Original Article

Efficacy and safety of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials

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Background: Dexamethasone is typically administered for multiple days after the start of chemotherapy to prevent delayed chemotherapy-induced nausea and vomiting (CINV). Frequent administration of corticosteroids has been associated with problematic side effects. Reducing the dose and frequency of corticosteroids administered during chemotherapy treatment may be beneficial in reducing the side effects experienced by patients, as long as it is possible to maintain its efficacy in the prophylaxis of CINV. The purpose of the review and meta-analysis is to compare the safety and efficacy of multi-day versus 1-day regimen of dexamethasone.

Methods: A comprehensive literature search was carried out in Ovid MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. The primary endpoints were the proportion of patients achieving complete response and complete control in the acute, delayed and overall phases. Secondary endpoints were the percentage of patients who experienced no nausea, no emesis, no use of rescue medication, no adverse events, no constipation, no headache and no fatigue/insomnia.

Results: Seven randomized controlled trials (RCTs) were included in this meta-analysis, and a total of 659 and 649 patients were randomized to receive dexamethasone on 1 day and 3 days, respectively. The two treatments were equivalent in 16 of 17 endpoints.

Conclusions: Despite the paucity of data in this setting, we find that the 1-day dexamethasone therapy provides a similar efficacy and safety profile as a treatment of 3-day dexamethasone in the prophylaxis of CINV. The similarities in efficacy and safety of the two interventions suggests that 1-day dexamethasone can be administered as an alternative to 3 days.

Keywords: Chemotherapy-induced nausea and vomiting (CINV); efficacy; safety; dexamethasone

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) can result in deterioration in a patient's quality of life and consequently lead to poorer compliance with further treatment (1-3). It is typically reported as occurring in the acute (0–24 hours post-chemotherapy) or delayed (24–120 hours post-chemotherapy) phases, and is known to cause dehydration and malnutrition (4-6).

To protect against CINV, many different types of antiemetics have been developed to inhibit pathways presumed to be associated with CINV (7). Palonosetron, ondansetron and granisetron are 5-hydroxytrypatmine type 3 receptor antagonists (5-HT_3RAs) that aim to disrupt the process of serotonin from enterochromaffin cells binding to 5-HT_3 receptors (7,8). Other antiemetics such as aprepitant, netupitant and rolapitant are neurokinin-1 receptor antagonists (NK_1RA) that are designed to block substance P from initiating impulses to the vomiting centre in the medulla (9,10).

A meta-analysis by Ioannidis *et al.* found that dexamethasone in conjunction with other antiemetics is superior to placebo with respect to complete protection (11). Combination therapy of antiemetics with dexamethasone has now become the standard of care for preventing CINV in patients receiving moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC), and the recommended line of therapy by the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) antiemetic guidelines (12).

Dexamethasone is typically administered for multiple days after the start of chemotherapy to help treat delayed CINV (13). However, frequent administration of corticosteroids has been associated with problematic side effects such as edema, bulimia, weight gain, digestive disorders, hyperglycemia and reactivation of the hepatitis B virus (14-16). Reducing the duration that steroids are administered during chemotherapy treatment may be beneficial in reducing the side effects experienced by patients, while at the same time potentially maintaining efficacy. The aim of our meta-analysis is to compare the safety and efficacy of multi-day versus 1-day regimens of dexamethasone in this setting.

Methods

Search strategy

A comprehensive literature search was carried out in Ovid MEDLINE, Embase and Cochrane Central Register of Controlled Trials. Key words included "neoplasms", "dexamethasone", "nausea", and "vomiting". The search was limited to English-language randomized controlled trials (RCTs) (Appendix 1). Reference lists of articles included in this review were also hand-searched to identify any further relevant literature.

Selection criteria

Studies were screened by title and abstract, and identified for full-text screening if they performed a head-to-head comparison of dexamethasone administered on day 1 relative to days 1–3 of chemotherapy in a RCT full-text articles were eligible for quantitative synthesis if they reported on at least one of the following endpoints in either the acute (0–24 hours post-chemotherapy), delayed (24–120 hours post-chemotherapy) or overall phases for cycle 1:

(I) Complete response (CR)—no emesis and no use of rescue medication;
(II) Complete control (CC)—no emesis, no use of rescue medication and no more than mild nausea;
(III) No nausea;
(IV) No emesis—no episodes of vomiting or retching;
(V) No use of rescue medication;
(VI) No adverse events—no episodes of treatment-related adverse events;
(VII) No constipation;
(VIII) No headache;
(IX) No fatigue/insomnia;

Studies were excluded if they were duplicates of other articles, were non-original research reports, or were small trials (<ten patients).

