and HR (e.g., daytime SBP/DBP increased by 3.5/2.6 mmHg in the ramipril group; $p < 0.05$ for all comparisons).

Finally, in 2022, MacIntyre et al. [20] conducted a large double-blind, crossover RCT in 103 patients. Regular acetaminophen use led to a significant increase in daytime systolic BP compared to placebo (from 132.8 to 136.5 mmHg vs. 133.9 to 132.5 mmHg; $p < 0.0001$), with a placebo-corrected difference of +4.7 mmHg (95% CI: 2.9–6.6). Diastolic BP also increased by a placebo-corrected 1.6 mmHg (95% CI: 0.5–2.7, $p = 0.005$). Similar findings were confirmed in 24-hour ambulatory and clinic BP measurements.

Discussion

This systematic review showed in 4 RCT [15,18-20] and 2 cohorts [11,13] that paracetamol contributes to elevations in systolic blood pressure, even at recommended doses and in both normotensive and hypertensive individuals. Given the heterogeneity of included studies, we did not perform a full meta-analysis.

Although paracetamol is considered as a relatively safe drug, it may result in hypertension in patients with or without known hypertension. This side effect may be harmful at large scale population. Indeed, even the small increases in BP have important clinical implications at a population level, as a rise in systolic BP of 2 mmHg is associated with a 7% and 10% increase in risk of death from ischemic heart disease and stroke, respectively [21].

Some systematic reviews have been published in the past aiming to respond to the question:

“Does the paracetamol increase the BP?” [22,23]. Our systematic review differentiates from others by including a largest number of patients and both observational and randomized clinical trials.

The results from the observational studies have showed that the risk of hypertension increased with the duration of the use [11] and with the dosage of paracetamol [12].

Clinical trials suggested that short term paracetamol use of paracetamol (2 weeks – 1 month) has a small effect on BP ranging from +0,2 mmHg to +4 mmHg [15,16]. When compared to NSAIDs, no significant changes in systolic BP were observed in the paracetamol group relative to baseline.

In our systematic review, we opted to include observational studies for several reasons.

Although methodologically less rigorous than randomized controlled trials, they provided access to a larger patient population, enhancing the generalizability of our findings.

The other advantage of observational studies was avoiding the white coat effect and the associated elevation in BP measurements [11,13]. These observational studies were conducted on patients who performed self-measurements of blood pressure, thereby eliminating

the potential confounding influence of healthcare provider presence on cardiovascular parameters. This methodological approach allowed for more accurate assessment of baseline BP values in the participants' natural environment, reducing measurement bias commonly observed in clinical settings.

The large amount of sodium contained in the effervescent paracetamol pills was considered the origin of hypertension. However, we are concerned that even non-effervescent paracetamol may cause an increase in BP [24,25]. Benitez-Camps et al. compared the effects of effervescent with non-effervescent paracetamol in 46 patients with known hypertension [26]. The comparison showed a significant increase in systolic BP of about 5 mmHg in patients treated with effervescent tablets.

Paracetamol has been regarded for long time as a significantly safer alternative to NSAIDs for managing mild to moderate pain in patient with associated cardiovascular risk. While it may still have a lower bleeding risk and remain preferable in patients with renal impairment, emerging evidence suggests that the safety margin between these agents may be narrower than previously believed when considering hypertension [27,28].

Our systematic review of the literature suggests that there is an association between paracetamol use and elevated BP in hypertensive patients. Caution is required when treating patients with high cardiovascular risk. To generalize our findings, further prospective studies are needed to clarify the impact of paracetamol on BP, utilizing 24- hour ambulatory blood pressure monitoring as the primary endpoint in large, well-defined cohorts or including patients with borderline conditions as renal impairment.

Conclusion

In conclusion, our study demonstrates a significant association between paracetamol use and elevated BP, reinforcing concerns about its cardiovascular safety particularly in patients with hypertension or high cardiovascular risk. Given these findings, clinicians should consider restricting paracetamol use to cases of clear clinical necessity and explore alternative analgesics when appropriate, especially for long-term pain management in at- risk populations

References:

1. Sheen CL, Dillon JF, Bateman DN, Simpson KJ, Macdonald TM. Paracetamol toxicity: epidemiology, prevention and costs to the health-care system. QJM Mon J Assoc Physicians 2002;95:609–19. https://doi.org/10.1093/qjmed/95.9.609.
2. Sussman NL, Remien CH. The Headache of Acetaminophen Overdose: Getting the NAC. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2017;15:563–4. https://doi.org/10.1016/j.cgh.2016.12.011.
3. Chidiac AS, Buckley NA, Noghrehchi F, Cairns R. Paracetamol (acetaminophen) overdose and hepatotoxicity: mechanism, treatment, prevention measures, and estimates of burden of disease. Expert Opin Drug Metab Toxicol 2023;19:297–317. https://doi.org/10.1080/17425255.2023.2223959.
4. Graham GG, Scott KF, Day RO. Tolerability of paracetamol. Drug Saf 2005;28:227– 40. https://doi.org/10.2165/00002018-200528030-00004.
5. Blot WJ, Fischer T, Nielsen GL, Friis S, Mumma M, Lipworth L, et al. Outcome of upper gastro-intestinal bleeding and use of ibuprofen versus paracetamol. Pharm World Sci PWS 2004;26:319–23. https://doi.org/10.1007/s11096-004-9008-5.
6. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 2002;40:3–20. https://doi.org/10.1081/clt-120002882.
7. Snowden S, Nelson R. The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardiol Rev 2011;19:184–91. https://doi.org/10.1097/CRD.0b013e31821ddcf4.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
9. Miladi S, Rouached L, Bouden S, Boussaa H et al. Effect of paracetamol on blood pressure: A systematic review protocol. La Tunisie Médicale.2025;103(5):557-559. doi:10.62438/tunismed.v103i5.5525.
10. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg. 2003;73(9):712-6. doi:10.1046/j.1445-2197.2003.02748.x.
11. Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 2002;162:2204–8. https://doi.org/10.1001/archinte.162.19.2204.
12. Kurth T, Hennekens CH, Stürmer T, Sesso HD, Glynn RJ, Buring JE, et al. Analgesic use and risk of subsequent hypertension in apparently healthy men. Arch Intern Med 2005;165:1903–9. https://doi.org/10.1001/archinte.165.16.1903.
13. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 2007;167:394–9. https://doi.org/10.1001/archinte.167.4.394.
14. Dawson J, Fulton R, McInnes GT, Morton R, et al. Acetaminophen use and change in blood pressure in a hypertensive population. J Hypertens. 2013;31(7):1485–90.
15. Chalmers JP, West MJ, Wing LM, Bune AJ, Graham JR. Effects of indomethacin, sulindac, naproxen, aspirin, and paracetamol in treated hypertensive patients. Clin Exp Hypertens A. 1984;6(6):1077–93.
16. Radack KL, Deck CC, Bloomfield SS. Ibuprofen interferes with the efficacy of antihypertensive drugs. A randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. Ann Intern Med. 1987;107(5):628–35.
17. Pavlicevic I, Kuzmanic M, Rumboldt M, Rumboldt Z. Interaction between antihypertensives and NSAIDs in primary care: a controlled trial. Can J Clin Pharmacol. 2008;15(2):372–82.
18. Sudano I, Flammer AJ, Roas S, Enseleit F, Noll G, Ruschitzka F. Nonsteroidal antiinflammatory drugs, acetaminophen, and hypertension. Curr Hypertens Rep. 2012;14(4):304–9.
19. Gualtierotti R, Zoppi A, Mugellini A, Derosa G, et al. Effect of naproxen and acetaminophen on blood pressure lowering by ramipril, valsartan and aliskiren in hypertensive patients. Expert Opin Pharmacother. 2013;14(13):1875–84.
20. MacIntyre IM, Turtle EJ, Farrah TE, Graham C, et al. Regular acetaminophen use and blood pressure in people with hypertension: the PATH-BP trial. Circulation. 2022;145(6):416–23.
21. Hypertension in adults: diagnosis and management | Guidance | NICE 2011. https://www.nice.org.uk/guidance/CG127 (accessed July 1, 2025).
22. Gupta R, Behnoush AH, Egeler D, Aronow WS. Effect of acetaminophen on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Eur J Prev Cardiol 2022;29:e326–30. https://doi.org/10.1093/eurjpc/zwac112.
23. Turtle EJ, Dear JW, Webb DJ. A systematic review of the effect of paracetamol on blood pressure in hypertensive and non-

hypertensive subjects. Br J Clin Pharmacol 2013;75:1396–405. https://doi.org/10.1111/bcp.12032.

24. Douglas L, Akil M. Sodium in soluble paracetamol may be linked to raised blood pressure. BMJ 2006;332:1133. https://doi.org/10.1136/bmj.332.7550.1133.
25. Rao S, Nazarzadeh M, Canoy D, Li Y, Huang J, Mamouei M, et al. Sodium-based paracetamol: impact on blood pressure, cardiovascular events, and all-cause mortality. Eur Heart J 2023;44:4448–57. https://doi.org/10.1093/eurheartj/ehad535.
26. Benitez-Camps M, Morros Padrós R, Pera-Pujadas H, Dalfó Baqué A, Bayó Llibre J, Rebagliato Nadal O, et al. Effect of effervescent paracetamol on blood pressure: a crossover randomized clinical trial. J Hypertens 2018;36:1656–62. https://doi.org/10.1097/HJH.0000000000001733.
27. Roberts E, Delgado Nunes V, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis 2016;75:552–9. https://doi.org/10.1136/annrheumdis-2014-206914.
28. Kaur J, Nakafero G, Abhishek A, Mallen C, Doherty M, Zhang W. Incidence of Side Effects Associated With Acetaminophen in People Aged 65 Years or More: A Prospective Cohort Study Using Data From the Clinical Practice Research Datalink. Arthritis Care Res 2025;77:666–75. https://doi.org/10.1002/acr.25471.