The use of ibuprofen as an anti-seizure medication: a systematic review

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SUMMARY

Background. Epileptic seizure is a transient period of signs and symptoms resulting from the abnormal excessive and synchronous neuronal activity in the brain, resulting in brain damage. To prevent complications, the antiseizure medication is needed. Several agents have a potency of anti-seizure effect, including ibuprofen. Unfortunately, there are few studies regarding the anti-seizure effect of ibuprofen.

Aim. To determine the anti-seizure effect of ibuprofen to reduce the symptoms of epileptic seizures.

Materials and Methods. A systematic review using the databases ScienceDirect, SpringerLink, Nature, and Pubmed. The article was obtained using the keywords "ibuprofen" and ("epilepsy" or "anticonvulsant" or "antiseizure" or "epileptic" or "neuroinflammation") in the period 2012 to 2022 and screened with inclusion and exclusion criteria. Out of the 1376 articles screened, there are three studies included in this review. The SYRCLE Risk of Bias Tool was used to assess the risk of bias, and the data was synthesised using SWiM guidelines.

Results. Ibuprofen affects seizures by reducing the number, grade, and duration of seizure intensity in the PTZ-induced rats. Despite the risk of bias assessment revealing some potential bias in the studies, our study shows that ibuprofen has potency as an additional agent for epileptic seizures among febrile convulsive patients.

Conclusion. In animal models of seizures, ibuprofen has an antiseizure effect by reducing the number, grade, and duration of seizures.

Key words: antiseizure • epilepsy • ibuprofen • neuroinflammation

INTRODUCTION

Epileptic seizure (ES) is a transient period of signs and symptoms due to the abnormal excessive and synchronous neuronal activity in the brain. The prevalence of ES is approximately 8 to 10% of the population; furthermore, about 2 to 3% of ES develop epilepsy, defined as a brain disease characterised by recurrent unprovoked seizures as a result of paroxysmal neuronal detachment from abnormally excited neurons with the

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consequence of the negative impact on quality of life, emotional wellbeing, daily function, and productivity of the patients and their caregivers (WHO, 2017; 2019). The key management of ES is to abort the seizure by administering anti-seizure medication (ASM). Although there are several agents for the treatment of ES, it is still issues regarding the use of ASM agents, such as allergy, the availability of drugs, and also the failure of treatment (WHO, 2017), resulting in the challenge of identifying a new agent that has the potency of antiseizure including the role of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Rawat et al., 2019; Vezzani et al., 2019). Nowadays, there are few studies regarding the antiseizure effect of ibuprofen despite being widely used as an NSAID. So herewith, we demonstrate the systematic review of the anti-seizure effect of ibuprofen to get a better understanding of the potency of ibuprofen for the additional ASM.

MATERIALS AND METHODS

A systematic review using the keywords "ibuprofen" and ("anticonvulsant", or "antiseizure" or "epileptic", "epilepsy", or "neuroinflammation") in the ScienceDirect, SpringerLink, Nature, and Pubmed databases was conducted. The search was specific to studies published between 2012 and 2022, which used animals as subjects and didn't use other anti-inflammation drugs. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist and Synthesis Without Meta-Analyses (SWiM) guidelines were used as the study's protocols (Page et al., 2020; Campbell et al., 2020). The results were compiled, and duplicates were removed using Mendeley Desktop; then, titles and abstracts underwent screenings. To determine their eligibility and relevance to the topic, articles that made it past the initial screening underwent a thorough screening that involved reading the full text of the article. Articles eligible for data synthesis were included in the study.

In total, 1376 articles were found from the database search results. Before conducting the first round of screening, 194 duplicates were removed using the "Check for Duplicates" tool in the Mendeley Desktop application. In the initial screening, 1182 articles were screened by looking at the title, abstract, or keyword.

For the following reasons such as 1) The articles contained research done on humans; 2) The articles lacked the keywords used in the search, although keyword search has been utilised; and 3) the articles were evaluated subjects, resulting in the exclusion of 1156 articles. For instance, a study by Roberts and Chaney (2018) titled "Heparin-induced Thrombocytopenia" was deemed to have no relation to the review. After the initial screening, 26 articles were retrieved and further examined to ascertain whether they were eligible to be included in the review. These articles were continued, with some requiring further reading, such as the title "NSAIDs in the treatment and/or prevention of neurological disorders" by Khansari and Coyne (2012), which the reviewer deemed may still be included.