Data extraction and endpoints

The primary endpoints were the proportion of patients achieving CR and CC in the acute, delayed and overall phases, as reported by study authors. Secondary endpoints were the proportion of patients who experienced no nausea,

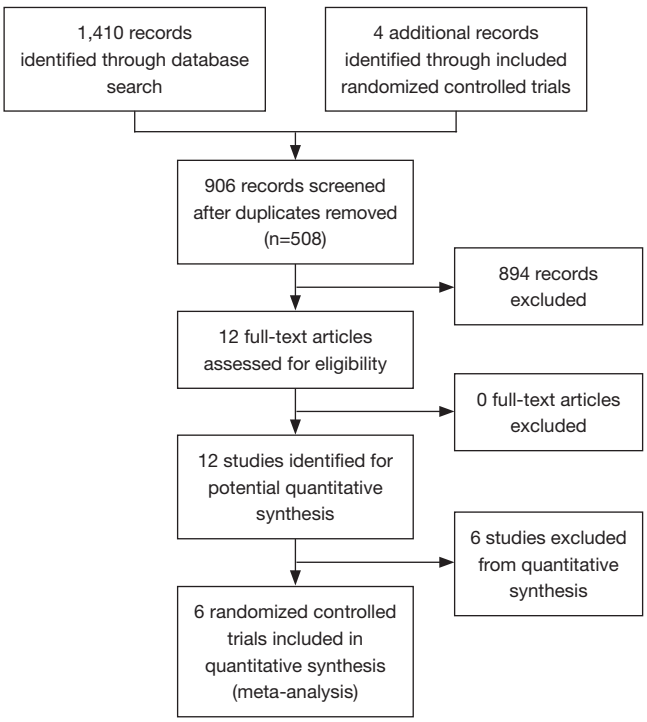

Figure 1 PRISMA flow diagram.

no emesis, no use of rescue medication, no treatment-related adverse events and no constipation. The "nausea" endpoint in the overall phase and "rescue medication" endpoints in the acute phase were not recorded, as only one study reported on each of these endpoints in their respective phase.

Statistical analyses

To perform the meta-analysis, a Mantel-Haenszel method with a random-effects analysis model was used to compute odds ratios (OR) and accompanying 95% confidence intervals (CI). P values less than 0.05 were considered significant with regards to the test for overall effect. All analyses were conducted using Review Manager (RevMan 5.3) by Cochrane IMS.

Results

From the 1,414 records identified from the search, 906 were screened at the title & abstract level after duplicates (n=508) were removed. Of the 12 full-text articles assessed for eligibility, seven RCTs (13,17-22) were included for this meta-analysis (*Figure 1*). For consistency in endpoints, two studies were excluded because delayed phase was defined as 2 to 6 days following treatment, rather than 2 to 5 days (23,24). A total of 659 and 649 patients were randomized to receive dexamethasone on 1 and 3 days, respectively.

Only two studies recruited patients who were treated with HEC, while the other five contained patients treated with MEC. The number of patients randomized to each intervention arm ranged from 39 to 166. All but two studies recruited exclusively female patients, and all but one only recruited patients who were chemotherapy-naïve. Other characteristics of included RCTs are displayed in *Table 1*.

Efficacy—CR and CC

Six studies documented rates of CR, and five studies reported on CC. CR in the acute phase was approximately equivalent between 1-day and multi-day dexamethasone (OR, 0.90; 95% CI, 0.64–1.26). The two treatment arms were similar in terms of CR in the delayed (OR, 1.18; 95% CI, 0.92–1.51) and overall (OR, 1.07; 95% CI, 0.84–1.37) phases (*Figure 2*). Three-day dexamethasone treatment was not superior to 1-day dexamethasone treatment with respect to CC in the acute (OR, 0.78; 95% CI, 0.51–1.19), delayed (OR, 1.17; 95% CI, 0.89–1.56) and overall (OR, 1.03; 95% CI, 0.78–1.35) phases (*Figure 3*).

Efficacy—no nausea, no emesis and no use of rescue medication

Only three studies recorded nausea in the acute and delayed phases. The analysis revealed that 1-day treatment was equivalent to 3-day treatment (*Figure S1*). The two interventions also yielded similar control of emesis in the acute, delayed and overall phases (*Figure S2*). A noticeably larger proportion of patients receiving 1-day dexamethasone treatment required rescue medication in the delayed phase; no similar finding was reported in the overall phase (*Figure S3*).

