PUBLICATIONS

Articles published:

1) **Ramasubbu MK**, Maji S, Padhan M, Maiti R, Hota D, Majumdar SKD, Srinivasan A. Chemotherapy-induced hand foot syndrome: comparative efficacy and safety of pharmacological prophylaxis - systematic review and Bayesian network meta-analysis. BMJ Support Palliat Care. 2022 Dec 23: spcare-2022-004011. doi: 10.1136/spcare-2022-004011. Epub ahead of print. PMID: 36564149

Book Chapter:

1) **Ramasubbu MK**, Kumar R, Paleja B, Srinivasan S, et al. Introduction to QSP – Quantitative systems pharmacology for Indian clinical Pharmacologists. 4th ed. Rituparna Maiti's Postgraduate Topics in Pharmacology 2023. Paras Medical Books (India).

Articles under consideration:

1) Shaikh Z, **Ramasubbu MK**, Sarkar S, et al. The study of drug utilisation and disease recurrence in patients with COVID Mucormycosis (CAM) on Posaconazole step-down therapy: an ambispective study. Authorea. 2022 Oct 18.
2) Maji S, Mishra A, **Ramasubbu MK**, et al. Efficacy and safety of monoamine reuptake inhibitors in attention deficit hyperactivity disorder: A Bayesian network meta-analysis. Brazilian Journal of Psychiatry.
3) **Ramasubbu MK** , Hota D, DasMajundar SK, et al.Add-on olanzapine plus pregabalin for the prevention of chemotherapy-induced nausea and vomiting: A Group Sequential Response-Adaptive Randomized Double-Blinded Clinical Trial. International Journal of Cancer
4) Sahoo A, Jain M, …, **Ramasubbu MK**. Does indirect decompression by oblique lateral interbody fusion produce similar clinical and radiological outcomes to direct decompression by open transforaminal lumbar interbody fusion. Journal of Neurosciences in Rural Practice
5) Velayutham, Bakialakshmi,…**Ramasubbu M,** et al. Immunohistochemical expression of perforin in adult systemic lupus erythematosus associated macrophage activation syndrome: clinicohematological correlation and literature review. Lupus

Research projects completed/ undergoing.

1) A factorial 2*2 randomized double-blinded clinical trial to evaluate the interaction between pregabalin and olanzapine for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapeutic regimens in a daycare setting.

Publication 1.pdf

Publication 2.pdf

Chemotherapy-induced hand foot syndrome: comparative efficacy and safety of pharmacological prophylaxis – systematic review and Bayesian network meta-analysis

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ABSTRACT

Background Hand-foot syndrome (HFS) is one of the most common toxicities experienced by patients receiving systemic chemotherapy agents such as capecitabine and multikinase inhibitors such as sorafenib. Several randomised controlled trials (RCTs) have investigated the efficacy and safety of prophylactic agents such as pyridoxine, celecoxib, urea cream and cystine/theanine in managing HFS. This network meta-analysis (NMA) evaluated data from high-quality trials to provide strong evidence in forming recommendations to prevent systemic cancer therapy-induced HFS.

Objective To examine the comparative efficacy and safety of interventions for preventing systemic chemotherapy-induced HFS in patients with cancer.

Methods We searched PubMed, Embase and clinical trial registry for RCTs of interventions for preventing HFS. Bayesian NMA was performed to estimate the OR with 95% credible intervals (CrI) from both direct and indirect evidence. The outcome measures were the incidence of HFS (grade ≥1) and moderate to severe HFS (grade ≥2). Adverse drug reactions were discussed descriptively.

Results A total of 15 RCTs with 2715 patients with 12 prophylactic strategies were included. The analysis showed only celecoxib could significantly prevent the incidence of moderate to severe HFS (grade ≥2) (OR 0.29, 95% CrI 0.13 to 0.68). But none of the preventive interventions could prevent the incidence of HFS (grade ≥1).

Conclusion Only celecoxib (200 mg two times per day) showed significant prevention of the incidence of moderate to severe HFS. Pyridoxine (400 mg once daily) and urea cream (10%) have to be evaluated further in larger randomised trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is no well-established standard of treatment for the prevention of hand-foot syndrome (HFS) induced by cancer chemotherapy, and network (Bayesian) meta-analysis can help in establishing the same.

WHAT THIS STUDY ADDS

⇒ Oral celecoxib 200 mg two times per day showed a significant reduction in the incidence of HFS due to cancer chemotherapy in the network meta-analysis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Urea cream and high-dose pyridoxine should be further evaluated in larger clinical trials as both agents had better surface under the cumulative ranking scores in our network meta-analysis.

INTRODUCTION

With the advancement of systemic chemotherapy, the survival period of patients with cancer has increased. However, due to the prolonged exposure to chemotherapy agents, patients face toxicity of chemotherapy agents. Hand-foot syndrome (HFS) is one of the most common toxicities experienced by patients receiving specific systemic chemotherapy agents.[1] The most common agents causing HFS are capecitabine, cytarabine, docetaxel,

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doxorubicin, 5-fluorouracil, pegylated liposomal doxorubicin, sorafenib and sunitinib.[2]

HFS is dose-dependent toxicity.[1] Hence for the patients experiencing this toxicity, physicians have to reduce the dose or remove the agent as a definite treatment of choice, but that will cause therapeutic failure and affect the survival of the patients. The literature search found that multiple prevention strategies have been tested in various randomised controlled trials (RCTs), but no clear strategy has been devised for the prevention of HFS. The recent meta-analysis by Pandy *et al*[3] suggested that urea cream and celecoxib are both effective in preventing HFS in patients receiving systemic cancer chemotherapy. However, no overall (direct and indirect) evidence has been generated from RCTs comparing different preventive agents used to manage HFS in patients receiving cancer chemotherapy. We have used multiple treatment Bayesian network meta-analyses (NMAs) to provide a valuable summary for guiding clinicians in their decision-making process to prevent the incidence of HFS. NMA combines information from all direct and indirect sources of evidence to compare various therapeutic choices. A network graph used in NMA comprises nodes that indicate interventions, and edges that connect the nodes signify direct comparisons. A weighted representation of the strength of the available evidence is provided by the node's size and the thickness of the lines on the edges.

METHODS

Development and registration of protocol

The standard NMA protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines and with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42022345583). This NMA was developed in accordance with the PRISMA extended statement on reporting systematic reviews incorporating a NMA of medical interventions.[4]

Search strategy

We searched MEDLINE, EMBASE and the International Clinical Trials Registry Platform (ICTRP) for RCTs database on pharmacological prevention strategies of HFS published till July 2022. Literature search strategies were developed using Medical Subject Headings (MeSH) and PICO-method. The key terms used were "HFS", "hand-foot syndrome", "palmar-plantar erythrodysesthesia", "cancer", "carcinoma", "tumor", "chemotherapy", "pharmacotherapy", "drug", "prevention", "preventive intervention", "prophylaxis".

Study selection criteria

RCTs investigating the pharmacological prevention strategies for systemic chemotherapy-induced HFS which had reported the outcome measures as prevention of any grade of (1–3) of HFS. All studies published in peer-reviewed English language journals were included. Studies were excluded if they investigated the ongoing treatment with existing HFS.

Type of participants and intervention

The trials should have included patients receiving systemic chemotherapy regimens that can cause HFS. Both the experimental and control arm should have included any intervention for the prevention of HFS, excluding alternative and complementary medicine therapy.

Outcome measures

Prevention of incidence of HFS (grade ≥1).

Prevention of incidence of moderate to severe HFS (grade ≥2).

Study selection and data collection

The selection of studies was carried out in a stepwise approach. Studies were included if the Participant Intervention Comparison and Outcome criteria and study type were appropriate. The studies were initially filtered based on title and summary. Then the full text of the selected study was obtained. The articles that met the inclusion criteria discussed previously in the field were included in the NMA. Three reviewers (MKR, MP and SM) reviewed each study individually, excluded unrelated studies and discussed results and discrepancies with another reviewer RM.

Data extraction and management

Data were extracted using a standard data extraction form, including study characteristics, participant details, interventions, controls and results. Data extraction and quality assessment were performed by three independent reviewers, MKR, MP and SM, and discrepancies were resolved in consultation with a fourth reviewer, AS.

Network plot

A network plot was constructed for all pharmacological agents as single or combined interventions. The network plot consists of a circle, each will represents the intervention, and the circle size represents the number of participants who received that intervention. The thickness of lines connecting the circles is proportional to the number of studies available. Node-splitting analysis, which enables comparison between direct effects with the indirect effects obtained via NMA, was performed if any closed triangles were to be found.

Data analysis

We performed an arm-based NMA using a Bayesian approach. Data were analysed by AS and MKR using R V.4.2.1 with 'gemtc' package for analysis.[5] A network plot was constructed for all pharmacological agents

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as single or combined treatments. The random-effects variance consistency model using Markov Chain Monte Carlo simulations and non-informative prior probabilities was used to estimate the OR (95% CI). Convergence was assessed using the visual inspection of Brooks-Gelman-Rubin diagnostic tool and visual inspection of time of series and density plots.

The potential scale reduction factor for each of the models was approximately 1 (<1.001). The results for relative effects have been represented as odds ratio (95% credible interval (CrI)). The distribution of probability for ranking various preventive agents for efficacy outcome was plotted. Using the dmetar package,[6] the surface under the cumulative ranking (SUCRA) scores were calculated. The model fit statistics like residual deviance (Dres) and leverage (pD) were calculated to check the model fit and assess each data point's influence on the model parameters. A meta-regression has been performed to account for the different baseline chemotherapy regimens as the incidence of HFS varies between chemotherapy regimens (capecitabine, sorafenib, doxorubicin, etc). The publication bias was assessed by performing Egger's regression analysis.