After in-depth reading, a total of 23 articles were not included in the review for the following reasons: 1) Four articles have their subject used unsuitable; for instance, the animal used was not a seizure model animal; 2) The in-depth article reading was subjectively deemed irrelevant by the reviewer because they felt it was not in accordance to the study; for instance, the article by Khansari and Coyne (2012) turned out to be a review article which slipped through the filter applied during the search. Only three articles were identified as eligible to be included in the data synthesis described in the PRISMA Flow Diagram (Fig. 1).

Using the systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias Tool, which consists of 10 questions, the quality of articles included in this study was appraised (Hooijmans et al., 2014). There were a total of 23 responses to each question item, with the options being Yes (Y), No (N), and Unclear (Un). The reviewer assessed objectively or subjectively by looking at the evidence from the article's sentences. The questions were organised into groups based on the questions. Items one, two, and three are grouped into selection bias; items four and five are grouped as performance bias; items six and seven are detection bias; item eight is attrition bias; item nine is reporting bias; and item 10 is other risk of bias. Some items have more than one question, so they are distinguished by letters; for instance, in item two, there were three questions: "a", "b", and "c".

The clinical outcomes were identified from three studies, including the occurrence of clinical seizures (latency, grade, duration of seizure, Racine convulsion score, first myoclonic jerk) as well interictal epileptiform discharges (spike, spine, slow wave), including spike percentage, amplitude of waves obtained from EEG recording.

The Local Research Ethics Committee approved this study, and the ethical clearance was obtained from

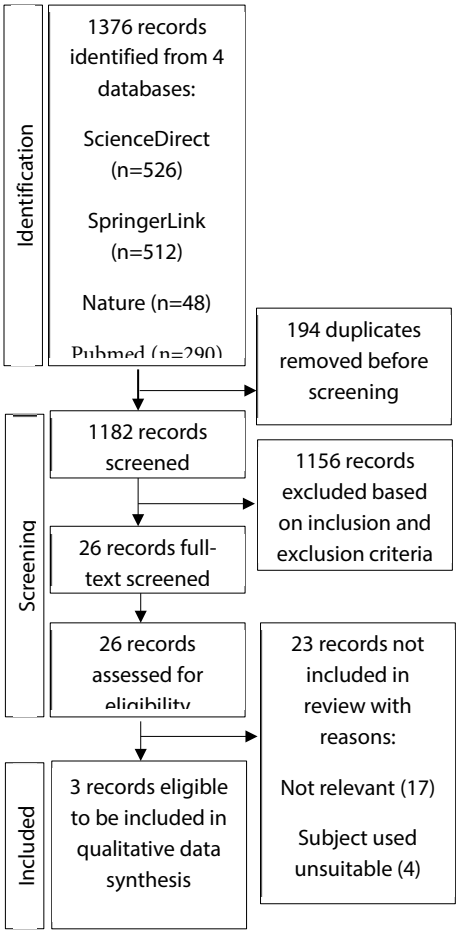


Figure 1. PRISMA Flow Diagram.

the Health Research Ethical Committee of the Faculty of Medicine Universitas Diponegoro Semarang Indonesia with the number of ethical clearance 47/EC/H/FK-UNDIP/VI/2022.

RESULTS

The SYRCLE Risk of Bias Tool was used to assess the risk of bias. Some potential biases were discovered, mostly in handling missing data and allocation concealment (Fig. 2). However, overall scores showed reliable evidence. The potential biases were believed to have a less likely impact on the experiment's outcomes (Hooijmans et al., 2014).

In the study conducted by Durankus et al. (2020), the formation of random sequences was considered unknown because the author did not explain the method used to randomise the allocation of subjects, only that they were written randomly in contrast to the study performed by Peng et al. (2022) and Liu et al. (2020), who wrote the sequence randomisation method using the random number table.