Safety

Five six studies reported on adverse events. Patients treated with 1-day and 3-day treatment were equally as likely to develop adverse events (OR, 0.88; 95% CI, 0.66–1.16). One-day dexamethasone was equally as safe as 3-day dexamethasone treatment in terms of constipation (OR, 0.72; 95% CI, 0.45–1.14), headaches (OR, 1.16; 95% CI, 0.69–1.95) and fatigue/insomnia (OR, 1.71;

Table 1 Characteristics of randomized controlled trials included in meta-analysis

Trial	Study design	Intervention	Sample size	Chemotherapy emetogenicity	Females (%)	Mean age (years)	Nonusers of alcohol (%)	Chemotherapy-naïve (%)
Aapro *et al.*, 2010 (17)	Double-blind, multicenter, non-inferiority	DEX 8 mg IV d1	151	MEC	100.0	52.1	57.7	100.0
		DEX 8 mg IV d1 + DEX 4 mg PO BID d2–3	149		100.0	51.2	48.8	100.0
Celio *et al.*, 2011 (18)	Open-label, parallel-group, active-comparator, non-inferiority	DEX 8 mg IV d1	166	MEC	62.0	56.9	60.8	100.0
		DEX 8 mg IV d1 + DEX 8 mg PO QD d2–3	166		68.0	57.2	59.6	100.0
Vardy *et al.*, 2012 (19)	Double-blind, placebo-controlled, cross-over	DEX 10 mg IV d1	49	HEC	100.0	n/a	n/a	100.0
		DEX 10 mg IV d1 + DEX 4 mg PO QD d2–3	42		100.0	n/a	n/a	100.0
Furukawa *et al.*, 2015 (20)	Open-label	DEX 8 mg IV d1	44	MEC	100.0	59.0*	n/a	100.0
		DEX 8 mg IV d1 + DEX 8 mg PO QD d2–3	44		100.0	62.0*	n/a	100.0
Komatsu *et al.*, 2015 (21)	Open-label, non-inferiority, comparative	DEX 9.9 mg IV d1	154	MEC	43.0	64.1	51.0	100.0
		DEX 9.9 mg IV d1 + DEX 8 mg PO QD d2–3	154		43.5	64.0	51.9	100.0
Matsuura *et al.*, 2015 (22)	Randomized	DEX 9.9 mg IV d1	56	MEC	100.0	57.7	64.3	n/a
		DEX 9.9 mg IV d1 + DEX 8 mg PO QD d2–3	53		100.0	56.7	64.2	n/a
Kosaka *et al.*, 2016 (13)	Single-blind, placebo-controlled, parallel	DEX 12 mg IV d1	39	HEC	100.0	52.6	64.1	100.0
		DEX 12 mg IV d1 + DEX 8 mg IV d2–3	41		100.0	53.5	61.0	100.0

*, median age. BID, bis in die; D, day; DEX, dexamethasone; HEC, highly emetogenic chemotherapy; IV, intravenously; MEC, moderately emetogenic chemotherapy; n/a, data not available or extractable; PO, per os; QD, quaque die.

95% CI, 0.83–3.53) (*Figure S4*).

Discussion

This is the first meta-analysis to our knowledge to investigate the efficacy and safety of 1-day versus multi-day dexamethasone treatment for the prophylaxis of CINV in combination with antiemetics.

The efficacy of dexamethasone administered on day 1 is equivalent to the efficacy of dexamethasone administered on days 1–3; the efficacy and safety were identical in 16 of 17 endpoints. The suggestion by Roscoe *et al.* (25) that the 3-day regimen is superior with respect to control of delayed nausea was not found in the present analysis—it is important to note that these conclusions are made on the basis of two included trials, and more studies should investigate these conflicting conclusions. The two treatments are also similar with respect to safety, specifically constipation, headache and fatigue/insomnia.

There were only seven studies in this review, of which five were studies recruiting only MEC patients. Future studies should further investigate the two dexamethasone arms in the HEC setting to see whether there are similar conclusions.