Assessment of risk of bias in included studies

Using the Cochrane Collaboration's standardised risk-of-bias assessment instrument 2 (RoB2), the risk of bias in individual studies was evaluated.[7] According to RoB2, bias is evaluated across five different domains (bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in the selection of the reported results). The responses to questions within each domain result in judgments of 'low risk of bias', 'some concerns' or 'high risk of bias'. For each included study, three reviewers, MKR, MP and DH, independently assessed it, noted their conclusions and provided reasons. The majority's agreement served as the deciding factor in any disputes.

RESULTS

Study selection and characteristics

Overall, 606 records were identified. After removing duplicated articles, 233 eligible articles were screened by title and abstract, from which 206 articles were excluded. There were 27 articles retrieved in full text, of which 15 were included in the NMA (figure 1). The study characteristics are summarised in table 1. The risk of bias was assessed and reported in figure 2.

NMA results

Moderate: severe HFS prevention (≥ grade 2)

Moderate-severe HFS (≥grade 2) was evaluated in 14 studies involving 2671 patients and 11 interventions arm, as shown in the network graph figure 3A. NMA suggests that only celecoxib 200 mg two times per day was associated with statistically significant reductions (OR 0.29, 95% CrI 0.13 to 0.68) in moderate-to-severe HFS compared with placebo (figure 4A). No significant differences were found in any other comparisons, as shown by indirect comparison of (online supplemental table 1A). The ranking of interventions based on SUCRA for reduced incidence of moderate-severe HFS (≥grade 2) showed that the best intervention with the highest probability of the first rank is pyridoxine 400 mg once daily (SUCRA score=0.8836). SUCRA scores depicting cumulative rank probabilities for each treatment are presented in online supplemental table 2A. Node-splitting model could not be created due to the lack of closed triangles in the network plot.

All grade HFS prevention (≥ grade 1)

Fourteen studies reported the incidence of ≥grade 1 of HFS, involving a total of 2659 patients with 11 prophylactic strategies, as shown in the network graph figure 3B. None of the interventions showed statistically significant risk reduction in the prevention of HFS (≥ grade 1) when compared with the placebo (figure 4B). No significant differences were found in any comparisons, as shown by indirect comparison results (online supplemental table 1B). The ranking of interventions based on SUCRA for reduced incidence of HFS of any grade showed the best intervention with the highest probability of the first rank is urea cream 10% (SUCRA score=0.8649). SUCRA scores depicting cumulative rank probabilities for each treatment are presented in online supplemental table 2B. Node-splitting model could not be created due to the lack of closed triangles in the network plot.

Adverse events

Studies involving pyridoxine, urea cream and cysteine theanine showed no significant difference in the incidence of drug-related adverse events.

Studies involving the celecoxib study by Zhang *et al*[8] reported grade 1 nephrotoxicity but was statistically not significant (p=0.961). None of the studies reported the cardiovascular adverse effects of any grade.

Publication bias

The publication bias was assessed by performing Egger's regression. The regression analysis did not show publication bias for both outcomes evaluated (p=0.56 for studies evaluating the incidence of HFS grade ≥1 and p=0.49 for studies evaluating the incidence of HFS grade ≥2).

Sensitivity analysis

A study by Köhne *et al*[9] showed a high risk of bias, so we did a sensitivity analysis by removing the study and measuring the relative effect. The analysis showed similar results in which none of the interventions was

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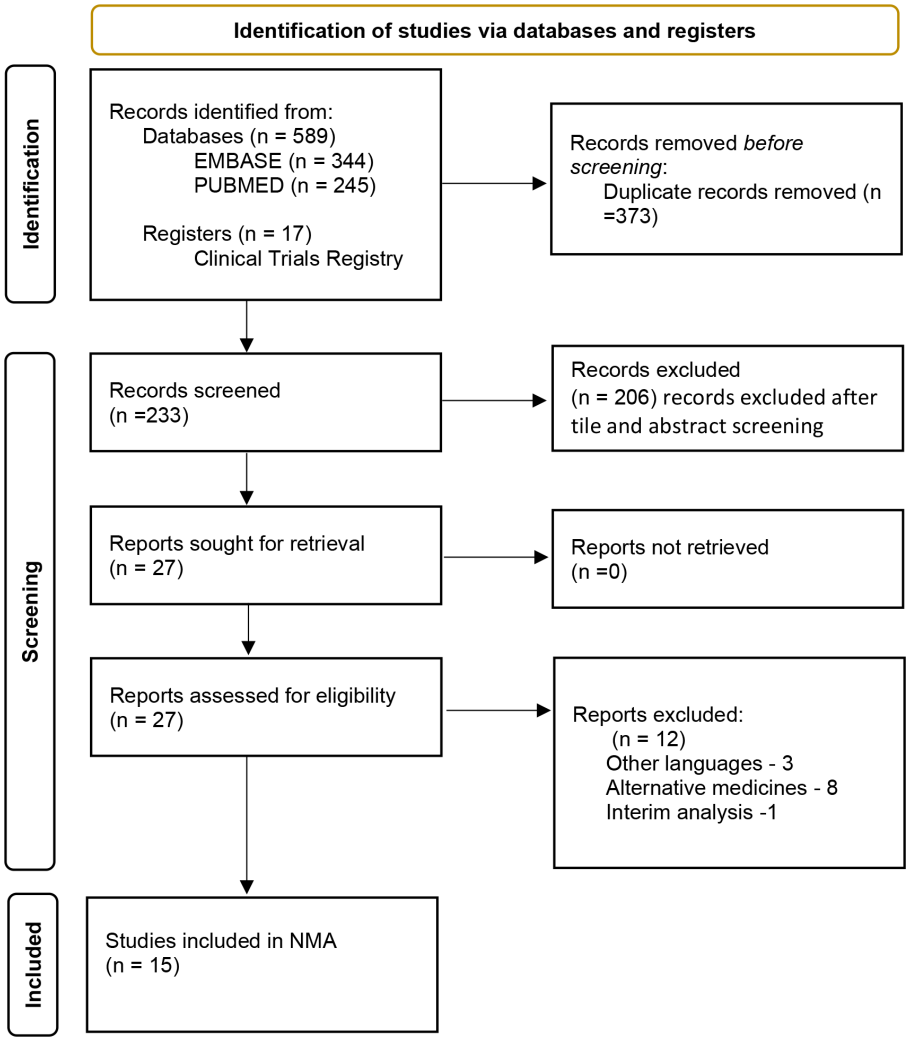

Figure 1 PRISMA flow chart of the search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

better in preventing the incidence of HFS of all grades (figure 4C).

Meta-regression analysis

Meta-regression analysis indicated that our results are not affected by the change in baseline chemotherapy regimens (online supplemental figure 2).

DISCUSSION

The present NMA summarises 15 RCTs, a total of 2715 patients with 12 prophylactic strategies for the prevention of HFS in patients receiving systemic chemotherapy agents. The Bayesian approach was used to calculate the relative effect sizes of interventions in preventing HFS with respect to one another as well as placebo. According to SUCRA scores, urea cream 10% cream appeared to be the most efficacious treatment among all interventions for the prevention of HFS (all grades), and pyridoxine 400 mg nce daily appeared to be the most efficacious treatment among all interventions for the prevention of HFS of grade 2 or more. However, celecoxib 20 mg two times per day alone was found to have significant efficacy over placebo for the prevention of moderate to severe grades of HFS. But, at the same time, none of the therapeutic agents proved to have a significant efficacy over placebo in preventing all grades of HFS.

This NMA was performed to assess the efficacy of several prophylactic agents that have shown promise in previous investigations. At present, there is no uniform prevention strategy for HFS incidence. The most commonly studied drugs, such as pyridoxine, urea-based cream and celecoxib, will prevent the incidence of HFS by preventing hyperplasia of epithelial cells, lowering hyperkeratosis and local inflammation, respectively.[1] The exact mechanism of HFS incidence is still unclear, even though many pathogenic mechanisms of HFS have been proposed.[10]

Celecoxib is a COX-2 inhibitor that will reduce the over-expression of COX-2 during tissue injury and necrosis caused by systemic chemotherapy agents and prevent HFS.[11] Various RCTs[8 9 12] have explored the role of celecoxib in HFS prevention. Our investigation showed that celecoxib effectively reduces grade 2 or more systemic chemotherapy-induced HFS, in line

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Table 1 Individual study characteristics

