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Effect of celecoxib on improving depression: A systematic review and meta-analysis

Wang Z *et al*. Meta-analysis of celecoxib improving depresssion

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Abstract

BACKGROUND

Anti-inflammation drugs were uncovered to be the potential therapy of anti-depression. Celecoxib as a selective COX2 inhibitor is also one of anti-inflammation drugs. Celecoxib is widely used in the clinic, which is well known by medical workers. It is uncertain that celecoxib could have the efficacy on improving depression.

AIM

To estimate the effect of celecoxib on improving depression.

METHODS

All literatures were searched until 2022. The databases included PubMed, OVID database, Cochrane library, web of science, CNKI, Clinicaltrials.gov database and Wanfang database. Random-effects model was used to estimate the standardized mean differences with 95%CIs. With determined diagnostic criteria, studies containing patients with depression in celecoxib group and control group were included in the meta-analysis. The primary outcomes measures were set for depression scale scores.

RESULTS

Twenty-nine randomized controlled studies were included in the meta-analysis (including 847 subjects with depression and 810 control subjects). The meta-analysis showed that celecoxib had an effect of anti-depression. At the same time, heterogeneity was observed (I^2 = 82.1%, P = 0.00) and meta-regression was implemented to estimate the source of heterogeneity, which showed that type of depression scale and depression type may lead to the heterogeneity. Subgroup analysis with respect to depression scale and depression type suggested that depression type was the possible main source of heterogeneity. Moreover, egger test, begg test, funnel plot and doi plot was implemented and publication bias was found to be significant. Next, trim and fill method was used to estimate the influence of publication bias on the outcome of meta-analysis, which showed that the outcome of meta-analysis was reliable. Sensitivity analysis was estimated by deleting a study one by one and outcome of meta-analysis was significantly stable. Quality of all randomised controlled trial studies was assessed by risk of bias, which indicated the rank of evidence in the meta-analysis was high.

CONCLUSION

Celecoxib could be effective on improving depression.

Key Words: Celecoxib; Depression; Systematic review; Meta; Inflammation

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Core Tip: There is inconsistent about the efficacy of celecoxib improving depression. Owning to less clinical trials in the previous meta-analysis, this is an updated systematic review and meta-analysis by including more than 10 clinical trials. We compared the depression scale scores between celecoxib group and control group and celecoxib had a significant reduction in depression scale scores and could be effective on improving depression.

INTRODUCTION

Depression as a psychical disorder severely threatened human health and life quality. The World Health Organization reported that over 300 million people currently are living with depression in 2018[1]. Depression has a wide array of symptoms affecting somatic, cognitive, affective, and social processes[2]. Depression is closely associated with suicide[3]. In addition, depression is associated with morbidity and mortality of cardiovascular disease[4]. According to the number, type and severity of symptoms, depressive disorder was classified into mild, moderate and major depression generally. Depression disorder also includes bipolar depression. The pathology of depression is still uncovered so far. Recently, the relationship between inflammation and depression is paid more and more attention. Inflammation is likely a critical disease modifier, promoting susceptibility to depression[5]. Inflammation as a potential target in the treatment of depression was focused and more and more anti-inflammation drugs were explored to clarify the efficacy on improving depression.

Celecoxib as a COX2 inhibitor is one of anti-inflammation drugs. Celecoxib has an Food and Drug Administration indication for the management of acute pain in adult women and primary dysmenorrhea[6]. Celecoxib is widely used in the inflammation diseases such as rheumatoid arthritis and celecoxib is widely used in clinic. Due to its clinical popularity, celecoxib is well known by many doctors and patients. Interestingly, if celecoxib has the effect of anti-depression, it is very meaningful to uncover the new function in clinic. In fact, depression is often with other diseases especially inflammation diseases such inflammation bowel diseases[7]. From the view of anti-inflammation, it is necessary to explore the efficacy of anti-depression.

