Original Article

Prophylaxis of radiation-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials

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Background: The aim of this article was to systematically review the efficacy and safety of various antiemetics in prophylaxis of radiation-induced nausea and vomiting (RINV).

Methods: A literature search of Ovid MEDLINE, EMBASE and Cochrane CENTRAL was performed to identify randomized controlled trials (RCTs) that evaluated the efficacy of prophylaxis for RINV in patients receiving radiotherapy to abdomen/pelvis, including total body irradiation (TBI). Primary endpoints were complete control of nausea and complete control of vomiting during acute and delayed phases. Secondary endpoints included use of rescue medication, quality of life (QoL) and incidence of adverse events.

Results: Seventeen RCTs were identified. Among patients receiving radiotherapy to abdomen/pelvis, our meta-analysis showed that prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist (5HT3 RA) was significantly more efficacious than placebo and dopamine receptor antagonists in both complete control of vomiting [OR 0.49; 95% confidence interval (CI): 0.33–0.72 and OR 0.17; 95% CI: 0.05–0.58 respectively] and complete control of nausea (OR 0.43; 95% CI: 0.26–0.70 and OR 0.46; 95% CI: 0.24–0.88 respectively). 5HT3 RAs were also more efficacious than rescue therapy and dopamine receptor antagonists plus dexamethasone. The addition of dexamethasone to 5HT3 RA compared to 5HT3 RA alone provides a modest improvement in prophylaxis of RINV. Among patients receiving TBI, 5HT3 RA was more effective than other agents (placebo, combination of metoclopramide, dexamethasone and lorazepam).

Conclusions: 5HT3 RAs are more effective than other antiemetics for prophylaxis of RINV in patients receiving radiotherapy to abdomen/pelvis and TBI. Future RCTs should investigate the efficacy of newer agents such as substance P neurokinin 1 receptor antagonists in addition to 5HT3 RAs in prophylaxis of RINV during both acute and delayed phases.

Keywords: 5-HT3 receptor antagonist; radiation-induced nausea and vomiting (RINV); prophylaxis; systematic review

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Introduction

More than a century ago, Walsh (1) reported acute constitutional symptoms in an X-ray worker. In 1953, it was further characterized by Brown (2) with a distinct pattern of symptomatic disturbance after a single radiation dose, now known as radiation-induced nausea and vomiting

(RINV). Of all patients receiving radiotherapy, 50–80% can develop RINV depending on the site of radiotherapy (3). In particular, those receiving total body irradiation (TBI), half body irradiation (HBI), and radiotherapy to upper abdomen are at a higher risk of RINV.

RINV is a distressing symptom and uncontrolled RINV can lead to potential complications such as dehydration and electrolyte disturbances. It could also result in interruption or even discontinuation of radiotherapy, thereby jeopardizing the treatment outcome. Recently, Poon *et al.* (4) showed that worse subjective experiences of RINV correlated with poorer quality of life (QoL). Therefore, awareness of RINV and more appropriate use of antiemetic agents could improve patients' subjective experience, leading to better QoL.

The pathophysiology of RINV is uncertain and is currently postulated to be similar to that of chemotherapy induced nausea and vomiting (CINV) (5). The gastrointestinal tract is a major reservoir of serotonin and the serotonin pathway is thought to play a major role in RINV (4,6). Radiation induces damage to the gastrointestinal mucosa and causes release of serotonin (7), which activates 5-hydroxytryptamine-3 (5-HT3) receptors on afferent vagal nerves that transmit the signal to the brainstem vomiting centre, thus mediating nausea and vomiting (8). Therefore, 5-HT3 receptor antagonists (5-HT3 RA) are indicated in the treatment and prophylaxis of RINV.

Current antiemetic guidelines classify radiotherapy treatment into minimal, low, moderate, and high risk of RINV, mainly based on the anatomical site being irradiated (3,9). Apart from the site of radiation, the incidence and severity of RINV is affected by other treatment factors (dose per fraction, total dose, radiation field size, radiation technique and concurrent chemotherapy) (3,10) and patient factors (previous CINV, gender, age, anxiety and daily alcohol consumption) (11).