The similarities in efficacy and safety of the two

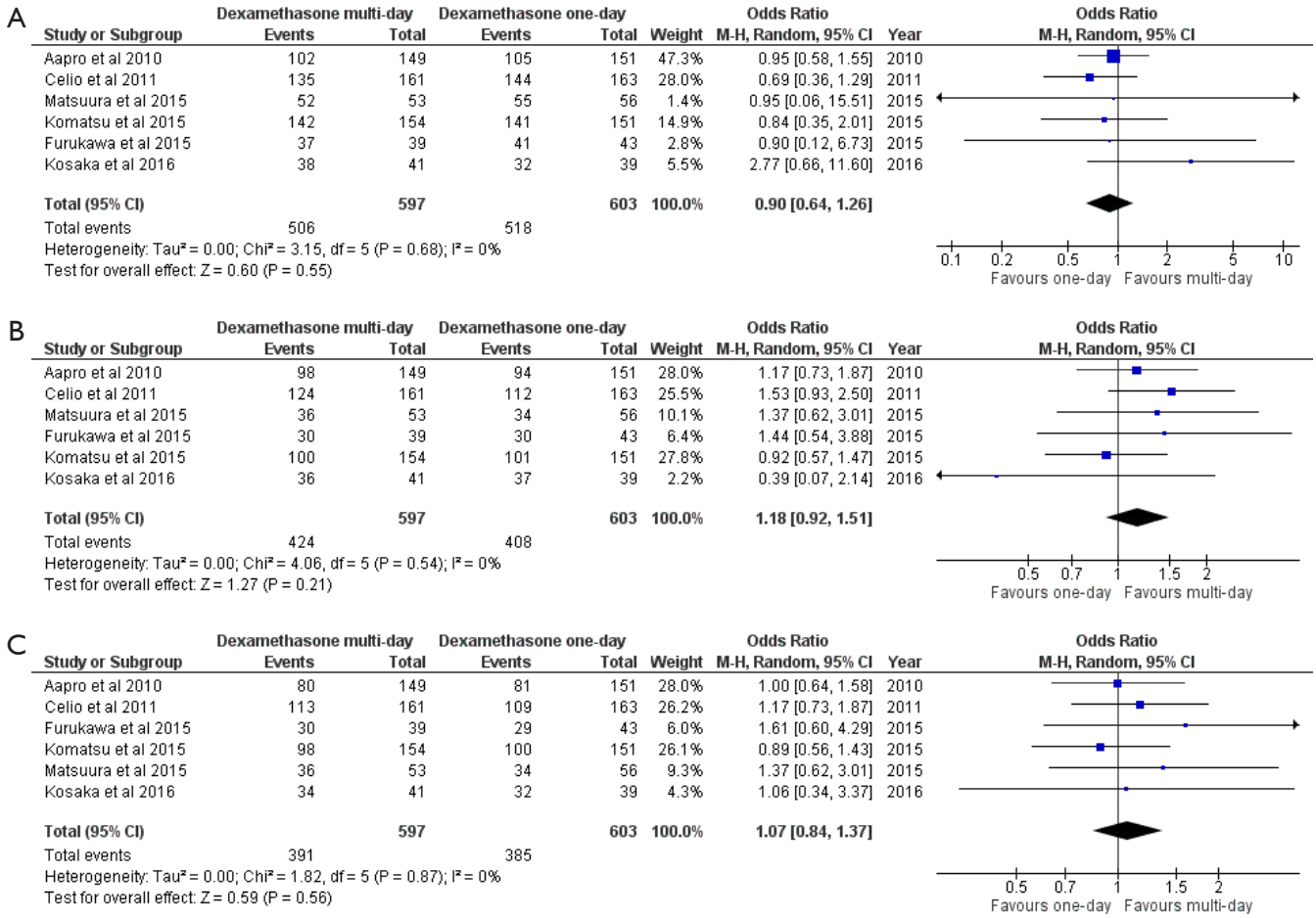

Figure 2 Efficacy of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting—complete response: (A) acute phase; (B) delayed phase; (C) overall phase.

interventions suggests that 1-day dexamethasone can achieve similar objectives as 3-day dexamethasone treatment, and can be administered as an alternative to the standard of care. For patients, this does not significantly decrease the cost of the treatment, as dexamethasone is over 22 times cheaper than other antiemetics (i.e., ondansetron, palonosetron) that are co-administered with the corticosteroid (26); the antiemetics will still be the cause of financial burden for CINV treatments. The transition to 1-day over 3-day treatment may also improve patient adherence. In fact, the latest American Society of Clinical Oncology's antiemetic guidelines suggests 1-day dexamethasone instead of 3-day dexamethasone for some patients receiving MEC (27).

There were limitations in this meta-analysis. There exists the possibility of a carry-over effect from acute phase data to delayed phase results, which is a reported and inherent limitation in the included RCTs (28). Additionally, this review only included seven RCTs in total, and hence some endpoints only have data on a few studies. The results of this review should be interpreted with caution and future RCTs are required to further compare the two dexamethasone treatment regimens.

In conclusion, 1-day dexamethasone seems to provide a similar efficacy and safety profile as 3-day dexamethasone in the prophylaxis of CINV. The similarities in efficacy and safety of the two interventions suggests that 1-day dexamethasone can be administered as an alternative to the standard of care. However, this review only includes six studies, of which five were studies recruiting only MEC patients. Further studies should continue to investigate whether these conclusions remain in the HEC setting.

