

Effect of paracetamol on blood pressure: A systematic review protocol

Effet du paracétamol sur la tension artérielle: Protocole d'une revue systématique

Saoussen Miladi¹, Leila Rouached², Selma Bouden², Hiba Boussaa¹, Yasmine Makhoul¹, Aicha Ben Tekaya², Ines Mahmoud², Raoudha Tekaya², Olfa Saidane², Kawther Ben Abdelghani¹, Alia Fazaa¹, Leila Abdelmoula², Ahmed Laatar¹

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

Introduction: Paracetamol is widely used as a first-line treatment for chronic pain because it is thought to be safe. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol is thought to have no cardiovascular effects and specially no effect on blood pressure (BP). However, some studies suggest that paracetamol may increase BP. Thus, our aim was to address a systematic review in order to investigate the effects of regular paracetamol intake on BP.

Methods: To address this systematic review, a search on PubMed, Cochrane and Scopus is planned. A search on grey literature, registries, thesis and congress abstracts will be performed. We will include randomized clinical trials, interventional studies and observational studies. Studies on child bearing women and those with eclampsia or preeclampsia will be excluded. Besides, only studies using recommended dosage of paracetamol will be included. The primary outcomes of interest will be the change of BP before and after the intake of paracetamol.

Discussion: Change of BP will be assessed on patients taking paracetamol. Any previous cardiovascular disease or hypertension will be raised in order to identify if there are risk factors of hypertension under paracetamol.

Key words: acetaminophen, hypertension, systolic blood pressure, diastolic blood pressure, adverse effect

RÉSUMÉ

Introduction: Le paracétamol est largement utilisé comme un antalgique de première intention car il est considéré comme un médicament peu nocif. En effet, contrairement aux anti-inflammatoires non stéroïdiens (AINS), le paracétamol est considéré dénué d'effets cardiovasculaires et d'effets sur la tension artérielle (TA). Cependant, certaines études suggèrent que le paracétamol peut augmenter la TA. Notre objectif était donc de mener une revue systématique de la littérature afin d'étudier les effets de la prise du paracétamol sur la TA.

Méthodes: Pour réaliser cet revue systématique, une recherche sur PubMed, Cochrane et Scopus est prévue. Une recherche sur la littérature grise, les registres, les thèses et les résumés de congrès sera aussi effectuée. Nous inclurons des essais cliniques randomisés, des études interventionnelles et des études observationnelles. Les études sur les femmes enceintes et celles souffrant d'éclampsie ou de pré-éclampsie seront exclues. De même que les études utilisant un dosage de paracétamol supérieure aux doses usuelles recommandées seront exclues. Les principaux résultats s'intéresseront à la variation de la TA avant et après la prise de paracétamol.

Discussion: La variation de la TA sera évaluée chez les patients prenant du paracétamol. Tout antécédent de maladie cardiovasculaire ou d'hypertension sera soulevé afin d'identifier s'il existe des facteurs de risque d'hypertension sous paracétamol.

Mots-clés: acetaminophen, hypertension, hypertension systolique, hypertension diastolique, effets indésirables

Correspondance

Selma Bouden

University of Tunis El Manar, Faculty of Medicine of Tunis, Charles Nicolle Hospital, Rheumatology department, Tunis, Tunisia

Email: selma.bouden@gmail.com

INTRODUCTION

Paracetamol is the most commonly used drug in the world (1). Its main indication is acute and chronic pain, due to its analgesic effect (1). It has long been thought that paracetamol is totally safe and has no adverse effects (2). And unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol was thought to have no cardiovascular effects and specially no effect on blood pressure (BP). However, some studies suggest that paracetamol may increase BP, incriminating similar mechanism of action between paracetamol and NSAIDs (3). It has also been suggested that there is a dose–response relationship between daily dose of paracetamol and cardiovascular side effects, especially hypertension (4).

Thus, our aim was to address a systematic review to investigate the effects of regular paracetamol intake on BP.

