Effectiveness of montelukast for uremic pruritus in hemodialysis patients
A protocol for systematic review and meta-analysis

Chao-qing Gao, MB, Jia-jun Zhou, MD, Ya-yin Tan, MM*, Chang-jun Tong, MM

Abstract

Background: Uremic pruritus (UP) is a common and tormenting symptom in end-stage renal disease patients undergoing maintenance hemodialysis. An increasing number of studies have been published in recent years to support the effectiveness of montelukast for UP. We will conduct a comprehensive systematic review and meta-analysis to evaluate effectiveness of montelukast for UP in hemodialysis patients.

Methods: The following electronic databases were searched: Pubmed, Embase, Web of Science, Cochrane Library, the China National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database. The range of publication time was from the inception of the database to December 2020. Two reviewers will independently conduct article selection, data collection, and assessment of risk of bias. Any disagreement will be resolved by discussion with the third reviewer. Meta-analysis will be performed by Review Manager 5.3. The Cochrane Collaboration tool will be used to assess the risk of bias.

Results: This study will provide a systematic synthesis of current published data to explore the effectiveness of montelukast for UP in hemodialysis patients.

Conclusions: This systematic review and meta-analysis will provide clinical evidence for the effectiveness of montelukast for UP in hemodialysis patients and inform our understanding of the value of montelukast in improving pruritus symptoms. This study will help clinicians, patients, and policy makers to make better decisions regarding the appropriate role of montelukast as a part of patient management routines.

Study registration number: INPLASY2020100043.

Abbreviation: UP = uremic pruritus.

Keywords: hemodialysis, montelukast, protocol, systematic review, uremic pruritus

1. Introduction

Uremic pruritus (UP) is a common and tormenting symptom in end-stage renal disease patients undergoing maintenance hemodialysis. The prevalence of UP in maintenance hemodialysis patients is 22% to 90%. It affects patients’ life quality, emotional state, social relations, and increases mortality. One study reported that UP was associated with two-year cardiovascular mortality in long term hemodialysis patients, and was 1 of the predictors of 24-month cardiovascular mortality in maintenance hemodialysis patients. The pathogenesis of UP remains obscure. Parathormone and histamine have been reported as possible mediators of UP. Parathyroidectomy can improve persistent pruritus in some secondary hyperparathyroidism patients. One study showed that plasma histamine levels in pruritic patients undergoing continuous ambulatory peritoneal dialysis were higher than in nonpruritic patients, and during ondansetron treatment, the severity of pruritus and plasma histamine levels were improved significantly.

Daily topical emollients such as tacrolimus ointments, gamma linolenic acid ointment should be regarded as baseline therapy. Ointment strongly improved pruritus during treatment period, while pruritus rose back to baseline values within days after end of treatment. Hence the addition of systemic therapy is necessary. It mainly contains μ-opioid receptor antagonists (naltrexone), κ-opioid receptor agonists (nalfurafine), gabapentin, pentoxifylline, thalidomide and so on. Treatment has been mainly empirical, and the efficacy of therapies is often insufficient to provide adequate relief of UP in hemodialysis patients.

Montelukast is a leukotriene receptor antagonist that has been used in asthma, eosinophilic peritonitis, atopic dermatitis and allergic rhinitis. Intradermally injected leukotriene B4
could provoke scratching in mice, and high urinary leukotriene E4 levels were connected with itch nightly.\textsuperscript{[21]} It can be seen that leukotriene can cause pruritus. Montelukast can suppress the expression of inflammatory mediators such as substance P that acts as a neurotransmitter in UP.\textsuperscript{[22]} These can explain the antipruritic effect of montelukast for UP. An increasing number of studies have been published in recent years to support the antipruritic effect of montelukast for UP.\textsuperscript{[23,24]}

Up to now, no systematic review and meta-analysis has been performed on the effectiveness of montelukast for UP in hemodialysis patients. In view of this, we will conduct a comprehensive systematic review and meta-analysis to evaluate effectiveness of montelukast for UP in hemodialysis patients.

2. Methods

2.1. Study registration

This study has been registered on INPLASY (INPLASY2020100043). This systematic review and meta-analysis will be performed under the guide of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement checklist.\textsuperscript{[25]}

2.2. Eligibility criteria

2.2.1. Types of studies. Randomized controlled trials of montelukast for UP in hemodialysis patients will be considered for inclusion without language limitation. The included trials were required to contain statistical methods and accurate data. Duplicate studies, animal experiments, reviews or case reports were excluded.

2.2.2. Types of participants. Hemodialysis patients with UP will be included without restrictions of the nationality, age, gender, and race.

2.2.3. Types of interventions. In the treatment group, patients were given montelukast with no limitations of dosage and duration of intervention. Randomized controlled trials that have control groups with conventional medication treatments or placebo will be included.