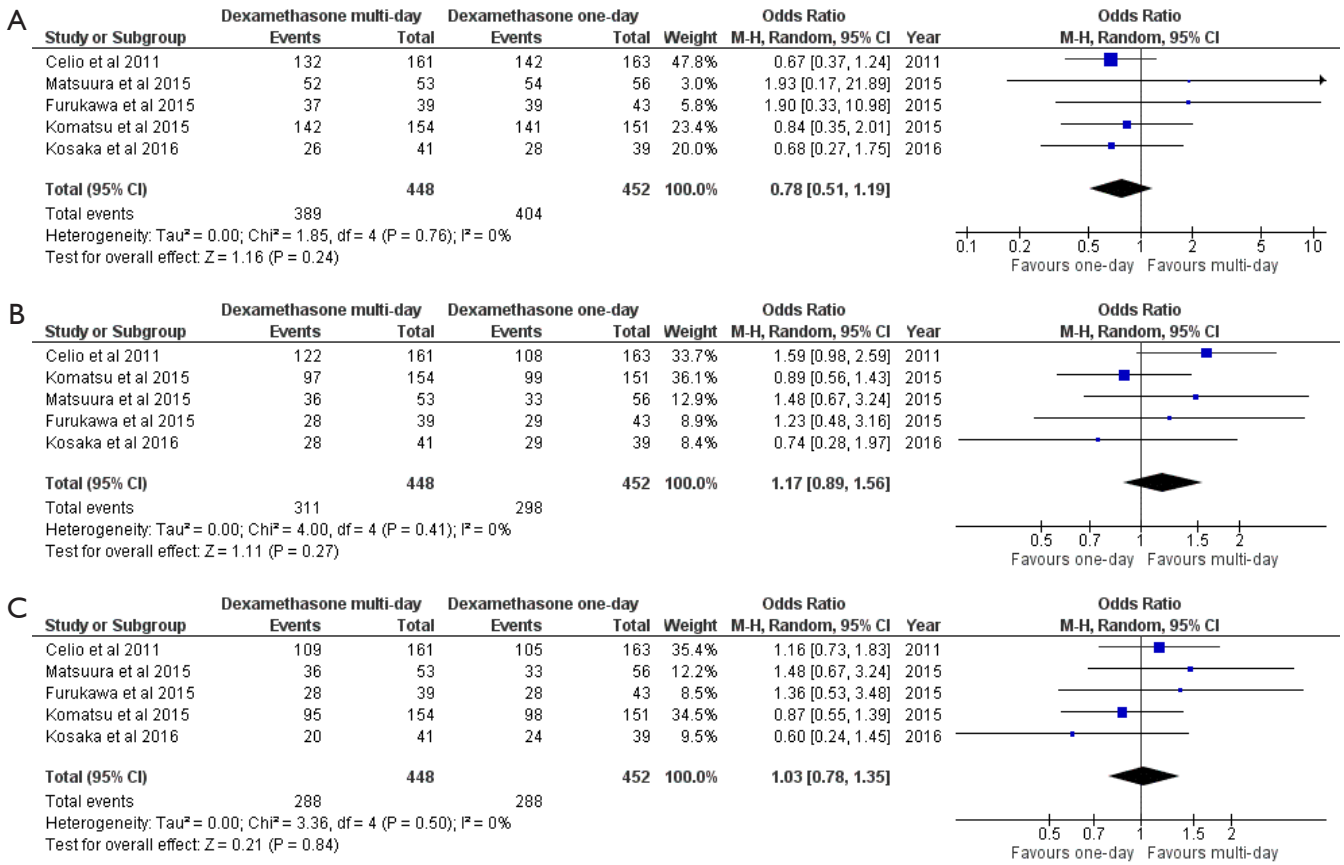

Figure 3 Efficacy of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting—complete control: (A) acute phase; (B) delayed phase; (C) overall phase.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jhmhp.2018.04.05). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) search strategy:

1. exp Neoplasms/ or (neoplasm or cancer).mp. [3423821]
2. palonosetron.mp. [566]
3. exp dexamethasone/ or dexamethasone.mp. [66470]
4. day.mp. [934734]
5. Comparative Study/ [1820429]
6. compar*.mp. [5489611]
7. (2 and 3) or (3 and (4 or 5 or 6)) [23252]
8. (chemotherapy adj5 induced adj5 nausea adj5 vomiting).mp. [1572]
9. CINV.mp. [731]
10. exp Nausea/ or (nausea or nauseous or nauseated).mp. [61685]
11. exp Vomiting/ or vomit*.mp. [30059]
12. or/8-11 [77890]
13. 1 and 7 and 12 [659]
14. limit 13 to randomized controlled trial [276]
15. ((randomized or randomised) adj5 (trial or controlled)).ti. [124122]
16. 13 and 15 [76]
17. 14 or 16 [281]
18. limit 17 to English language [260]
19. from 18 keep 1-260 [260]