S.no	Author and year	Population	Chemotherapy drug	Intervention prophylaxis	Comparator	Outcomes
1.	Köhne 2008[9]	N=85 Metastatic colorectal adenocarcinoma	Capecitabine-based CAPARI	N=42 Celecoxib 400 mg two times per day	N=43 Placebo	No significant difference in any grade of HFS prevention (30.4% vs 33.3%, p=0.96)
2.	Zhang 2011[36]	N=150 Stages II and III colorectal cancer patients	Capecitabine-based CAPEOX	N=68 Celecoxib 200 mg two times per day	N=71 No celecoxib	Celecoxib prevents all-grade HFS (57.4% vs 74.6% p=0.034) and moderate to severe HFS (14.7% vs 29.6% p=0.035)
3.	Chen 2020[37]	N=116 Advanced HCC patients	Sorafenib	N=58 Celecoxib 200 mg two times per day	N=58 No celecoxib	Celecoxib significantly prevents moderate to severe HFSR (29.31% vs 63.8% p<0.001).
4.	Kang 2010[17]	N=389 GI tract cancers patients	Capecitabine containing chemotherapy	N=180 Pyridoxine 100 mg two times per day	N=180 Placebo	No significant difference in prevention of HFS of any grade (77.8% vs 81.7%, p=0.94) and moderate to severe grade (31.7% vs 30.6%, p=0.82)
5.	Von Gruenigen 2010[18]	N=34 Ovarian, breast, endometrial cancer patients	Pegylated liposomal doxorubicin	N=18 Pyridoxine 100 mg two times per day	N=16 Placebo	No significant difference in prevention of HFS of any grade (44.4% vs 43.8%, p=0.857) and moderate to severe grade (33.3% vs 25%,p=0.60)
6.	Chalermchai 2010[19]	N=56 Breast cancer or colorectal cancer patients	Capecitabine started at 2000–2500 mg/m^2 daily	N=28 Pyridoxine 200 mg once daily	N=28 Pyridoxine 400 mg once daily	Pyridoxine 400 mg once daily arm had less moderate to severe HFS than the pyridoxine 200 mg once daily arm (39% vs or 71%, p=0.031)
7.	Corrie 2012[20]	N=106 Advanced breast or colorectal	Capecitabine	N=53 Pyridoxine 50 mg three times per day	N=53 Placebo	No significant difference in prevention of HFS of any grade (53% vs 51%, p=0.85) and moderate to severe grade (9% vs 17%, p=0.26)
8.	Braik 2014[38]	N=77 Cancer (solid tumours) patients receiving	Capecitabine	N=38 Pyridoxine 100 mg once daily	N=39 Placebo	No significant difference in prevention of HFS of any grade (26% vs 21%, p=0.55) and moderate to severe HFS (16% vs 15%, p=0.96)
9.	Ota 2014[21]	N=60 Colorectal patients	Capecitabine	N=30 Pyridoxine 60 mg/day	N=30 Placebo	No significant difference in prevention of HFS of any grade (67% vs 77%, p=0.86) and moderate to severe HFS (60% vs 60%, p=1.00
10.	Yap 2017[22]	N=210 Breast and colorectal cancers	Capecitabine	N=105 Pyridoxine 200 mg/day	N=105 Placebo	No significant difference in prevention of HFS of any grade (60% vs 66%, p=0.39) and moderate to severe grade HFS (31.4% vs 37.1%, p=0.38)
11.	Toyama 2018[23]	N=133 Advanced or metastatic breast cancer	Capecitabine	N=66 Pyridoxine 60 mg once daily	N=67 No Pyridoxine	No significant difference in prevention of HFS of any grade (74% vs 67%, p=0.37) and moderate to severe grade HFS (29% vs 31%, p=0.75)
12.	Wolf 2010[25]	N=137 Cancer patients (colon, lung, breast)	Capecitabine	N=67 Topical urea cream 12%+lactic acid 6 % ½ to 1 teaspoon cream two times per day	N=60 Placebo emollient cream	No significant difference in prevention of HFS of any grade (urea cream 33% vs placebo 27%, p=0.822) moderate-severe HFS (urea cream 8% vs placebo 9% p=0.822)
13.	Ren 2015[26]	N=871 HCC	Sorafenib	N=439 10% Urea cream Topical three times per day	N=432 No urea cream	Urea cream superior to no urea cream in preventing all-grade HFSR (56.0% vs 73.6%, p=0.02) and moderate to severe grade HFSR (20.50 vs 29%, p=0.003)
14.	Hamaguchi 2019[39]	N=100 Colorectal patients with cancer	Capecitabine	n=52 L-cystine 700 mg and L-theanine 280 mg	N=48 placebo	No significant difference in prevention of HFS of any grade (67.4% vs 77.8%, p=0.185) and moderate to severe grade 67.3% vs 80.0%, p=0.124,
15.	Lee 2020[27]	N=288 HCC patients	Sorafenib	N=148 Urea cream 20% two times per day	N=140 Placebo	No significant difference in prevention of HFS of any grade (57% vs 64%, p=0.09) and moderate to severe grade (38% vs 46%, p=0.18)

HCC, Hepatocellular carcinoma; HFS, hand-foot syndrome; HFSR, HFS reaction.

with the earlier meta-analysis.[3 13–15] The pooled trials did not find any cardiovascular side effects, such as a rise in the risk of stroke and myocardial infarctions, which are known to be linked to prolonged celecoxib use. However, our examination of the long-term safety profile is constrained by the short mean follow-up times (1–2 years) of RCTs.

Pyridoxine insufficiency will cause acrodynia which is identical to the HFS reaction (HFSR). Pyridoxine (vitamin B_6) metabolite—pyridoxal can speed up skin barrier repair and prevent epithelial hyperplasia.[16] With a large number of RCTs[17–24] in comparison to other therapies, pyridoxine seemed to have been the most commonly studied drug for HFS. Our NMA showed the highest SUCRA score for pyridoxine 400 mg once daily intervention in preventing HFS grade 2 or more. But it failed to show any significant HFS prevention impact, as shown in the previous meta-analysis[3 13–15] but the upper boundary of the CrI is gracing the value 1 for pyridoxine 400 mg

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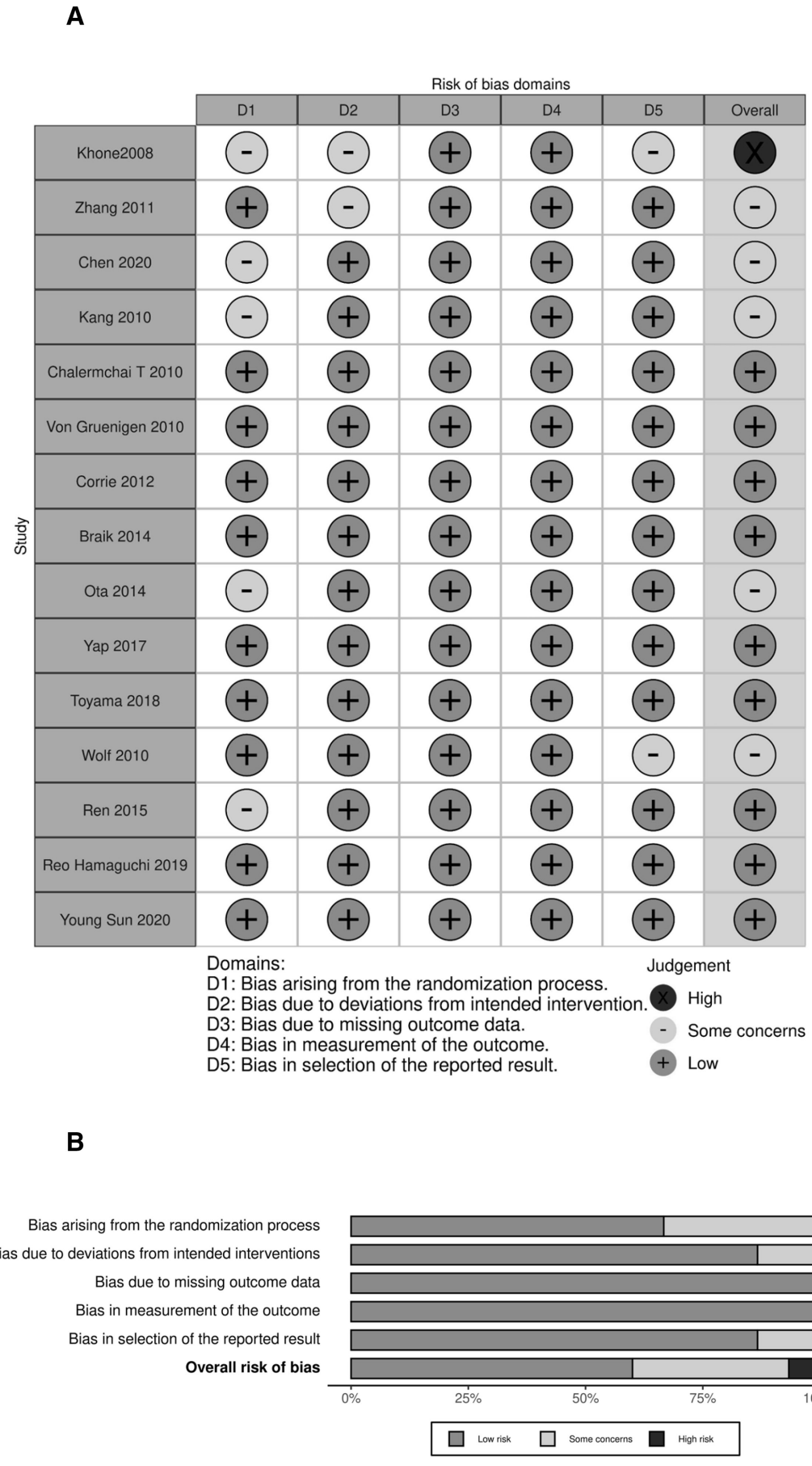

Figure 2 (A) Risk of bias traffic light plot of Risk of Bias 2 (RoB2) assessment. (B) Risk of bias summary plot of RoB2 assessment.