2.2.4. Types of outcomes. Pruritus severity as assessed using a visual analog scale, and the Detailed Pruritus Scale will be designated as the primary outcomes. Secondary outcome will included adverse events due to the medication.

2.3. Search strategy

The following electronic databases were searched: Pubmed, Embase, Web of Science, Cochrane Library, the China National Knowledge Infrastructure, Chinese Biomedical Literature Database, and China Science and Technology Journal Database. The range of publication time was from the inception of the database to December 2020. The detailed search strategy for PubMed is shown in Table 1. The similar search strategies will be used for other electronic databases.

2.4. Selection of studies

All searched articles will be imported into EndNote 7.0 software, and duplicates will be excluded by software. After removing duplicates, 2 reviewers will independently evaluate all the eligible articles for inclusion. Titles and abstracts will be scanned to eliminate all irrelevant records. The remaining records will be read by full texts in further assessing the inclusion of the study. Any disagreement will be resolved by discussion with the third reviewer. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart will be designed to describe the details of selection process.

2.5. Data extraction and management

After selection, 2 reviewers will independently conduct data extraction. Any disagreement will be resolved by discussion with the third reviewer. The following information was extracted independently by reviewers: author’s name, publication year, country, title of journal, study design, sample sizes, treatment and control intervention and outcome measures. If some important information is missing, we will contact original authors by email to request detailed information.

2.6. Assessment of risk of bias

The Cochrane Collaboration tool will be used to assess the risk of bias of the selected studies. The following aspects were assessed independently by 2 reviews: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Disagreements were analyzed by the third reviewer.

2.7. Data synthesis and analysis

2.7.1. Data synthesis. Data synthesis will be performed by Review Manager 5.3. Continuous outcomes will be used for mean difference with 95% confidence interval. Risk ratio will be

| Table 1 |
| --- |
| Search strategy of PubMed. |
| Number | Search terms |
| 1 | pruritus |
| 2 | itch |
| 3 | uremic pruritus |
| 4 | Or 1–3 |
| 5 | end-stage renal disease |
| 6 | uremia |
| 7 | toxuria |
| 8 | chronic kidney disease |
| 9 | chronic renal failure |
| 10 | Or 5–9 |
| 11 | hemodialysis |
| 12 | renal dialysis |
| 13 | continuous renal replacement therapy |
| 14 | Or 11–13 |
| 15 | montelukast |
| 16 | montelukast sodium |
| 17 | leukotriene antagonists |
| 18 | Or 15–17 |
| 19 | Randomized controlled trial |
| 20 | Clinical trial |
| 21 | Random |
| 22 | Randomized |
| 23 | Randomly |
| 24 | Trial |
| 25 | Placebo |
| 26 | Or 19–25 |
| 27 | 4 and 10 and 14 and 18 and 26 |
used for dichotomous outcomes with 95% confidence interval. Heterogeneity will be examined using the I² test. If the I² value > 50%, the random effects model will be used. Otherwise, the fixed effects model will be utilized. If significant heterogeneity still exists after subgroup analysis, descriptive summary will be reported.

2.7.2. Subgroup analysis. If included studies have greater heterogeneity, subgroup analysis will be conducted to explore potential sources of heterogeneity. Subgroup analysis will be divided by different participant characteristics, disease course, controls, interventions and outcome measures.

2.7.3. Sensitivity analysis. Sensitivity analysis will be applied to check the robustness and reliability of pooled results made in the review process. We will perform meta-analysis again after deleting low-quality studies and apply different statistical methods.

2.7.4. Reporting bias. If there are enough trials (≥10 trials) for meta-analysis, we will evaluate the reporting bias with funnel plot and Egger regression analysis.[26,27]

2.8. Ethics and dissemination

The ethics approval is not necessary because the data are extracted from the published literature and they are not related to the individual patient’s data. The results of this systematic review and meta-analysis will be published in a peer-reviewed journal.

3. Discussion

To our knowledge, this is the first systematic review and meta-analysis to conduct a comprehensive literature search and provide a systematic synthesis of current published data to explore the effectiveness of montelukast for UP in hemodialysis patients. Seven electronic literature databases will be searched to avoid missing any potential eligible studies, and rigorous methodology will be applied to examine studies reporting montelukast for UP in hemodialysis patients. We believe that this systematic review and meta-analysis will provide clinical evidence for the effectiveness of montelukast for UP in hemodialysis patients and inform our understanding of the value of montelukast in improving pruritus symptoms. This study will help clinicians, patients, and policy makers to make better decisions regarding the appropriate role of montelukast as a part of patient management routines.