Database: Embase Classic + Embase <1947 to 2017 Week 28> search strategy:

1. exp neoplasm/ [4092608]
2. exp palonosetron/ or palonosetron.mp. [1682]
3. exp dexamethasone/ or dexamethasone.mp. [146855]
4. day.mp. [1351637]
5. exp comparative study/ [1226778]
6. compar*.mp. [6862254]
7. (2 and 3) or (3 and (4 or 5 or 6)) [50891]
8. exp "chemotherapy induced nausea and vomiting"/ [2563]
9. (chemotherapy adj5 induced adj5 nausea adj5 vomiting).mp. [3882]
10. CINV.mp. [1463]
11. exp nausea/ or (nausea or nauseous or nauseated).mp. [243227]
12. exp vomiting/ or vomit*.mp. [234992]
13. or/8-12 [332334]
14. 1 and 7 and 13 [4222]
15. limit 14 to randomized controlled trial [603]
16. ((randomized or randomised) adj5 (trial or controlled)).ti. [146469]
17. 14 and 16 [208]
18. 15 or 17 [643]
19. limit 18 to English language [624]

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2017> search strategy:

1	exp Neoplasms/ or (neoplasm or cancer).mp. [103999]
2	palonosetron.mp. [305]
3	exp dexamethasone/ or dexamethasone.mp. [6812]
4	day.mp. [135221]
5	Comparative Study/ [8]
6	compar*.mp. [483121]
7	(2 and 3) or (3 and (4 or 5 or 6)) [4578]
8	(chemotherapy adj5 induced adj5 nausea adj5 vomiting).mp. [780]
9	CINV.mp. [359]
10	exp Nausea/ or (nausea or nauseous or nauseated).mp. [30381]
11	exp Vomiting/ or vomit*.mp. [22883]
12	or/8-11 [34715]
13	1 and 7 and 12 [620]
14	limit 13 to English language [526]

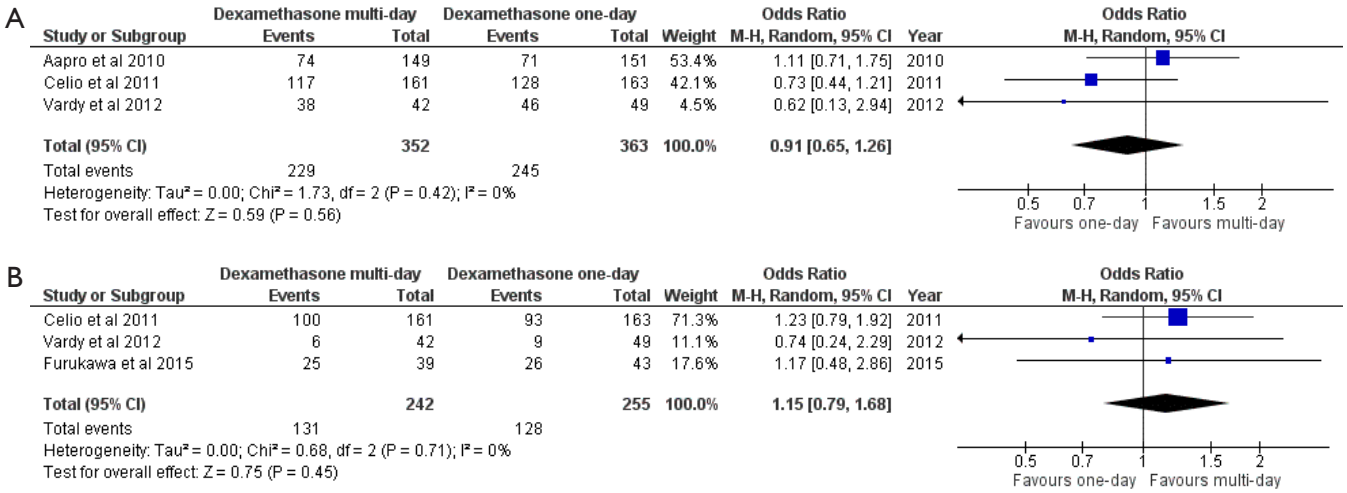

Figure S1 Efficacy of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting—no nausea. (A) acute phase; (B) delayed phase.