The efficacy of celecoxib on improving depression is inconsistent. Some studies showed celecoxib could improve depression[8,9]. On the contrary, a study showed that celecoxib was not superior to placebo for the treatment of bipolar depression[10]. A meta-analysis[11] about celecoxib on depression was published in 2014 and the number of randomised controlled trial (RCT) is only five. Another meta-analysis[12] in 2019 estimated the efficacy of celecoxib on bipolar depression and the number of RCT is only

three. Obviously, the number of RCT included in previous meta-analysis was not enough. So it is necessary to estimate the effect of celecoxib on depression by including more clinical trials. This meta-analysis was mainly to estimate whether celecoxib could improve depression including bipolar depression, major depression and so on.

MATERIALS AND METHODS

The meta-analysis was made up of four parts including search strategy, study selection, quality assessment, and data extraction and data synthesis.

Search strategy

Conducting and reporting meta-analysis data are strictly in accordance with PRISMA statement guidelines. PICOS scheme was followed in the selected studies. A systematic literature search was implemented by two persons (Zhi Wang and Qiao Wu). Retrieval fields included "celecoxib"、"celecreb"、"depression" and so on. Retrieval mode included basic retrieval and advanced retrieval. The process of retrieval was presented in Supplementary Table 1. We searched databases including PubMed, OVID database, Cochrane library, web of science, CNKI, Clinicaltrials.gov database and Wanfang database. There is no language restriction in the retrieval process. No restrictions about humans, clinical trials or RCT were used, aiming at promising the comprehensiveness of retrieval. In addition, we retrieved the references using the Reference Citation Analysis database. For searching all databases, the latest time is until 2022.

Study selection

Studies that reported celecoxib and depression were screening.

Inclusive criteria: (1) randomized controlled trials included celecoxib group and control group; (2) with determined criteria, patients were diagnosed with depression including bipolar depression or unipolar depression or major depression and so on; (3) patients diagnosed with depression were along with other non-mental diseases such as cancer and so on.

Exclusive criteria: (1) with the diagnostic depression, patients were also diagnosed with other mental diseases such as Alzheimer's disease and so on; (2) clinical trials lack of control group were excluded; (3) case reports, letters, editorials, and conference abstracts were excluded; (4) data about depression scores could be not obtained.

To get more relevant studies, the references were also searched. According to the PRISM literature-searching method, the primary inclusions were obtained through scanning titles and abstracts. Then, the full texts were screened carefully. Two researchers (Zhi Wang and Qiao Wu) searched the literatures and determined the selected studies independently. The final inclusions were decided through consultations.

Quality assessment

Basing on the Cochrane Handbook for Systematic Reviews, risk of bias was used to evaluate the quality of all selected studies. Bias evaluation was conducted by estimating 7 items including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment, incomplete outcome data (attrition bias), selection reporting (reporting bias) and other bias. All selected studies were evaluated according to above 7 items. Finally, risk of bias graph and risk of bias summary plot are plotted by RevMan 5.3 software.

Data extraction and data synthesis

All data was extracted from all selected studies. A standardized data extraction form was used: name of the first author, year of publication, diagnostic criteria, study design, number of the celecoxib group and control group, type of depression scale, depression scale scores in celecoxib group and control group. If the clinical trial included multiple treatment groups (different intervention), we only extracted data about the celecoxib and control group. Based on the Cochrane Handbook for Systematic Reviews, if the clinical trial contained different doses and intervention periods, the trial will be divided

into different trials with the same control group. The process of abstraction was administered by two persons (Zhi Wang and Qiao Wu). Two persons are in agreement with the outcome of extraction.

We collected data including mean ± SD, and *n* from selected studies. If the study provided mean ± SEM, data transformation would be implemented by formulas: SD = SE × square root *n*.

Statistical analysis

All processes included forest plots, meta-regression analysis, funnel plot and egger tests were finished by STATA 16. Heterogeneity was assessed by the Cochran's Q statistic and the I^2 score. Heterogeneity was divided into homogeneity, moderate heterogeneity and high heterogeneity by I^2 values of 0%-25%, 25%-50% and > 50% respectively. If heterogeneity was significant, random-effects model was applied to estimate the standardized mean differences (SMDs) with 95% CIs. Meta-regression and galbraith plot were used to find the source of heterogeneity. With I^2 values less than 50%, heterogeneity was considered to be small and fixed-effects model was used.