On the baseline characteristics, the subjects in the three studies attempted to have similar characteristics in each subject, starting from the gender of the rat and the weight in the specific range for the same rat species, so that question 2a was given the „yes" category. Meanwhile, the equalisation of unequal subject characteristics in question 2b was assessed as „no" because it was not carried out, and the reviewer evaluated that

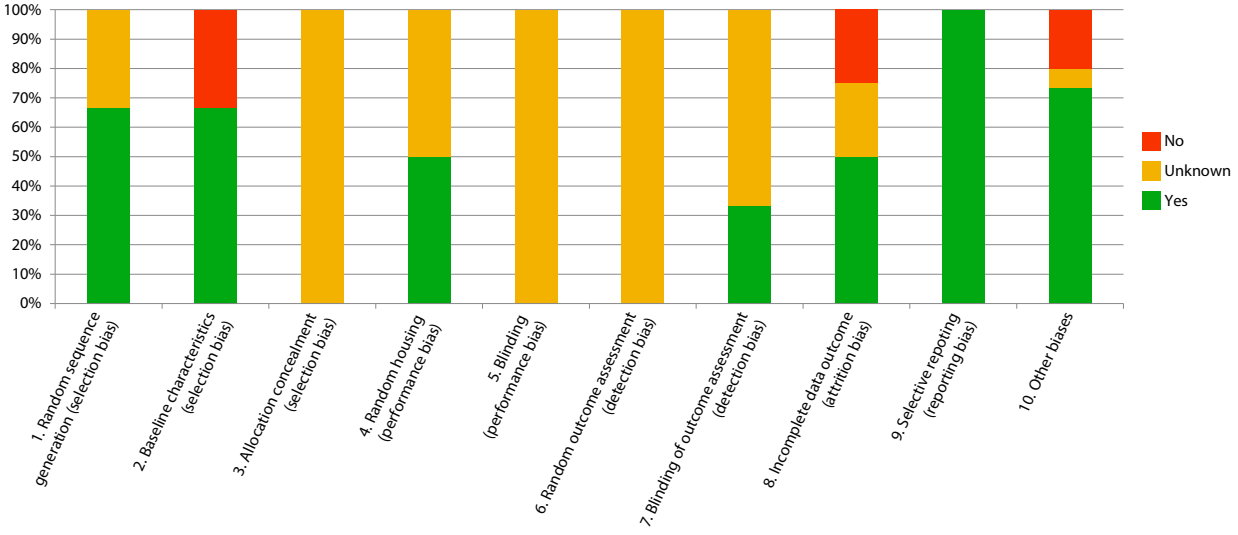


Figure 2. Summary of SYRCLE Risk of Bias Tool assessment.

Table 1. Summary of article selection results

No.	Author, year	Design	Samples	Intervention	Induction	Results
1.	Durankus et al., 2020	Experimental	48 male Sprague-Dawley rats	200 mg/kg and 400 mg/kg ibuprofen injection intraperitoneally 30 minutes before disease induction	Pentylenetetrazole 35 mg/kg intraperitoneally	Reduced spike percentage in EEG, Racine Convulsion Score and low first myoclonic jerk
2.	Peng et al., 2019	Experimental	60 male Sprague-Dawley rats	30 mg/kg ibuprofen injection intraperitoneally 30 minutes before disease induction	Pentylenetetrazole 35 mg/kg intraperitoneally	Reduced, number, grade, latency, shortened duration of seizures and number of small amplitude spikes and spine slow waves in EEG
3.	Liu et al., 2020	Experimental	64 male Sprague-Dawley rats	30 mg/kg ibuprofen injection intraperitoneally 30 minutes before disease induction	Pentylenetetrazole 35 mg/kg intraperitoneally	Reduced frequency, latency and duration of seizures

it was not necessary because the characteristics of the subjects had been equalised in the three studies. The induction of disease was also considered adequate with the equalisation of the time of disease induction in the treatment groups, so in question 2c, the value of „yes" was given to all three studies. In allocation concealment, the three studies did not specifically explain the existence of blindness during allocating subjects. Still, there was also no evidence that the researcher could see the allocation of subjects, so the value of unknown was given to the three studies.

None of the three studies explained random housing, but the reviewer felt that subject placement did not impact the study's findings; hence, questions 4a and 4b were answered with unknown values in all three studies. The researchers should have explained the blinding procedure, and there is no proof that the researchers were aware of the characteristics of the participants who received the intervention and those who had control, leaving the three studies with unknown answers.