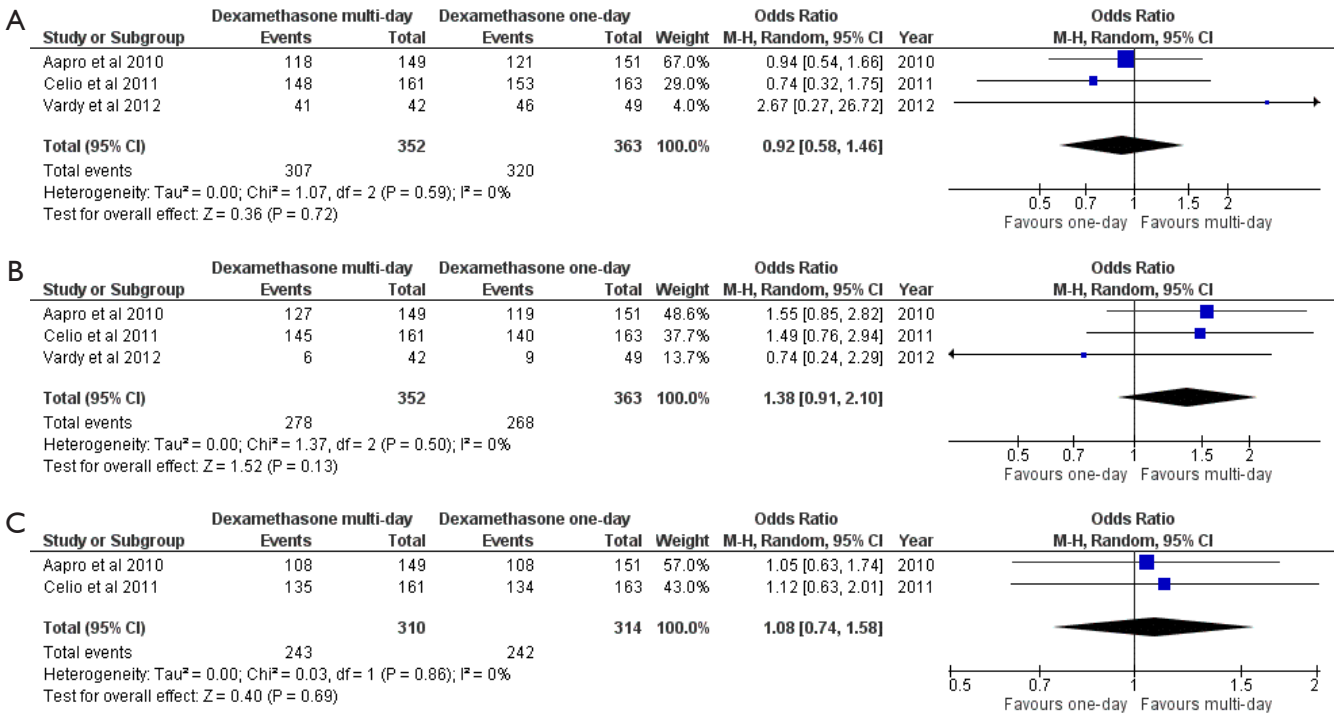

Figure S2 Efficacy of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting—no emesis. (A) acute phase; (B) delayed phase; (C) overall phase.

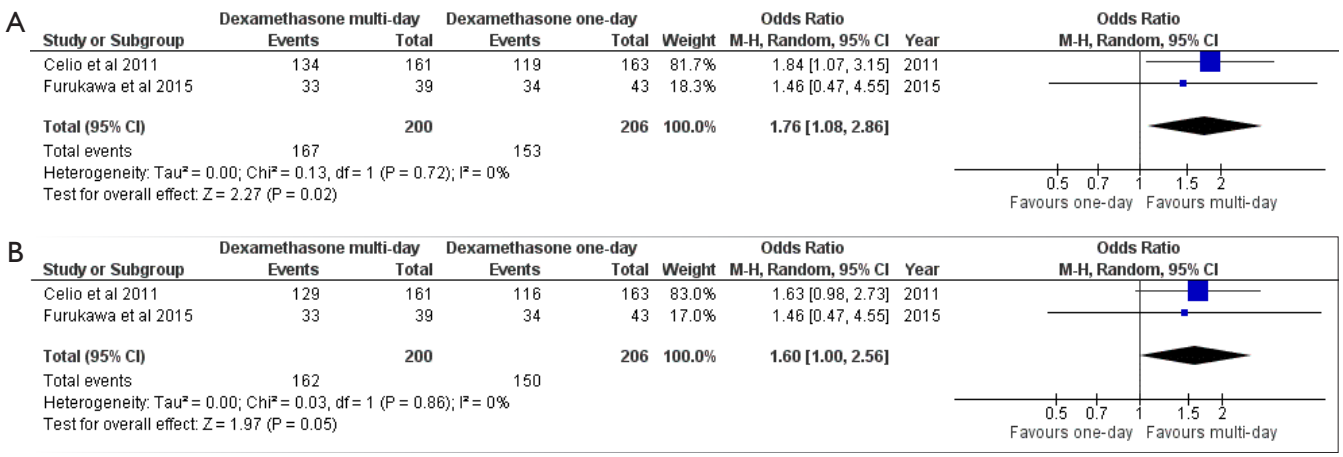

Figure S3 Efficacy of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting—no use of rescue medication. (A) delayed phase; (B) overall phase.