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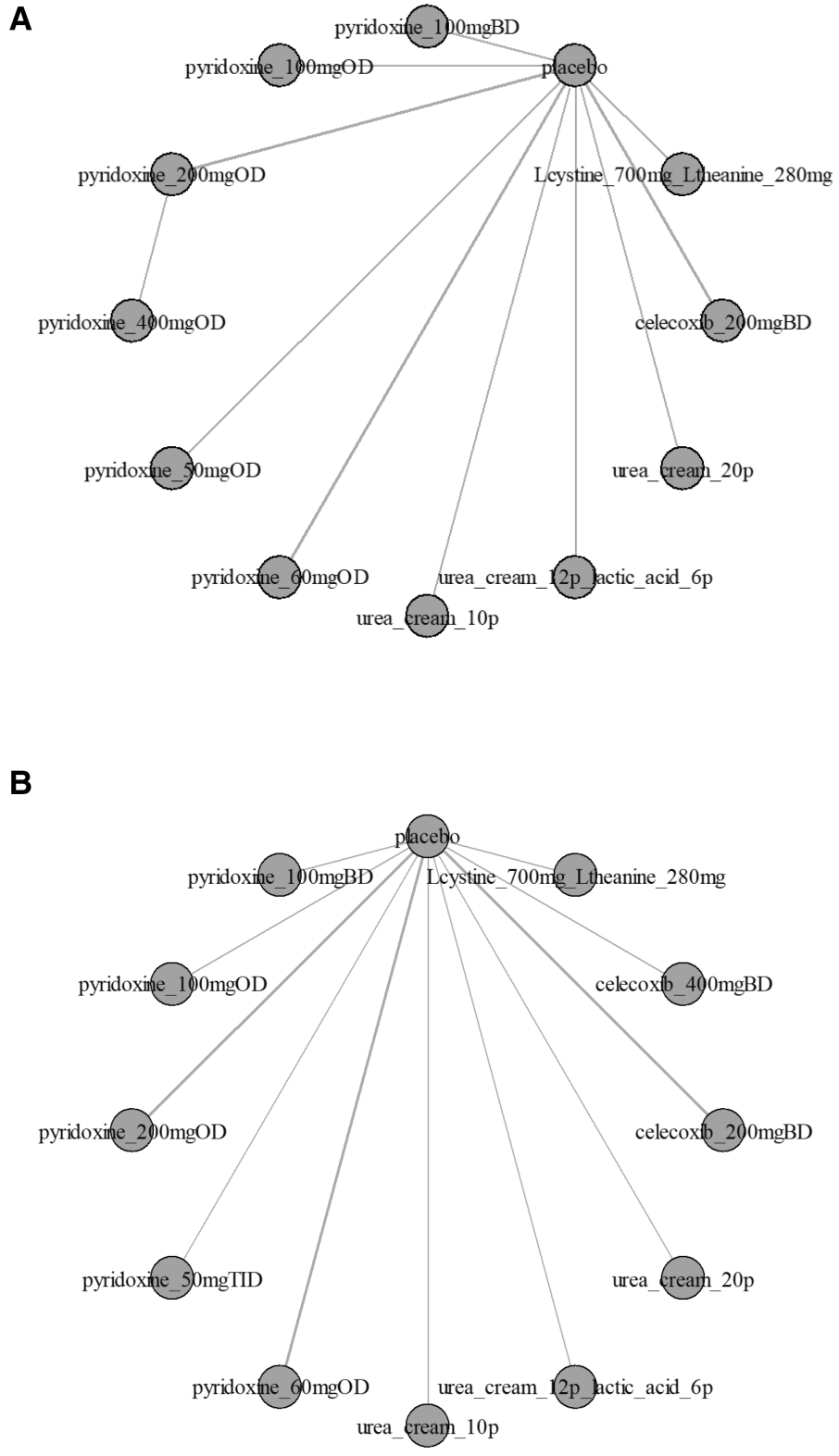

Figure 3 (A) Network graph of the prevention of moderate to severe hand-foot syndrome (HFS, grade ≥2), (B) Network graph of the prevention of all grades of HFS (grade ≥1). (Pyridoxine_100 mg two times per day—tablet pyridoxine 100 mg two times per day, pyridoxine_100 mg once daily—tablet pyridoxine 100 mg once daily, pyridoxine_200 mg once daily—tablet pyridoxine 200 mg two times per day, pyridoxine_400 mg once daily—tablet pyridoxine 400 mg once daily, pyridoxine_50 mg once daily—tablet pyridoxine 50 mg once daily, pyridoxine_60 mg once daily—tablet pyridoxine 60 mg once daily, urea_cream_10 p—topical ointment urea cream 10%, urea_cream_12 p_lactic_acid_6 p—topical ointment urea cream 12%+ lactic acid 6%, urea_cream_20 p—topical ointment urea cream 20%, celecoxib_200 mg two times per day—tablet celecoxib 200 mg two times per day, celecoxib_400 mg two times per day—tablet celecoxib 400 mg two times per day, Lcystine_700 mg_Ltheanine_280 mg - tablet L-cystine 700 mg+L-theanine 280 mg once daily).

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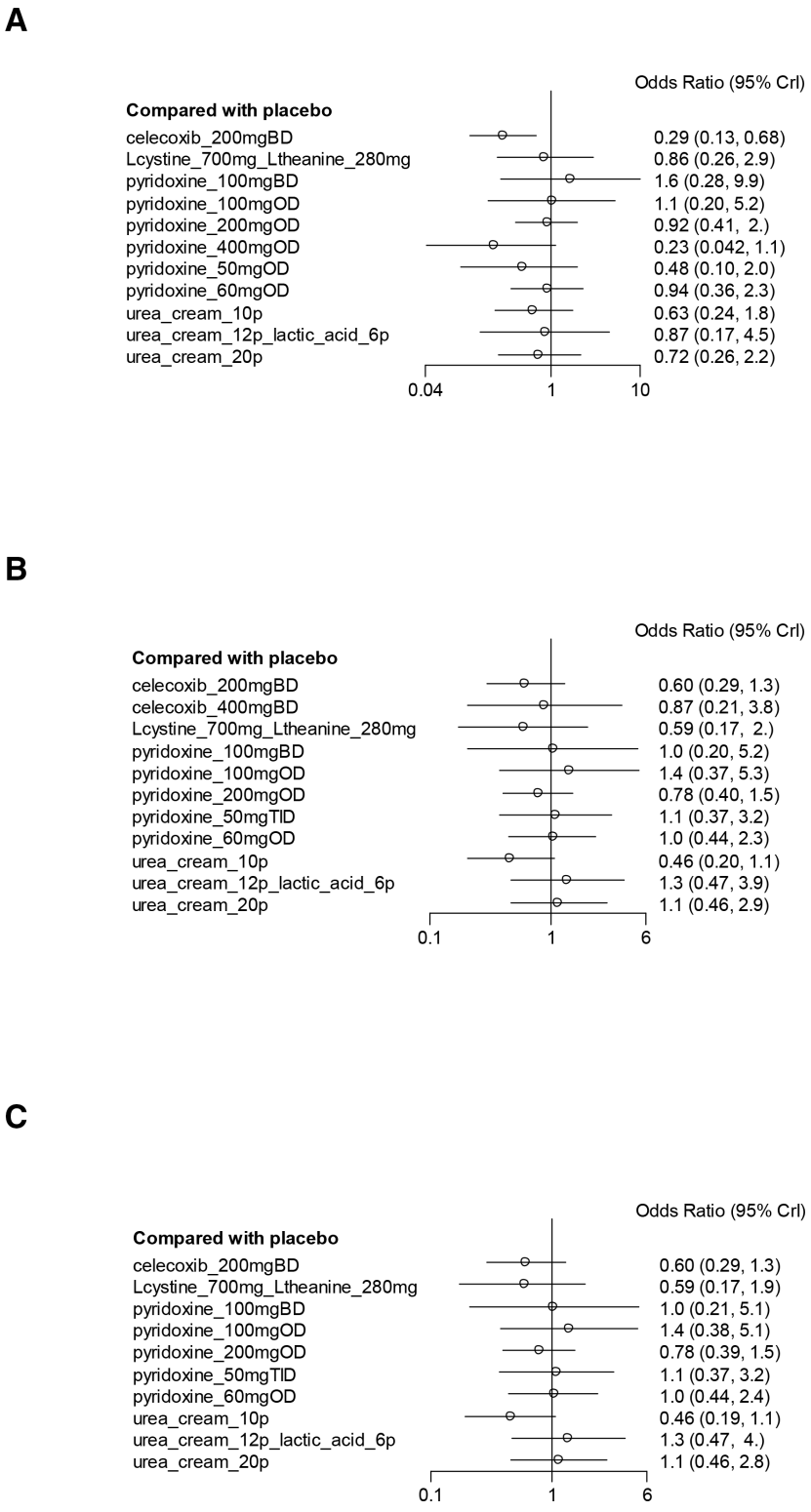

Figure 4 (A) Forest plot showing the OR (95% credible interval (CrI)) in terms of incidence of moderate to severe grade hand-foot syndrome (HFS, grade ≥2), (B) Forest plot showing the OR (95% CrI) in terms of incidence of all grades of HFS (grade ≥1), (C) Forest plot showing the OR (95% CrI) in terms of incidence of all grades of HFS (grade ≥1) with sensitivity analysis. (pyridoxine_100 mg two times per day—tablet pyridoxine 100 mg twice daily, pyridoxine_100 mg once daily—tablet pyridoxine 100 mg once daily, pyridoxine_200 mg once daily—tablet pyridoxine 200 mg two times per day, pyridoxine_400 mg once daily—tablet pyridoxine 400 mg once daily, pyridoxine_50 mg once daily—tablet pyridoxine 50 mg once daily, pyridoxine_60 mg once daily—tablet pyridoxine 60 mg once daily, urea_cream_10 p—topical ointment urea cream 10%, urea_cream_12 p_lactic_acid_6 p—topical ointment urea cream 12%+ lactic acid 6%, urea_cream_20 p—topical ointment urea cream 20%, celecoxib_200 mg two times per day—tablet celecoxib 200 mg two times per day, celecoxib_400 mg two times per day—tablet celecoxib 400 mg two times per day, Lcystine_700 mg_Ltheanine_280 mg—tablet L-cystine 700 mg+L-theanine 280 mg once daily).