The three studies did not provide a specific explanation for the randomised intervention outcome assessment in the random outcome assessment, so an unknown value was given. The blindness of the result taker is not explained by the blinding of the assessor when taking data. Still, the reviewer considered that the lack of blinding does not influence the results because specific indicators are applied when retrieving data. So, the unknown value was given in questions 7a and yes in 7b. Assessments on handling incomplete data were not described in all three studies but were considered complete data by the reviewer.

Regarding the selected reporting question items, the three studies answered all the questions and research objectives previously stated, so items 9a and 9b were given a yes value in all three studies. Meanwhile, the reviewer assesses other biases subjectively based on reading the articles.

The results of the selection of journals obtained from the ScienceDirect, SpringerLink, Nature, and Pubmed databases are collected into a table (Table 1), which contains the title, author, year, research design, number of samples in journals, interventions used, induction substances used, and results. In general, the three included articles covered 172 Sprague-Dawley rats. These three articles reported a decrease in the intensity of seizures in subjects who were given ibuprofen before inducing seizures with pentylenetetrazole (PTZ). Experiments were carried out in Turkey and China. The average subject weighs 200 to 300 grams and is 4–8 weeks old. Based on the data extracted and synthesised, it was found that ibuprofen could reduce the intensity of the seizure, showed from the amplitude of Electroencephalogram (EEG) was decreased in the ibuprofen+pentylenetetrazole (PTZ) group compared to PTZ only group (Durankus et al., 2020; Peng et al., 2022; Liu et al., 2020).

DISCUSSION

Ibuprofen is a non-specific NSAID drug that inhibits Prostaglandin (PG) synthesis on the cyclooxygenase (COX) enzyme (Goodman et al., 2018). Therefore, ibuprofen is usually used due to its anti-inflammatory, antipyretic, and analgesic effects. One seizure mechanism is excessive neuroinflammatory processes, which result in neuron hyperexcitability, making seizures appear unprovoked (Rawat et al., 2019).

Based on the data synthesis, it was found that ibuprofen reduced the seizures, which was shown by a reduced latency, grade, and duration of seizures as well as Racine convulsion score and first myoclonic jerk clinically and reduced spike percentage and lower amplitude in EEG recording them in a pentylenetetrazole (PTZ)-induced models which maybe correlate with the occurrence of seizures (Durankus et al., 2020; Peng et al., 2022; Liu et al., 2020). One study by Durankus et al. (2020) found that a 400 mg/kg dose had a greater effect on seizure intensity than a 200 mg/kg dose.

The mechanisms of antiseizure of ibuprofen are still unknown; one of the possibilities is through its anti-inflammatory effects. It is known that seizures can be induced by neuroinflammation. Ibuprofen inhibited PG synthesis, which played a role in the neuroinflammatory response aside from systemic inflammation. Other studies have also found that ibuprofen can help reduce neuroinflammation in different disease models, possibly contributing to reduced seizure.

A study conducted by Costa et al. (2021) demonstrated the combination of 1-Deoxynojirimycin and Ibuprofen reduced further degeneration due to microglia activation, which triggered neuroinflammation in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease models in mice.

Another study conducted by Zhang et al. (2018) also demonstrated that ibuprofen reduced proinflammatory cytokines in the brain, including Tumor Necrosis Factor-α (TNF-α) and Interleukin-1β (IL-1β) in a mouse Alzheimer's disease model.

While these articles gave results on the anticonvulsant effects of ibuprofen by decreasing the intensity of seizures, they did not provide the answer to whether ibuprofen could reduce the frequency of seizures in seizure animal models. Furthermore, an assessment by the SYRCLE Risk of Bias Tool showed the articles lacked detailed explanations when the intervention was carried out. It was not clear in some procedures, especially in random outcome assessment and blinding (Goodman et al., 2018).

The weakness of this review was the number of reviewers, which was only one. This could create a risk of bias when screening articles and a less accurate risk of bias assessment. Another area for improvement is that only three articles can be included. Hence, the direction of the research results still needs to be clarified, and further research is needed. However, it is also helpful for further research because it shows a knowledge gap between the theory and research.