Author contributions

Conceptualization: Chao-qing Gao, Ya-yin Tan.
Data curation: Chao-qing Gao, Jia-jun Zhou.
Formal analysis: Jia-jun Zhou, Ya-yin Tan.
Investigation: Jia-jun Zhou, Ya-yin Tan.
Methodology: Chao-qing Gao, Jia-jun Zhou, Chang-jun Tong.
Project administration: Ya-yin Tan.
Resources: Chao-qing Gao, Jia-jun Zhou, Ya-yin Tan.
Software: Jia-jun Zhou, Chang-jun Tong.
Supervision: Chao-qing Gao, Jia-jun Zhou, Ya-yin Tan.
Validation: Ya-yin Tan.
Visualization: Chao-qing Gao, Jia-jun Zhou, Chang-jun Tong.
Writing – original draft: Chao-qing Gao, Jia-jun Zhou.
Writing – review & editing: Chao-qing Gao, Jia-jun Zhou, Ya-yin Tan, Chang-jun Tong.

References

[1] Combs SA, Teixeira JP, Germain MJ. Pruritus in kidney disease. Semin Nephrol 2015;35:383–91.
[2] Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. J Am Soc Nephrol 2000;11:314–9.
[3] Kimata N, Fuller DS, Saito A, et al. Pruritus in hemodialysis patients: results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). Hemodial Int 2014;18:637–67.
[4] Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2006;21:3495–505.
[5] Satti MZ, Arshad D, Javed H, et al. Uremic pruritus: prevalence and impact on quality of life and depressive symptoms in hemodialysis patients. Cureus 2019;11:e5178.
[6] Shurazian S, Kline M, Sakhiya V, et al. Longitudinal predictors of uremic pruritus. J Ren Nutr 2013;23:428–31.
[7] Weng CH, Hu CC, Yen TH, et al. Uremic pruritus is associated with two-year cardiovascular mortality in long-term hemodialysis patients. Kidney Blood Press Res 2018;43:1000–9.
[8] Massry SG, Popovtzer MM, Coburn JW, et al. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. N Engl J Med 1968;279:697–700.
[9] Zhou FF, Ho JC, Huang SC, et al. A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. J Am Coll Surg 2000;190:65–70.
[10] Balaskas EV, Bamihas GI, Karamouzis M, et al. Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. Nephron 1998;78:395–402.
[11] Kuyper DS, Claes KE, Evenepoel P, et al. A prospective proof of concept study of the efficacy of tacrolimus ointment on uremic pruritus (UP) in patients on chronic dialysis therapy. Nephrol Dial Transplant 2004;19:1895–901.
[12] Pauli-Magnus C, Klumpp S, Alscher DM, et al. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. Perit Dial Int 2000;20:802–3.
[13] Legroux-Crespel E, Cledes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. Dermatology 2004;208:326–30.
[14] Nakao K, Machuzuki H, Nalfurafine hydrochloride: a new drug for the treatment of uremic pruritus in hemodialysis patients. Drugs Today (Barc) 2009;45:323–9.
[15] Eusebio-Alpapara KM, Castillo RL, Dofitas BL. Gabapentin for uremic pruritus: a systematic review of randomised controlled trials. Int J Dermatol 2020;59:412–22.
[16] Simonsen E, Komenda P, Lerner B, et al. Treatment of uremic pruritus: a systematic review. Am J Kidney Dis 2017;70:638–55.
[17] Kouwenhoven TA, van der Kerkhof PCM, Kamsteeg M. Use of oral antidepressants in patients with chronic pruritus: a systematic review. J Am Acad Dermatol 2017;77:1068–73.
[18] Glickler-Lauf SD, Finkelstein Y, Zhu J, et al. Montelukast and neuropsychiatric events in children with asthma: a nested case-control study. J Pediatr 2019;209:176–82.
[19] Forbes TA, Lunn AJ. Montelukast: a novel therapeutic option in eosinophilic peritonitis. Pediatr Nephrol 2014;29:1279–82.
[20] Chin WK, Lee SWH. A systematic review on the off-label use of montelukast in atopic dermatitis treatment. Int J Clin Pharm 2018;40:963–76.
[21] Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. Allergy 2010;65:805–21.
[22] Schmidt R, Staats P, Groneberg DA, et al. Effect of montelukast on platelet activating factor- and tachykinin induced mucus secretion in the rat. J Occup Med Toxicol 2008;3:5.
[23] Nasrollahi AR, Miladpour A, Ghanie E, et al. Montelukast for treatment of refractory pruritus in patients on hemodialysis. Iran J Kidney Dis 2007;1:73–7.
[24] Mahmudpour M, Rouzbah J, Rass Jalali GA, et al. Therapeutic effect of montelukast for treatment of uremic pruritus in hemodialysis patients. Iran J Kidney Dis 2017;11:50–5.
[25] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[26] Allen RP. Restless leg syndrome/Willis-Ekbom disease pathophysiology. Sleep Med Clin 2015;10:207–14.
[27] Trotti LM. Restless legs syndrome and sleep-related movement disorders. Continuum 2017;23:1005–16.