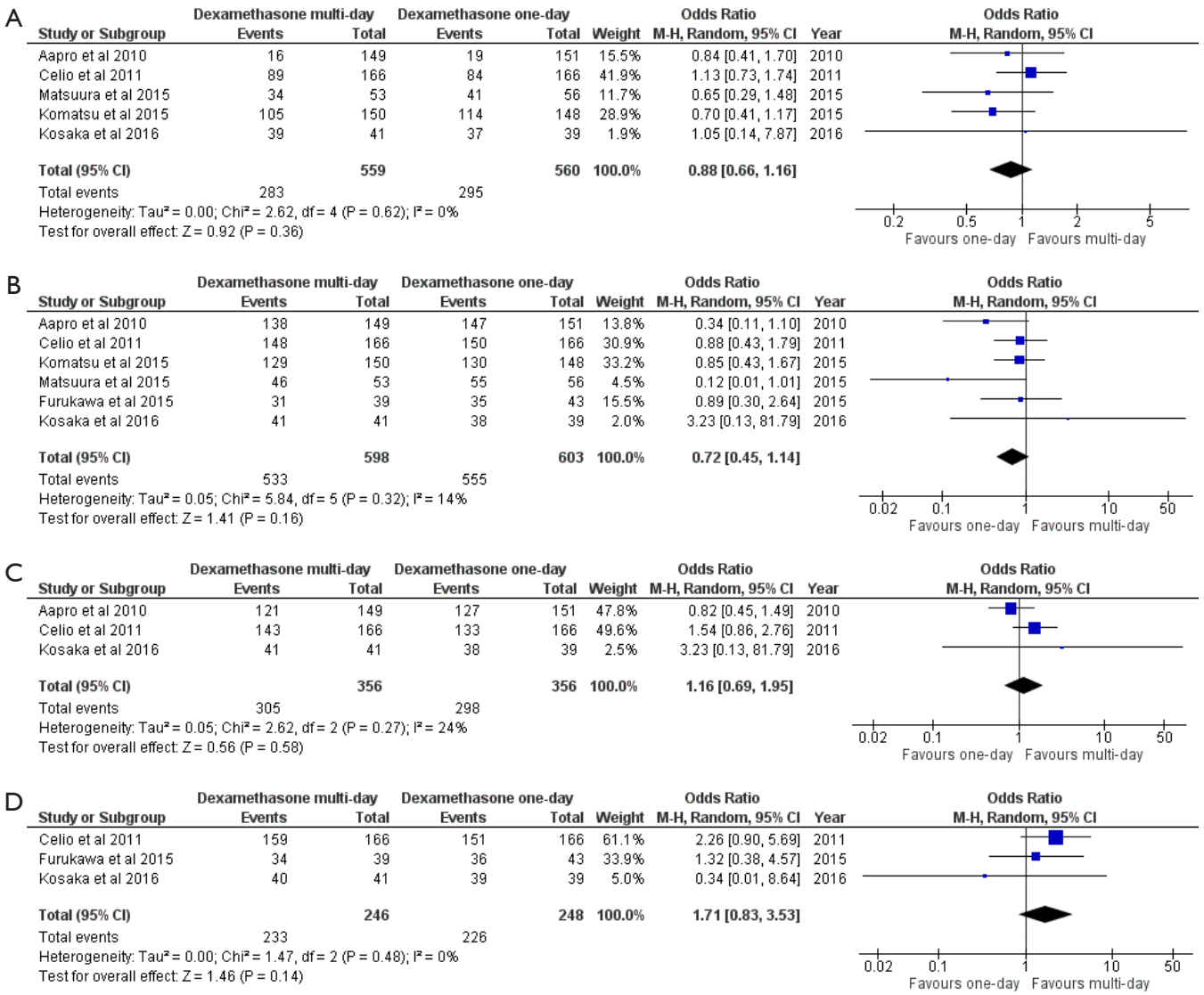

Figure S4 Safety of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting. (A) no adverse events; (B) no constipation; (C) no headache; (D) no fatigue/insomnia.