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high dose in the prevention of HFS of grade ≥1. So further studies on high-dose pyridoxine (400 mg) with a larger sample size may be conducted to obtain clinically helpful efficacy data.

Urea cream, a keratolytic agent that is affordable, easily accessible and well tolerated, was tested in many RCTs[25–27] in the prophylactic management of HFS. It is hypothesised that urea cream will prevent hyperkeratosis, cause keratocyte necrosis and inhibit cutaneous inflammation caused by chemotherapy agents.[28] Our network metanalysis showed that urea cream 10% has a higher SUCRA score for preventing all grades of HFS but failed to show significant results when compared with a placebo, which is in contrast to the findings of a recent meta-analysis.[3 13–15] This may be due to the lesser number of included studies available for the analysis, as the upper boundary of the CrI is gracing the value 1. This phenomenon occurred because the CrIs generated from the Bayesian analysis also incorporate the randomness of both the variance of OR and the population OR, which is not the case with the frequentist approach used in other studies. So further studies on the effect of urea cream on chemotherapy-induced HFS are required.

Apart from these pharmacological agents, various other complementary medicine treatments such as traditional Chinese medicine compound LC09,[29] topical silymarin,[30] mapisal cream,[31] TJ-28 (eppikajutsuto),[32] topical henna,[33 34] EVOSKIN palm and sole moisturising cream,[35] and topical henna and curcumin (Alpha) ointment[33] have been explored through RCTs for the preventive management of HFS. We did not include these agents as we focused only on the drugs where the active ingredients' composition was clearly mentioned and excluded the alternative and complementary medicine therapy. An NMA published by Kao *et al*[14] suggests topical silymarin had significantly reduced the incidence of HFS. Since topical silymarin is a herbal preparation, we excluded the study by Elyasi *et al*[30] as our NMA had relatively strict inclusion criteria.

Our study has several drawbacks. The most significant drawback of this analysis was the lack of clinical trials with direct comparisons between different active preventive interventions. Initially, we intended to use data integration from direct and indirect comparisons to compile the findings of multiple RCTs evaluating the effects of individual or combination therapies. However, the majority of research compared preventive interventions against placebo and only one of the studies compared active treatments. This led to performing only indirect or direct comparisons, and we were unable to check the consistency of our network model. As many of the included studies did not record any significant adverse events, the safety data for the interventions could not be analysed.

CONCLUSION

Among the various agents evaluated for the prevention of HFS, only celecoxib demonstrated a significant reduction in the incidence of HFS (grade ≥2). Other pharmacological interventions did not show any significant role in preventing HFS. However, the SUCRA scores indicated that pyridoxine (400 mg once daily) and urea cream (10%) could play a potential role in the prevention of HFS. These two agents have to be evaluated further with larger randomised clinical trials.

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Supplementary material

Search Strategy

Search Strategy in PubMed on 1/8/2022
(((((HFS) OR (hand foot syndrome)) OR (palmar plantar erythrodysesthesia)) AND (((cancer) OR (carcinoma)) OR (tumor))) AND (((chemotherapy) OR (pharmacotherapy)) OR (drug))) AND (((prevention) OR (preventive intervention)) OR (prophylaxis))

Search Strategy in Embase on 1/8/2022
((HFS or hand foot syndrome or palmar plantar erythrodysesthesia) and (cancer or carcinoma or tumor) and (chemotherapy or pharmacotherapy or drug) and (prevention or preventive intervention or prophylaxis)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] limit 1 to (human and english language and (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial))

Supplementary table 1 a) Comparison of all included interventions for prevention of grade 2 or more of HFS as calculated by Bayesian approach. Data is presented as odds ratio (95% CrI). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention (pyridoxine_100mgBD – tablet pyridoxine 100mg twice daily, pyridoxine_100mgOD – tablet pyridoxine 100mg once daily, pyridoxine_200mgOD – tablet pyridoxine 200mg twice daily, pyridoxine_400mgOD – tablet pyridoxine 400mg once daily, pyridoxine_50mgOD – tablet pyridoxine 50 mg once daily, pyridoxine_60mgOD – tablet pyridoxine 60 mg once daily, urea_cream_10p – topical ointment urea cream 10 % , urea_cream_12p_lactic_acid_6p – topical ointment urea cream 12% + lactic acid 6 %, urea_cream_20p – topical ointment urea cream 20 %, celecoxib_200mgBD – tablet celecoxib 200mg twice daily, celecoxib_400mgBD- tablet celecoxib 400mg twice daily, Lcystine_700mg_Ltheanine_280mg - tablet L-cystine 700mg + L-theanine 280 mg once daily)

	celecoxib_200mgBD	Lcystine_700mg_Ltheanine_280mg	placebo	pyridoxine_100mgBD	pyridoxine_100mgOD	pyridoxine_200mgOD	pyridoxine_400mgOD	pyridoxine_50mgOD	pyridoxine_60mgOD	urea_cream_10p	urea_cream_12p_lactic_acid_6p	urea_cream_20p
celecoxib_200mgBD	celecoxib_200mgBD	2.96 (0.57, 14.1)	3.36 (1.39, 8.2)	5.26 (0.73, 41.71)	3.57 (0.56, 22.57)	3.14 (0.91, 9.89)	0.76 (0.12, 5.22)	1.69 (0.26, 9.38)	3.11 (0.85, 11.51)	2.14 (0.54, 8.58)	2.95 (0.45, 18.79)	2.43 (0.57, 9.99)
Lcystine_700mg_Ltheanine_280mg	0.34 (0.07, 1.76)	Lcystine_700mg_Ltheanine_280mg	1.15 (0.32, 4.34)	1.79 (0.2, 17.68)	1.22 (0.15, 9.55)	1.07 (0.23, 5)	0.26 (0.03, 2.23)	0.58 (0.07, 4.28)	1.08 (0.21, 5.52)	0.73 (0.14, 4.05)	1.01 (0.13, 9.11)	0.82 (0.16, 4.9)
placebo	0.3 (0.12, 0.72)	0.87 (0.23, 3.15)	placebo	1.55 (0.27, 9.96)	1.05 (0.21, 5.42)	0.93 (0.4, 2.01)	0.22 (0.04, 1.21)	0.5 (0.1, 2.3)	0.93 (0.37, 2.29)	0.64 (0.22, 1.89)	0.87 (0.17, 4.43)	0.72 (0.24, 2.25)
pyridoxine_100mgBD	0.19 (0.02, 1.37)	0.56 (0.06, 4.93)	0.65 (0.1, 3.69)	pyridoxine_100mgBD	0.66 (0.06, 7.5)	0.59 (0.08, 4.01)	0.14 (0.01, 1.59)	0.31 (0.03, 3.08)	0.59 (0.07, 4.46)	0.41 (0.05, 3.09)	0.57 (0.04, 6.56)	0.47 (0.06, 3.77)
pyridoxine_100mgOD	0.28 (0.04, 1.78)	0.82 (0.1, 6.5)	0.95 (0.18, 4.73)	1.53 (0.13, 16.38)	pyridoxine_100mgOD	0.88 (0.15, 5.37)	0.21 (0.02, 2.38)	0.47 (0.05, 4.22)	0.88 (0.14, 5.65)	0.6 (0.09, 4.21)	0.83 (0.09, 8.84)	0.68 (0.1, 5.21)
pyridoxine_200mgOD	0.32 (0.1, 1.1)	0.94 (0.2, 4.28)	1.08 (0.5, 2.53)	1.68 (0.25, 12.58)	1.13 (0.19, 6.85)	pyridoxine_200mgOD	0.24 (0.06, 1.08)	0.54 (0.09, 2.9)	1.01 (0.3, 3.3)	0.68 (0.19, 2.57)	0.95 (0.16, 6.27)	0.77 (0.2, 3.33)
pyridoxine_400mgOD	1.31 (0.19, 8.48)	3.85 (0.45, 30.36)	4.46 (0.83, 23.01)	7 (0.63, 79.54)	4.68 (0.42, 47.8)	4.09 (0.93, 17.77)	pyridoxine_400mgOD	2.21 (0.22, 19.14)	4.11 (0.61, 25.45)	2.86 (0.42, 19.4)	3.92 (0.39, 39.9)	3.21 (0.45, 23.04)
pyridoxine_50mgOD	0.59 (0.11, 3.85)	1.73 (0.23, 13.8)	2.01 (0.43, 10.32)	3.21 (0.32, 35.71)	2.12 (0.24, 21.1)	1.86 (0.34, 11.24)	0.45 (0.05, 4.57)	pyridoxine_50mgOD	1.88 (0.31, 12.38)	1.28 (0.21, 8.56)	1.81 (0.2, 17.68)	1.45 (0.22, 10.96)
pyridoxine_60mgOD	0.32 (0.09, 1.18)	0.93 (0.18, 4.68)	1.07 (0.44, 2.73)	1.7 (0.22, 13.48)	1.14 (0.18, 7.22)	0.99 (0.3, 3.36)	0.24 (0.04, 1.63)	0.53 (0.08, 3.19)	pyridoxine_60mgOD	0.69 (0.17, 2.68)	0.94 (0.14, 6.56)	0.78 (0.18, 3.22)
urea_cream_10p	0.47 (0.12, 1.85)	1.36 (0.25, 7.13)	1.57 (0.53, 4.63)	2.42 (0.32, 19.46)	1.66 (0.24, 11.14)	1.47 (0.39, 5.21)	0.35 (0.05, 2.4)	0.78 (0.12, 4.81)	1.46 (0.37, 5.98)	urea_cream_10p	1.37 (0.2, 9.73)	1.14 (0.24, 5.37)
urea_cream_12p_lactic_acid_6p	0.34 (0.05, 2.22)	0.99 (0.11, 7.94)	1.15 (0.23, 5.82)	1.75 (0.15, 22.58)	1.21 (0.11, 11.69)	1.06 (0.16, 6.23)	0.26 (0.03, 2.55)	0.55 (0.06, 5)	1.06 (0.15, 7.02)	0.73 (0.1, 4.91)	urea_cream_12p_lactic_acid_6p	0.83 (0.11, 5.85)
urea_cream_20p	0.41 (0.1, 1.74)	1.22 (0.2, 6.34)	1.38 (0.44, 4.22)	2.13 (0.27, 18.14)	1.46 (0.19, 10.14)	1.29 (0.3, 4.96)	0.31 (0.04, 2.24)	0.69 (0.09, 4.51)	1.28 (0.31, 5.44)	0.88 (0.19, 4.19)	1.2 (0.17, 8.92)	urea_cream_20p