RESULTS

Characteristics of the included studies and assessment of quality

Total 825 potentially relative records which were the sum of each database mentioned in the Search Strategy were identified. After screening the titles, 338 duplicates were removed. 474 records (review or meta-analysis, 71; animal experiment, 67; case report or letters, 19; no relationship or others, 317) were removed and 13 records were obtained after screening the abstract. Because we could not obtain the raw data, three articles[13-15] were removed. Then, 10 records[8-10,16-22] were included into the meta-analysis. Except a study[19], other studies were divided into separate studies according to different period of therapy. Finally, 29 studies were included in the meta-analysis. All procedures were shown in Figure1. The baseline characteristics in all included studies were presented in Supplementary Table 2. Twenty-nine case-control studies included

847 subjects in celecoxib group and 810 subjects in control group. Study type of all studies was RCT. Major matched factors for celecoxib group and control group were mainly composed of publication year, diagnostic criteria, depression type, period of therapy, design of experiment group, design of control group, dose of celecoxib, depression scale. Basing on risk of bias graph and risk of bias summary plot, quality of all studies is high, which is shown in Figure 2. All data was shown as mean ± SD. Results of some studies were shown as mean ± SEM. SEM was transformed into SD according to sample size and SEM.

Meta-analysis

All data of 29 studies was pooled in the meta-analysis. The outcome was shown in the forest plot (Figure 3). The depression scores in celecoxib group was significantly lower than control group (SMD = -0.49, 95%CI: -0.74 to -0.25, $P < 0.05$). Heterogeneity was observed to be severe ($I^2 = 82.1\%$ and $P < 0.001$) and random-effect model was applied.

Meta regression

A multivariate meta-regression analysis was used to estimate the source of heterogeneity. We conducted meta-regression including 3 aspects (study design, depression scale and depression type). The results showed that depression scale (regression coefficient: 0.268; $P = 0.016$; 95%CI: 0.054-0.483) and depression type (regression coefficient: 0.157; $P = 0.020$; 95%CI: 0.027-0.287) are the possible main source of heterogeneity.

Subgroup analysis

After meta-regression, subgroup analysis about depression scale and depression type was implemented to identify the possible source of heterogeneity (Figure 4 A and B). Heterogeneity in subgroup analysis about depression type was decreased, which showed that depression type may be the main source of heterogeneity. Moreover,

subgroup analysis about period of therapy was plotted (Figure 4 C), which indicated that celecoxib could improve depression whatever period is ≤ 4 wk or > 4 wk.

Sensitivity analysis

Sensitivity analysis was conducted by deleting a study one by one and outcome of meta-analysis was significantly stable.

Publication bias

Funnel plot (Figure 5A), egger test (Figure 5B), begg test (Figure 5C) and doi plot (Figure 5D) were implemented to estimate publication bias. Funnel plot, egger test, begg test and doi plot showed publication bias was significant. Further, trim and fill method was used to estimate the influence of publication bias on the outcome of meta-analysis. The result of trim and fill method (SMD = -0.679, 95%CI: -0.961 to -0.398, $P <$ 0.01) indicated the outcome of meta-analysis was reliable.

DISCUSSION

The result of meta-analysis showed that celecoxib could improve depression. Depression type in all studies was different. The meta-analysis was only to estimate the efficacy of celecoxib on depression generally. Meta-analysis of celecoxib was deserved to be implemented about a specific type of depression in the future when the number of RCT studies are enough. In this meta-analysis, publication bias was significant. The result of trill and fill method showed this meta-analysis was still reliable. Obviously, heterogeneity was significant and depression scale and depression type were the main source of heterogeneity by meta-regression and subgroup analysis. The result of meta-analysis was probably interpreted by obvious heterogeneity. More studies should be included in meta-analysis to reduce the heterogeneity.