OBJECTIVE

We conducted a systematic literature review to assess changes in BP before and after paracetamol intake. Our secondary purpose will be to evaluate the other cardiovascular risks associated with paracetamol use.

METHODS

Eligibility Criteria

All data analyzed will be extracted from published studies. For the present paper, no ethical approval or written informed consent is required. All the search strategy, literature selection and data extraction will be conducted by two independent investigators (RL and BS), then discussed and any disagreement will be resolved by a third investigator (MS).

Search strategy

Before starting the literature of relevant studies, we fixed our search question PICO as follow: P: all the patients receiving paracetamol, I: paracetamol use, C: controls receiving placebo or not O: blood pressure changes.

Then, a systematic comprehensive search using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (5) will be performed in the following databases: Medline via PubMed, Cochrane Library and Scopus. Besides, a search on ongoing protocols will be addressed on Prospero and Cochrane Library (Protocols).

The literature search will 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 will use a search equation associating Mesh (Medical Subject Headings) and free words. Our equation is represented on Box 1.

Box 1. search equation for Medline search

(" A c e t a m i n o -	("Cardiovascular Diseases"[Mesh] OR
phen"[Mesh] OR "Aryl-	"Blood Pressure Determination"[Mesh]
sulfotransferase"[Mesh]	OR "Blood Pressure"[Mesh]
OR "Acetamidophenol"	OR "Hypotension"[Mesh] OR
OR "Acetaminophen"	"Hypertension"[Mesh] OR
OR "APAP" OR "Parac-	"Cardiovascular Disease" OR
etamol" OR "Algotro-	"Cardiac Events" OR "Cardiac Event"
pyl" OR "Acamol" OR	OR "Pressure, Pulse" OR "Diastolic
"Panadol" OR "Tylenol"	Pressure" OR "Pressure, Diastolic"
OR "Acephen")	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 will be based on the following inclusion criteria:

- 1) The study population: adults aged above 18 years
- 2) Patients with previous hypertension or cardiovascular disease or not
- 3) Paracetamol taken for chronic pain
- 4) Oral paracetamol at a standard therapeutic dose of 0.5–1 g every 4–6 h to a maximum of 4 g/day compared with placebo or non-use.

Studies on BP of child-bearing women or those with eclampsia or preeclampsia will be excluded.

Articles with insufficient data provided to evaluate our objectives, meta-analyses, reviews, editorials, letters and comments will be excluded.

Only studies published in English or French will be considered as eligible. Additional articles will be manually retrieved based on the references of selected articles. If any study included overlapping data, the most comprehensive one will be selected. After deep analysis of titles and abstracts, articles unrelated to the inclusion criteria will be excluded.

Data extraction and quality assessment

An artificial intelligence tool will be used in the step of data extraction: Covidence (free version). Information collected will be: characteristics of the studies (year of publication, design and follow-up period), patients (total number of patients, age and gender), paracetamol intake (dose, duration, indication), blood pressure (blood pressure variation before and after paracetamol intake, systolic blood pressure, diastolic blood pressure) and other cardiovascular events (type). Extracted data from each study will be scrutinized by both investigators independently (BS and RL).

Risk of bias assessment

The risk of bias in the included studies will be evaluated independently by two authors, following the Cochrane RoB2 Tool for randomized studies, and the Newcastle-Ottawa Scale (NOS) and Joanna Bridge Institute (JBI) for non-randomized studies. Any disagreements regarding the risk of bias will be resolved through discussion.

DISCUSSION

There is no recent review assessing the effect of paracetamol on BP (6). That is why our review will be pertinent to report recent data concerning change of BP in patients taking paracetamol. Any previous cardiovascular disease or hypertension will be raised to identify if there are risk factors of hypertension under paracetamol.

CONCLUSION

In conclusion, our study will demonstrate if there is any significant correlation between the use of paracetamol and the variation of BP. This adds to concern regarding the safety of regular paracetamol use for patients dealing with chronic pain.

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