Supplementary table 1 b) Comparison of the all included interventions for prevention of all grade of HFS as calculated by Bayesian approach. Data presented as odds ratio (95% CrI). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention (pyridoxine_100mgBD – tablet pyridoxine 100mg twice daily, pyridoxine_100mgOD – tablet pyridoxine 100mg once daily, pyridoxine_200mgOD – tablet pyridoxine 200mg twice daily, pyridoxine_400mgOD – tablet pyridoxine 400mg once daily, pyridoxine_50mgOD – tablet pyridoxine 50 mg once daily, pyridoxine_60mgOD – tablet pyridoxine 60 mg once daily, urea_cream_10p – topical ointment urea cream 10 % , urea_cream_12p_lactic_acid_6p – topical ointment urea cream 12% + lactic acid 6 %, urea_cream_20p – topical ointment urea cream 20 %, celecoxib_200mgBD – tablet celecoxib 200mg twice daily, celecoxib_400mgBD- tablet celecoxib 400mg twice daily, Lcystine_700mg_Ltheanine_280mg - tablet L-cystine 700mg + L-theanine 280 mg once daily)

	celecoxib_200mgBD	celecoxib_400mgBD	Lcystine_700mg_Ltheanine_280mg	placebo	pyridoxine_100mgBD	pyridoxine_100mgOD	pyridoxine_200mgOD	pyridoxine_50mgTID	pyridoxine_60mgOD	urea_cream_10p	urea_cream_12p_lactic_acid_6p	urea_cream_20p
celecoxib_200mgBD	celecoxib_200mgBD	1.46 (0.28, 7.42)	0.97 (0.23, 3.88)	1.66 (0.78, 3.39)	1.73 (0.28, 9.87)	2.36 (0.49, 10.67)	1.3 (0.47, 3.42)	1.78 (0.48, 6.65)	1.73 (0.54, 5.16)	0.76 (0.25, 2.28)	2.22 (0.61, 8.13)	1.89 (0.6, 5.98)
celecoxib_400mgBD	0.69 (0.13, 3.62)	celecoxib_400mgBD	0.67 (0.1, 4.79)	1.15 (0.26, 4.84)	1.19 (0.13, 10.27)	1.58 (0.24, 12.34)	0.9 (0.19, 4.55)	1.24 (0.21, 8.08)	1.21 (0.22, 6.52)	0.52 (0.1, 2.84)	1.57 (0.25, 9.72)	1.32 (0.25, 6.99)
Lcystine_700mg_Ltheanine_280mg	1.03 (0.26, 4.29)	1.5 (0.21, 10.46)	Lcystine_700mg_Ltheanine_280mg	1.7 (0.51, 5.78)	1.75 (0.23, 13.07)	2.43 (0.39, 13.75)	1.32 (0.35, 5.27)	1.83 (0.38, 8.94)	1.79 (0.4, 7.58)	0.77 (0.18, 3.28)	2.31 (0.43, 11.77)	1.94 (0.44, 8.74)
placebo	0.6 (0.29, 1.28)	0.87 (0.21, 3.82)	0.59 (0.17, 1.97)	placebo	1.04 (0.2, 5.2)	1.41 (0.37, 5.29)	0.78 (0.4, 1.51)	1.09 (0.37, 3.15)	1.04 (0.44, 2.33)	0.46 (0.2, 1.05)	1.34 (0.47, 3.94)	1.14 (0.46, 2.9)
pyridoxine_100mgBD	0.58 (0.1, 3.53)	0.84 (0.1, 7.42)	0.57 (0.08, 4.34)	0.96 (0.19, 4.9)	pyridoxine_100mgBD	1.34 (0.17, 11.37)	0.75 (0.13, 4.25)	1.03 (0.15, 7.28)	1 (0.16, 6.54)	0.44 (0.07, 2.72)	1.3 (0.19, 9.07)	1.09 (0.17, 6.91)
pyridoxine_100mgOD	0.42 (0.09, 2.04)	0.63 (0.08, 4.2)	0.41 (0.07, 2.56)	0.71 (0.19, 2.67)	0.74 (0.09, 5.88)	pyridoxine_100mgOD	0.55 (0.13, 2.47)	0.76 (0.14, 4.38)	0.74 (0.16, 3.39)	0.32 (0.07, 1.51)	0.97 (0.17, 5.32)	0.8 (0.16, 3.94)
pyridoxine_200mgOD	0.77 (0.29, 2.12)	1.11 (0.22, 5.4)	0.76 (0.19, 2.89)	1.28 (0.66, 2.48)	1.33 (0.24, 7.46)	1.81 (0.41, 7.71)	pyridoxine_200mgOD	1.39 (0.39, 4.71)	1.34 (0.45, 3.69)	0.58 (0.2, 1.65)	1.72 (0.5, 6.15)	1.45 (0.48, 4.5)
pyridoxine_50mgTID	0.56 (0.15, 2.09)	0.8 (0.12, 4.8)	0.55 (0.11, 2.63)	0.92 (0.32, 2.68)	0.97 (0.14, 6.59)	1.31 (0.23, 7.05)	0.72 (0.21, 2.57)	pyridoxine_50mgTID	0.95 (0.24, 3.64)	0.42 (0.11, 1.68)	1.25 (0.28, 5.54)	1.05 (0.25, 4.21)
pyridoxine_60mgOD	0.58 (0.19, 1.84)	0.83 (0.15, 4.59)	0.56 (0.13, 2.52)	0.96 (0.43, 2.25)	1 (0.15, 6.28)	1.36 (0.29, 6.24)	0.75 (0.27, 2.23)	1.05 (0.27, 4.13)	pyridoxine_60mgOD	0.44 (0.15, 1.43)	1.28 (0.34, 5.05)	1.08 (0.32, 4)
urea_cream_10p	1.32 (0.44, 3.95)	1.92 (0.35, 9.97)	1.29 (0.3, 5.56)	2.19 (0.95, 4.91)	2.28 (0.37, 13.92)	3.1 (0.66, 13.85)	1.72 (0.61, 4.88)	2.36 (0.59, 9.26)	2.29 (0.7, 6.82)	urea_cream_10p	2.94 (0.77, 11.44)	2.47 (0.74, 8.6)
urea_cream_12p_lactic_acid_6p	0.45 (0.12, 1.65)	0.64 (0.1, 4.06)	0.43 (0.08, 2.33)	0.75 (0.25, 2.13)	0.77 (0.11, 5.19)	1.03 (0.19, 5.73)	0.58 (0.16, 1.98)	0.8 (0.18, 3.58)	0.78 (0.2, 2.93)	0.34 (0.09, 1.3)	urea_cream_12p_lactic_acid_6p	0.85 (0.21, 3.34)
urea_cream_20p	0.53 (0.17, 1.66)	0.76 (0.14, 4.06)	0.52 (0.11, 2.27)	0.88 (0.34, 2.16)	0.91 (0.14, 5.85)	1.24 (0.25, 6.21)	0.69 (0.22, 2.07)	0.95 (0.24, 3.94)	0.92 (0.25, 3.09)	0.4 (0.12, 1.36)	1.18 (0.3, 4.83)	urea_cream_20p

- Table 2a (Figure 1a) - Rank probabilities of various interventions based on SUCRA score for prevention of moderate to severe grade (≥2 grade) of HFS

Interventions	SUCRA
pyridoxine_400mgOD	0.8836
celecoxib_200mgBD	0.8701
pyridoxine_50mgOD	0.6561
urea_cream_10 %	0.5938
urea_cream_20 %	0.5172
urea cream 12% + lactic acid 6%	0.4313
Lcystine_700mg + Ltheanine_280mg	0.4168
pyridoxine_200mgOD	0.3778
pyridoxine_60mgOD	0.3759
pyridoxine_100mgOD	0.3550
placebo	0.3051
pyridoxine_100mgBD	0.2168