The result indicated the anti-inflammation may be the potential target of anti-depression. Celecoxib, a COX2 inhibitor and one of non-steroidal anti-inflammatory drugs, was used in the clinic generally. Other non-steroidal anti-inflammatory drugs

are supported to be effective on improving depression in some studies[23,24]. Extensive studies have confirmed the proinflammatory status in depression and causal relationships with neurotransmitter dysregulation[25]. On the contrary, a trail failure of anti-inflammation drugs in depression was published in 2020[26]. According to the trial failure, the authors replied and indicated that drug's selection and certain inflammation status in depression status were the necessary consideration. This meta-analysis did not estimate the inflammation status for celecoxib in depression owning to lack of inflammation data in most studies. So the relationship between inflammation and depression for celecoxib needed to be analyzed in the future furthurly. Celecoxib on improving depression along with determined inflammation status should be estimated in the subsequent work. On the other hand, not all depression patients co-exist with abnormal inflammation level. Aiming to these depression patients without abnormal inflammation, it is probable that celecoxib could not improve depression. Of course, above issues are the weaknesses in the meta-analysis. So far, there are not enough researches to support the meta-analysis about celecoxib on improving depression with inflammation status or without inflammation status respectively, which is also the possible source that caused the heterogeneity. Comparing with other anti-inflammation drug such as aspirin, there is lacking a comparison about better efficacy on improving depression. Before comparing the efficacy between celecoxib and other anti-inflammation drugs on improving depression, the issue whether inflammation status or non-inflammation status are associated with the efficacy of anti-inflammation should be resolved. If the issue was not resolved, the result of comparison between celecoxib and other anti-inflammation drug is not probably credible.

The relationship between inflammation and depression was explored by more and more researches. Inflammation is usually a reflection of cell damage caused by infections, physical injury or the response of tissues to an antibody challenge[27]. However, it has become apparent that psychological stress can also initiate the inflammatory response, thereby linking inflammation to both physical and mental ill health recently[27]. Inflammosone complex is expressed in microglia located in the

hippocampus and other mood regulating regions that are particularly vulnerable to the effects of chronic stress, which was probably linked to depression[27]. Stress plays a critical role in depression ultimately leading to pervasive mental status changes, chronic low-grade inflammatory reaction[25]. Stress-induced activation of the immune response alters neurotransmission leading to neurotransmitter imbalances such as serotonergic deficiency, which was the possible mechansim of inflammation and depression[25]. Interestingly, inflammation plays a key role in depression's pathogenesis for a subset of depressed individuals[28]. Furtherly, bidirectional relationship between inflammation and depression was mentioned. Depression can promote intestinal permeability, that is, greater inflammation-inducing endotoxin translocation, described as a "leaky gut" and inflammatory mediators can also induce clinical depression[28]. So mechanism pathway between inflammtion and depression was so complex. Other factors such as gut microbiota, stress and so on can also participate in the complex net of inflammation and depression. The complex relationship and mechanism of inflammation and depression needed more evidences to be uncovered in the future.

Moreover, dose of celecoxib in depression was deserved to explore. 400 mg/d celecoxib was described in nearly all RCT studies included in the meta-analysis. No gradient of dose for celecoxib could be explored in this meta-analysis. So more studies about different dose of celecoxib should be included to estimate the relationship between dose and depression for celecoxib. Safety of celecoxib was not mentioned in the meta-analysis owning to less description in the primary RCT. All in all, celecoxib is probably effective on improving depression. Weakness mentioned in the above context needed to be resolved in the future work.

CONCLUSION

In summary, the results of this meta-analysis demonstrated that celecoxib could be effective on improving depression. Depression scale scores in celecoxib group were less than control group. For depression with or without inflammation, the efficacy of celecoxib on improving depression needs to be estimated respectively in the future.

ARTICLE HIGHLIGHTS

Research background

There is inconsistent about the efficacy of celecoxib on improving depression.

Research motivation

To estimate the efficacy of celecoxib on improving depression.

Research objectives

To provide more evidences to support the efficacy of celecoxib on improving depression.

Research methods

The meta-analysis was pooled.

Research results

Depression scores in celecoxib group were lower than control group.

Research conclusions

Celecoxib has an effect on improving depression.

Research perspectives

The meta-analysis was explored from the view of COX2 selective inhibitor, an anti-inflammation drug.

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