CONCLUSION

This systematic review showed the potential of ibuprofen to treat seizures, including febrile seizures. Ibuprofen could reduce the intensity of seizures. This could be a good consideration for future clinical applications, but future research is needed to ascertain the anticonvulsant effects and application in a clinical setting.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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REFERENCES

WHO: *Public Health Imperative, E-book ed*. 2019;1. Available from: https://apps.who.int/iris/rest/bitstreams/1235662/retrieve

WHO: *Atlas: Country resources for neurological disorders*. 2017, 175–178 p. Available from: https://apps.who.int/iris/rest/bitstreams/1088639/retrieve

Campbell M., McKenzie J.E., Sowden A., Katikireddi S.V., Brennan S.E., Ellis S. et al.: *Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline*. BMJ, 2020, 368: 1–6. doi: 10.1136/bmj.l6890.

Costa T., Fernandez-Villalba E., Izura V., Lucas-Ochoa A., Menezes-Filho N., Santana R. et al.: *Combined 1-Deoxynojirimycin and Ibuprofen Treatment Decreases Microglial Activation, Phagocytosis and Dopaminergic Degeneration in MPTP-Treated Mice*. J. Neuroimmune Pharmacol., 2021, 16: 390–402. doi: 10.1007/s11481-020-09925-8.

Durankuş F., Şenkal E., Sünnetçi E., Albayrak Y., Beyazyüz M., Atasoy Ö. et al.: *Beneficial Effects of Ibuprofen on Pentylenetetrazol-induced Convulsion*. Neurochem. Res., 2020, 45: 2409–2416. doi: 10.1007/s11064-020-03101-3.

Goodman L.S., Gilman A. In: *Goodman & Gillman's The Pharmacological Basis of Therapeutics*. E-book 13th ed. **Brunton L.L., Hilal-Dandan R., Knollmann B.C. (eds.)** McGraw-Hill Education, 2018.

Hooijmans C.R, Rovers M.M., De Vries R.B.M., Leenaars M., Ritskes-Hoitinga M., Langendam M.W.: *SYRCLE's risk of bias tool for animal studies*. BMC Med. Res. Methodol., 2014, 14: 1–9. doi: 10.1186/1471-2288-14-43.

Khansari P.S., Coyne L.: *NSAIDs in the treatment and/or prevention of neurological disorders*. Inflammopharmacology Jun., 2012 p. 159–167. doi: 10.1007/s10787-011-0116-2.

Liu R., Wu S., Guo C., Hu Z., Peng J., Guo K. et al.: *Ibuprofen Exerts Antiepileptic and Neuroprotective Effects in the Rat Model of Pentylenetetrazol-Induced Epilepsy via the COX-2/NLRP3/IL-18 Pathway*. Neurochem. Res., 2020, 45: 2516–2256. doi: 10.1007/s11064-020-03109-9.

Page M.J,. McKenzie J.E., Bossuyt P.M., Boutron I., Hoffmann T.C., Mulrow C.D. et al.: *The PRISMA 2020 statement: An updated guideline for reporting systematic reviews*. BMJ, 2021, 372. doi: 10.1136/bmj.n71.

Peng J., Wu S., Guo C., Guo K., Zhang W., Liu R. et al.: *Effect of Ibuprofen on Autophagy of Astrocytes During Pentylenetetrazol-Induced Epilepsy and its Significance: An Experimental Study*. Neurochem. Res., 2019, 44: 2566–2576. doi: 10.1007/s11064-019-02875-5.

Rawat C., Kukal S., Dahiya U.R., Kukreti R.: *Cyclooxygenase-2 (COX-2) inhibitors: future therapeutic strategies for epilepsy management*. J. Neuroinflammation, 2019, 16: 197. doi: /10.1186/s12974-019-1592-3.

Roberts M.K., Chaney S.: *Heparin-induced Thrombocytopenia*. J. Nurse Pract., 2018, 14: 402-408.e3. doi: 10.1016/j.nurpra.2018.02.007.

Vezzani A., Balosso S,. Ravizza T. :*Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy*. Nat. Rev. Neurol., 2019, 15: 459–472. doi: 10.1038/s41582-019-0217-x

Zhang C., Qin H., Zheng R., Wang Y., Yan T., Huan F. et al.: *A new approach for Alzheimer's disease treatment through P-gp regulation via ibuprofen*. Pathol. Res. Pract., 2018, 214: 1765–1771. doi: 10.1016/j.prp.2018.08.011.