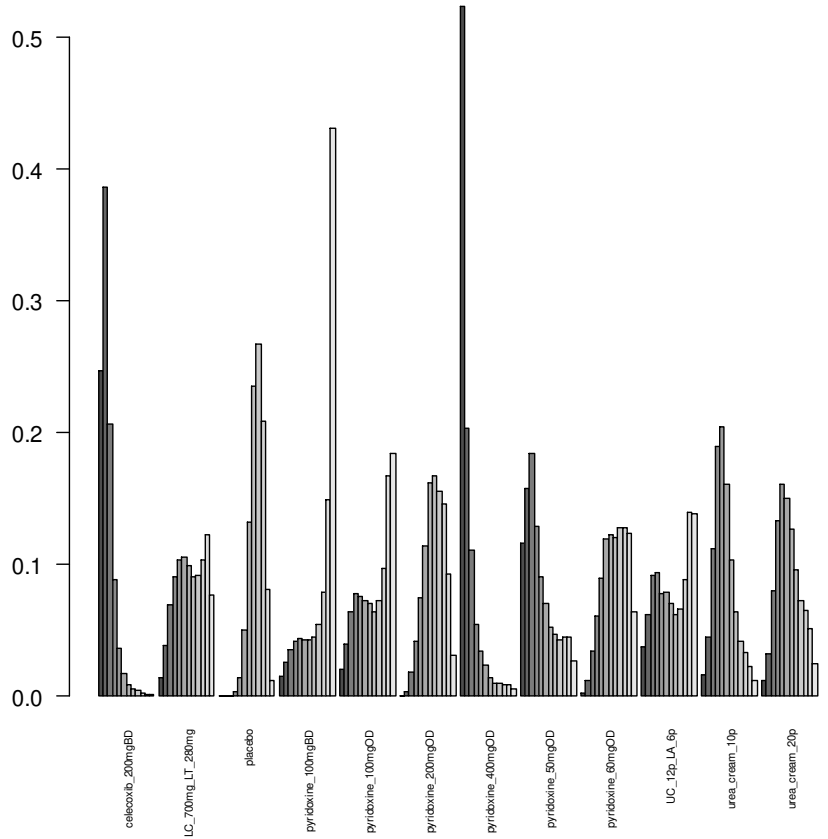
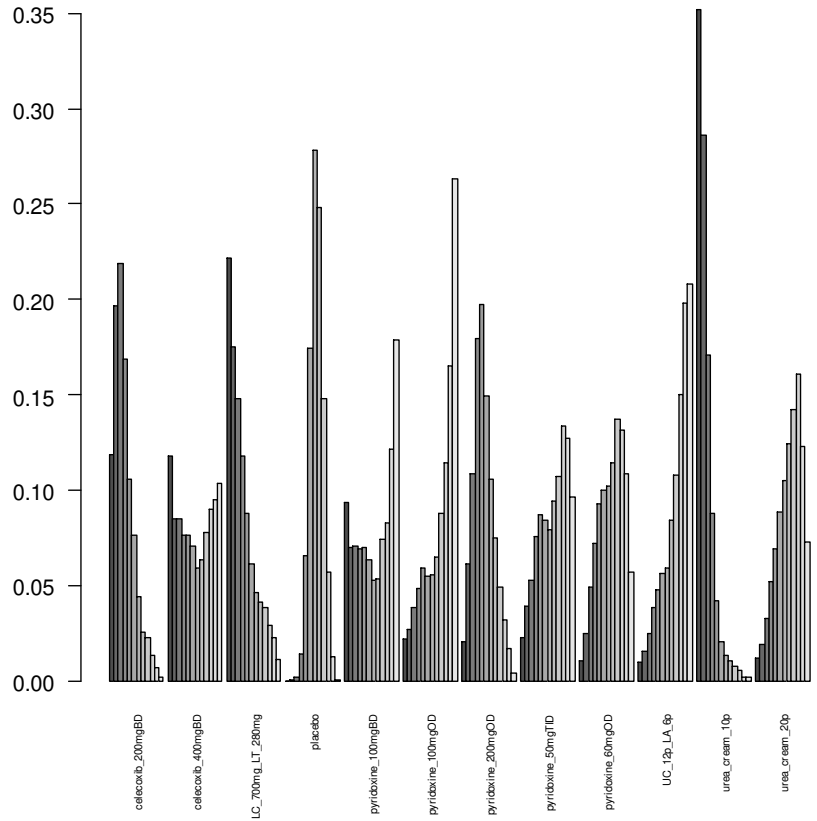
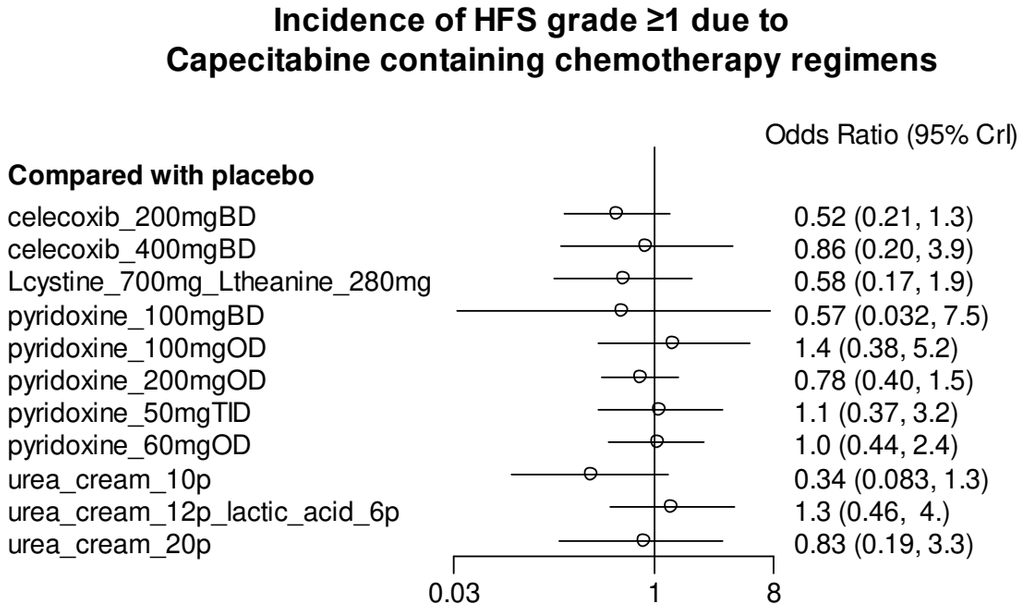
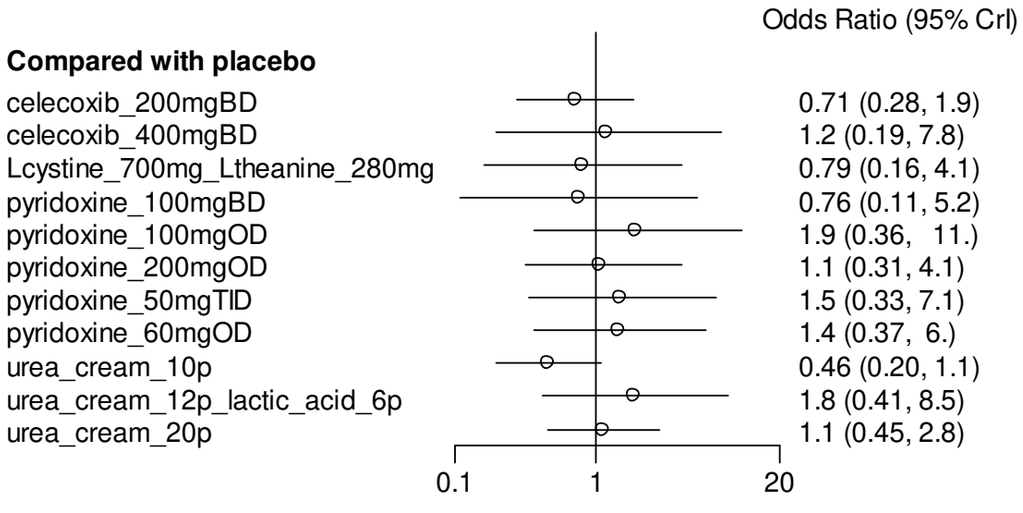


Table 2b (Figure 1b) - Rank probabilities of various interventions based on SUCRA score for prevention of all grade of HFS (≥1 grade)

Interventions	SUCRA
urea_cream_10 %	0.8649
celecoxib_200mgBD	0.7366
Lcystine_700mg + Ltheanine_280mg	0.7211
pyridoxine_200mgOD	0.6028
celecoxib_400mgBD	0.5154
pyridoxine_100mgBD	0.4402
placebo	0.4153
pyridoxine_60mgOD	0.4084
pyridoxine_50mgTID	0.3922
urea_cream_20 %	0.3466
pyridoxine_100mgOD	0.2847
urea_cream_12% + lactic_acid_6%	0.2712