For patients at high emetogenic risk (i.e., receiving TBI or total nodal irradiation), current guidelines recommend prophylaxis with a 5HT3 RA and a short course of dexamethasone (3,9). For patients at moderate emetogenic risk (i.e., receiving radiotherapy to the upper abdomen or HBI), the guidelines recommend prophylaxis with a 5HT3 RA plus an optional short course of dexamethasone. For patients at low emetogenic risk, the guidelines recommend prophylaxis or rescue with a 5-HT3 RA. For patients at minimal emetogenic risk, the recommendation is rescue with a dopamine receptor antagonist or 5HT3 RA.

Despite the publication of various guidelines on the management of RINV, the use of antiemetics is often reported to be suboptimal. Maranzano *et al.* (10) prospectively analyzed 1,020 patients undergoing radiotherapy in 45 Italian radiation oncology centres. An antiemetic was only prescribed to a minority (17%) of patients, despite the fact that 27.9% of patients had nausea and/or vomiting. Enblom *et al.* (12) reported that one third of patients with radiation induced nausea considered their antiemetic treatment insufficient. More recently, a survey on international pattern of practices by Dennis *et al.* (11) noted the low awareness of antiemetic guidelines among 1,022 radiation oncologists from 12 countries and the insufficient recommendation of antiemetics compared with guideline recommendations, especially for moderate risk cases.

The objective of our systematic review was to evaluate the efficacy of various antiemetics in the prophylaxis of RINV among randomized controlled trials (RCTs).

Methods

Search strategy

A literature search was performed on Ovid MEDLINE (1946 to September 2015), EMBASE (1947 to September 2015), and Cochrane CENTRAL (until September 2015) databases. The following keywords were used: "neoplasms", "neoplasm", "cancer", "tumor", "tumour", "radiotherapy", "nausea", "vomiting" and "drug therapy". Reference lists of identified articles were also searched to find additional studies.

Study selection

We included all RCTs that evaluated the efficacy of prophylaxis for RINV in patients receiving radiotherapy to the abdomen and/or pelvic region, including TBI. We only included articles that were written in English and studies that were published. We excluded studies where concomitant chemotherapy was used to avoid the confounding effect of chemotherapy on nausea and vomiting. We also excluded studies with previously published duplicate data.

Four reviewers (Wing S. Li, Joanne M. van der Velden, Vithusha Ganesh and Sherlyn Vuong) were organized in pairs to screen the titles and abstracts of identified citations independently. Full texts of citations were obtained if judged as potentially eligible by at least one reviewer. Full texts were then screened by the reviewers and selected according

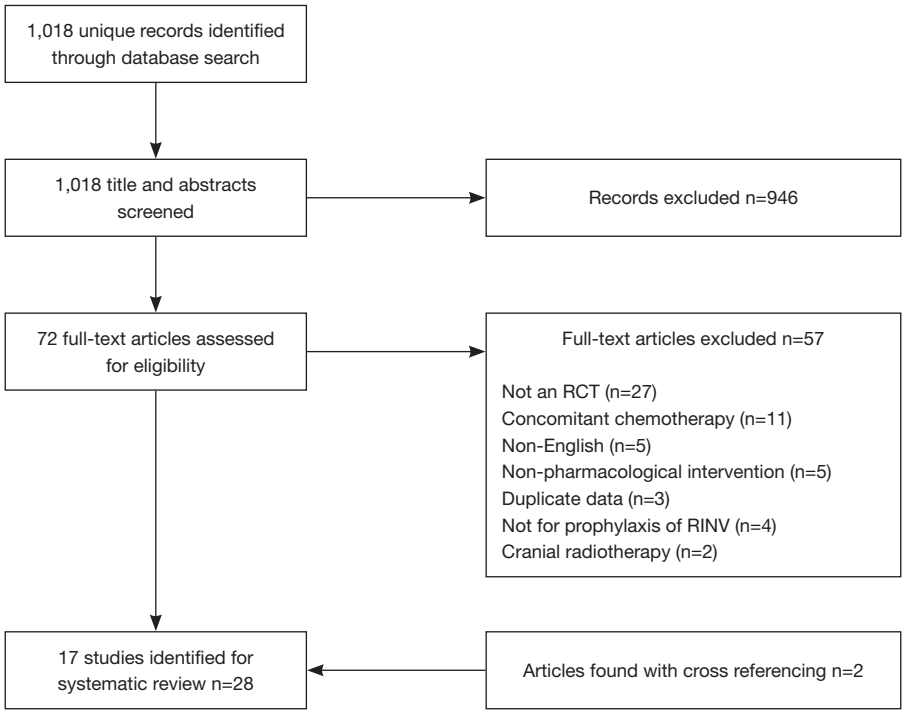

Figure 1 Flow of information for articles included in systematic review.

to eligibility criteria. Disagreements were resolved by consensus.