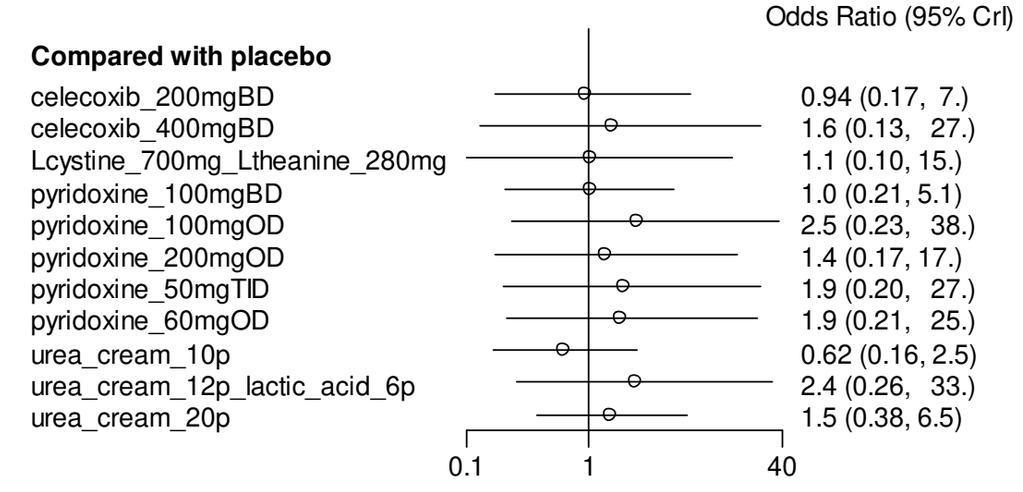
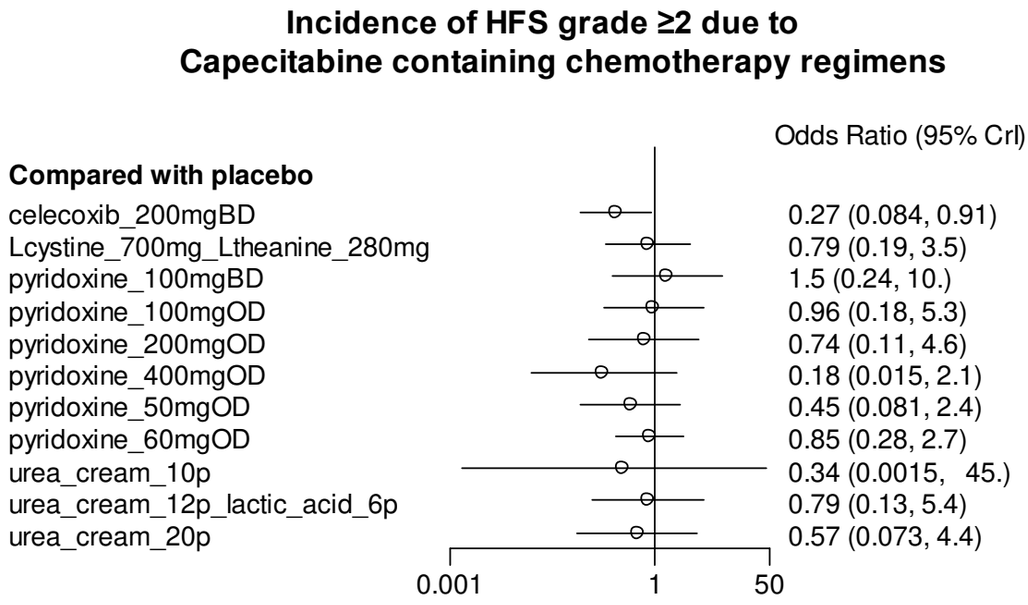
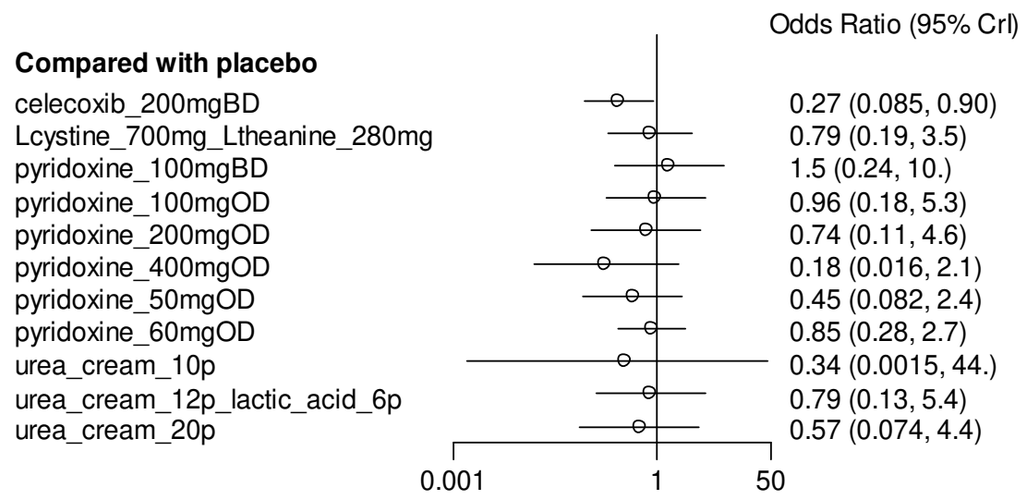


Figure 2a) Forest plot showing the odds ratio (95 % CrI) in terms of incidence of all grades of HFS (grade ≥ 1) by baseline chemotherapy agent. (pyridoxine_100mgBD – tablet pyridoxine 100mg twice daily, pyridoxine_100mgOD – tablet pyridoxine 100mg once daily, pyridoxine_200mgOD – tablet pyridoxine 200mg twice daily, pyridoxine_400mgOD – tablet pyridoxine 400mg once daily, pyridoxine_50mgOD – tablet pyridoxine 50 mg once daily, pyridoxine_60mgOD – tablet pyridoxine 60 mg once daily, urea_cream_10p – topical ointment urea cream 10 % , urea_cream_12p_lactic_acid_6p – topical ointment urea cream 12% + lactic acid 6 %, urea_cream_20p – topical ointment urea cream 20 %, celecoxib_200mgBD – tablet celecoxib 200mg twice daily, celecoxib_400mgBD- tablet celecoxib 400mg twice daily, Lcystine_700mg_Ltheanine_280mg - tablet L-cystine 700mg + L-theanine 280 mg once daily)





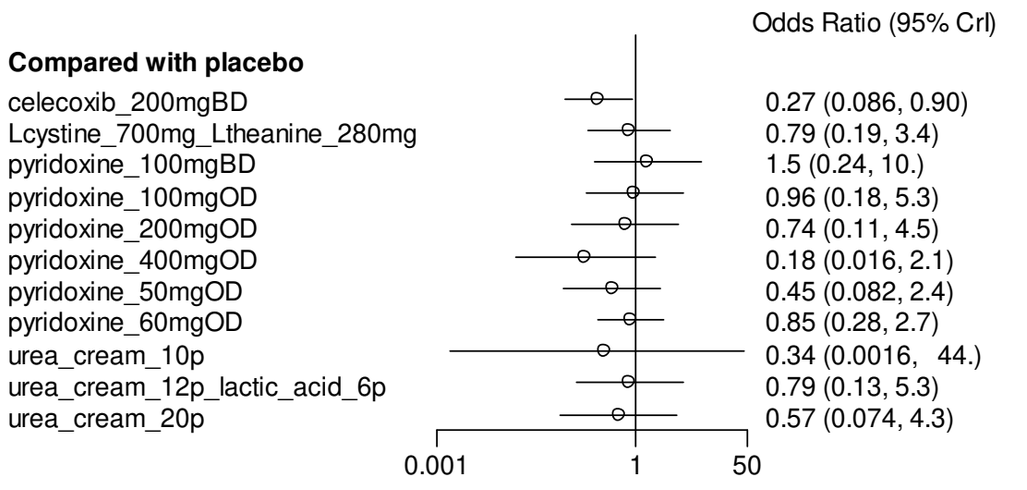


Figure 2b) Forest plot showing the odds ratio (95 % CrI) in terms of incidence of moderate to severe grade hand-foot syndrome (HFS, grade ≥ 2) by baseline chemotherapy agent. (pyridoxine_100mgBD – tablet pyridoxine 100mg twice daily, pyridoxine_100mgOD – tablet pyridoxine 100mg once daily, pyridoxine_200mgOD – tablet pyridoxine 200mg twice daily, pyridoxine_400mgOD – tablet pyridoxine 400mg once daily, pyridoxine_50mgOD – tablet pyridoxine 50 mg once daily, pyridoxine_60mgOD – tablet pyridoxine 60 mg once daily, urea_cream_10p – topical ointment urea cream 10 % , urea_cream_12p_lactic_acid_6p – topical ointment urea cream 12% + lactic acid 6 %, urea_cream_20p – topical ointment urea cream 20 %, celecoxib_200mgBD – tablet celecoxib 200mg twice daily, celecoxib_400mgBD- tablet celecoxib 400mg twice daily, Lcystine_700mg_Ltheanine_280mg - tablet L-cystine 700mg + L-theanine 280 mg once daily).

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The study of drug utilisation and disease recurrence in patients with COVID Mucormycosis (CAM) on Posaconazole step-down therapy: an ambispective study.

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Abstract

Background and Purpose: Invasive mucormycosis is a fatal disease caused by Mucorales species. Treatment therapy for CAM includes aggressive surgical debridement and systemic antifungals in Amphotericin B and Posaconazole as step-down therapy in the follow-up period. Despite being on oral antifungal Posaconazole therapy, patients have been observed to have a recurrence of mucormycosis in the follow-up period. Experimental Approach: An ambispective cohort study was done in the department of ENT and Pharmacology of All India Institute of Medical Sciences (AIIMS), Bhubaneswar, from April 2021 to September 2022. It includes patients on follow-up on the step-down therapy of Posaconazole. Medication adherence was measured based on the half-life of Posaconazole and participants not skipping a single dose. Key Results: The demographic data between the recurrence and non-recurrence groups, including age, sex and duration of stay, was not significant. Recurrence in mucormycosis was not found to be associated with medication adherence. By both methods of calculating medication adherence, the results were statistically insignificant. The difference in onset of recurrence of the disease between the two groups was statistically significant, with a p-value of 0.027 in patients who did not skip a single dose of Posaconazole with a hazard ratio of 3.887. There was a statistically significant difference in cost-effective analysis with a p-value of 0.042 between groups. Conclusion and Implications: Posaconazole medication adherence in the postoperative period does not affect the recurrence of mucormycosis during step-down therapy. However, it helps prolong the onset of disease recurrence in patients adhering to the medication.

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