Endpoints

The primary endpoints were complete control of nausea (defined as no nausea episodes) and complete control of vomiting (defined as no emetic episodes) during the acute phase (from the first day to last day of radiotherapy) and delayed phase (study period after completion of radiotherapy). Secondary endpoints included the use of rescue medication, QoL and incidence of adverse events.

Data analysis

Statistical analysis was performed using Review Manager (RevMan 5.3) from Cochrane IMS. The Mantel-Haenszel method was applied and a random effects analysis model was used to generate odds ratios (OR), absolute risk differences (RD), and accompanying 95% confidence intervals (CI). A P value of less than 0.05 was considered statistically significant in the test for overall effect, whereas heterogeneity test with a P value greater than 0.05 was considered suitable.

Results

The search yielded 1,018 unique citations. After title and abstract screening, we retrieved and screened the full-texts of 72 articles. Two references were identified for the study by Collis *et al.* (13,14). Reference (14) was the interim analysis of the study with description of the methodology while reference (13) reported the final analysis of the study. Two additional studies were retrieved by cross-referencing. These two studies were not identified in our primary search because the keyword 'cancer' or 'neoplasm' was not selected by the authors of the studies (15,16). In total, 17 RCTs were included in this systematic review (*Figure 1*).

The characteristics of the included 17 RCTs are summarized in *Table 1*. Fourteen studies included patients receiving radiotherapy to the abdomen and/or pelvic regions. Among these 14 RCTs, three studies (22,23,28) compared a 5HT3 RA against placebo, three studies (13,20,24) compared a 5HT3 RA against a dopamine receptor antagonist and one study (25) compared a 5HT3 RA against rescue therapy. One study (30) compared the combination of a 5HT3 RA and dexamethasone against a 5HT3 RA plus placebo, another study (26) compared a 5HT3 RA against chlorpromazine plus dexamethasone,

Table 1 Details of all randomized control trials

Study	Study design	Sample size	Intervention	Radiotherapy details	Outcome	Toxicity
Sicher *et al.* 1968 (17)	Open-labelled RCT	Group 1: 50 patients for induction of artificial menopause; Group 2: 15 patients with pelvic malignancy	Thiethylperazine 10 mg tds or pyridoxine 20 mg tds	Group 1: ovarian ablation with RT to pelvis 10–12 Gy/5 Fr. Group 2: RT to whole abdomen and pelvis, 35 Gy/1 month	Group 1: complete control of RINV: 78.3% *vs.* 50%; complete control of vomiting: 87% *vs.* 87.5%. Group 2: complete control of RINV: 71.4% *vs.* 0%; complete control of vomiting: 100% *vs.* 25%	No specific enquiry was made for side-effects in this investigation, but no patient made complaint in either group
Stryker *et al.* 1979 (18)	Non-blinded RCT	35 patients with pelvic irradiation	Oral ibuprofen 400 mg qid throughout RT course; control group received no treatment; both groups received rescue therapy with oral prochlorperazine 10 mg tid as needed	Whole pelvis irradiation, 1.7–1.8 Gy/Fr, 5 Fr/week, for 5–6 weeks	Complete control of vomiting: 100% *vs.* 73% ($P<0.05$). Complete control of nausea: 65% *vs.* 60%	Dizziness in 2 patients, 'heart pounding' in 1 patient in the ibuprofen group
Lucraft *et al.* 1982 (19)	Open-labelled RCT	43 patients receiving palliative RT	Chlorpromazine 25 mg or Levonantradol 0.5 mg or Levonantradol 0.75 mg; half an hour before RT	Single fraction palliative RT to sites close to upper abdomen (lower thoracic spine and/or lumbar spine; hypochondrium), 10–15 Gy	Complete control of vomiting at 0–4 hr: Chlorpromazine 25 mg: 50%; Levonantradol 0.5 mg: 35.7%; Levonantradol 0.75 mg: 47%	The most frequent side effects in all three groups were mild, transient drowsiness and dry mouth. Two patients received Levonantradol 0.5 mg during the pilot study became mildly confused and disorientated for a few hours after treatment
Collis *et al.* 1991 (13,14)	Multi-center, double-blind RCT	121 patients receiving SF RT	Oral ondansetron 8 mg tds or oral metoclopramide 10 mg tds, continued for a minimum of 3 days and for up to 5 days if needed	Single RT fraction, 8–10 Gy midpoint dose, to upper abdomen, 80–100 cm^2 T10–L2 or >100 cm^2 T8–L3	Complete control of emesis in the first 24 hours: 92% *vs.* 46%. Complete control of nausea in the first 24 hours: 67% *vs.* 39%. Complete or major control (≤2 episodes) of emesis: day 1 100% *vs.* 71%; day 2 98% *vs.* 86%; day 3 100% *vs.* 93%; day 4 98% *vs.* 91%; day 5 98% *vs.* 96%. Control of nausea (none or mild): day 1 88% *vs.* 60%; day 2 82% *vs.* 76%; day 3 75% *vs.* 76%; day 4 79% *vs.* 84%; day 5 74% *vs.* 83%	NA

Table 1 (*continued*)

Table 1 (*continued*)

Study	Study design	Sample size	Intervention	Radiotherapy details	Outcome	Toxicity
Priestman *et al.* 1993 (20)	Multi-center, double-blind RCT	192 patients receiving at least 5 fractions RT	Oral ondansetron 8 mg tds or oral prochlorperazine 10 mg tds throughout radiation course and for up to 3 days after completion of RT	≥5 daily fractionated RT to the upper abdomen T11–L3, >100 cm^2, minimum dose of 1.8 Gy/Fr	Complete control of emesis: 59.2% *vs.* 35.1% (P<0.001). Complete control of nausea: 30.6% *vs.* 21.3%	Constipation 11.2% *vs.* 0%. Dysphagia 1% *vs.* 1.1%. Diarrhoea 0% *vs.* 1.1%. Headache 3.1% *vs.* 0%
Spitzer *et al.* 1994 (21)	Single-center placebo-controlled double-blind RCT	20 patients with leukemia, lymphoma, or aplastic anemia	Oral ondansetron 8 mg, 1.5 hours before each dose of RT or placebo	Total body irradiation 1.2 Gy/Fr, for 11 fractions over 4 days (3 Frs on day 1–3 and 2 Frs on day 4)	Day 1: control of emesis (≤2 emetic episodes): 60% *vs.* 10% (P=0.022). Day 1–4: control of emesis (≤2 emetic episodes): 50% *vs.* 0% (P=0.012). Need of rescue therapy: 40% *vs.* 0%	No serious adverse events. Most common adverse event was headache as reported by 6 patients (60%) in ondansetron arm and 5 patients (50%) in placebo arm who also received IV ondansetron as rescue
Prentice *et al.* 1995 (15)	Double-blind RCT	30 patients receiving TBI prior to bone marrow transplantation	Granisetron 3 mg IV. or metoclopramide 20 mg IV plus dexamethasone 6 mg/m^2 IV and lorazepam 2 mg IV (standard therapy)	TBI with an average total dose of 7.5 Gy over a mean period of 1.2 h	Complete control of vomiting during first 24 h: 53% *vs.* 13.3% (P=0.001). Complete control of vomiting over 7 days: 13.3% *vs.* 6.7% (P=0.004). Use of rescue medication during first 24 hr: 26.7% *vs.* 46.7%. Use of rescue medication over 7 days: 46.7% *vs.* 93.3% (P=0.005)	Headache 53.3% *vs.* 20%. Drowsiness 33.3% *vs.* 46.7%
Bey *et al.* 1996 (22)	Multi-center, placebo-controlled, double-blind RCT	50 patients with abdominal malignancies	0.3, 0.6, 1.2 mg/kg IV dolasetron mesilate or placebo 30 minutes before RT	Single fraction at least 6 Gy to the upper abdomen (RT fields of either 80–100 cm^2 T10–L2 or 100–150 cm^2 T8–L3)	Complete response (no emetic episodes and no rescue medication during the 24 hours study period): 0.3 mg/kg: 91% (P=0.05); 0.6 mg/kg: 71% (P=0.372); 1.2 mg/kg: 58% (P=0.804); Placebo: 54%. Complete + major response (0–2 emetic episodes and no rescue therapy): 0.3 mg/kg: 100% (P=0.011); 0.6 mg/kg: 93% (P=0.019); 1.2 mg/kg: 83% (P=0.103); Placebo: 54%. No nausea (investigator assessment): 0.3 mg/kg: 91%; 0.6 mg/kg: 86%; 1.2 mg/kg: 67%; Placebo: 54%. Use of rescue medication: 0.3 mg/kg: 9%; 0.6 mg/kg: 7%; 1.2 mg/kg: 8%; Placebo: 46%	The majority of adverse events were mild to moderate in intensity: overall 43.2% *vs.* 7.7%; abdomen pain 8.1% *vs.* 0%; tachycardia 5.4% *vs.* 7.7%; headache 2.7% *vs.* 0%

Table 1 (*continued*)

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Study	Study design	Sample size	Intervention	Radiotherapy details	Outcome	Toxicity
Franzén *et al.* 1996 (23)	Multi-center, placebo-controlled, double-blind RCT	111 patients with gastrointestinal, genitourinary, gynaecological and haematological malignancies	Oral ondansetron 8 mg bid or placebo	A course of 10 or more daily fractionated RT including the abdomen	Complete control of emesis: 67% *vs.* 45% (P<0.05). Major emetic response (0-2 emetic episodes): 85% *vs.* 61% (P<0.01). Complete control of nausea: 17% *vs.* 9% (P=0.075)	NA
Aass *et al.* 1997 (24)	Single-centre, open-labelled RCT	23 patients with stage I seminoma	Oral tropisetron 5 mg daily or oral metoclopramide 10 mg tid	Adjuvant abdominal radiotherapy covering para-aortic and ipsilateral iliac region 30 Gy/15 Fr/ 3 weeks	Emesis 9.1% *vs.* 50% (P=0.07). Mean score of nausea (based on daily visual analogue scale) 0.14 *vs.* 1.32 (P=0.03). Significant nausea (a score of >25 mm on visual analogue scale) on at least one day 18.2% *vs.* 75% (P=0.01)	Constipation 18.2% *vs.* 0%
Khoo *et al.* 1997 (25)	Randomized 2x2 factorial design	20 patients with stage I seminoma of testis	Prophylactic oral ondansetron 8mg 8-hourly or oral metoclopramide 10–20 mg 8-hourly when requested by patient	Dog-leg or para-aortic RT 30 Gy/15 Fr/ 3 weeks	Complete prophylaxis of nausea: 40% *vs.* 0% (P=0.02). Proportion of treatment days with no nausea 67% *vs.* 34% (P=0.02). Complete prophylaxis of vomiting: 80% *vs.* 30% (P=0.06). Use of rescue medication: 20% *vs.* 70%	Headache 60% *vs.* 80%. Lethargy 80% *vs.* 100%. A trend of less diarrhoea with para-aortic RT and ondansetron (P=0.06)
Sykes *et al.* 1997 (26)	Open-labelled RCT	66 patients with palliative RT	Oral ondansetron 8 mg 1–2 h before RT and 12 mg 12 h after RT, then ondansetron; 8 mg bid for 3 more days after RT; oral chlorpromazine 25 mg 1h before RT and 8 h after RT plus dexamethasone 6 mg 1 h before RT, then chlorpromazine 25 mg tds for 3 more days after RT	Lower half body RT with a mid-plane dose 8 Gy or RT to the upper lumbar spines, single fraction with of 12.5 Gy incident dose	Complete or major control (0–2 emetic episodes) of emesis on day 1: 93.9% *vs.* 34.4% (P<0.001). Delayed emesis (days 2–4): day 2: 96.2% *vs.* 42.9% (P<0.001); day 3: 96.2% *vs.* 39.3% (P<0.001); day 4: 96% *vs.* 37% (P<0.001). Complete control of nausea on day 1: 70% *vs.* 28% (P<0.001)	No significant difference in the levels of adverse effects between the two regimens, though there was less drowsiness in the ondansetron group
Kirkbride *et al.* 2000 (27)	Multi-center, placebo-controlled, double-blind RCT	154 patients receiving fractionated RT	Prophylactic dexamethasone (2 mg tid, starting in the morning of first treatment and continuing until after fifth treatment) or placebo	RT involving an area of at least 80 cm^2 in upper abdomen T11–L3, minimum 20 Gy total dose and minimum 5 fractions	Complete prophylaxis of emesis: 70% *vs.* 49% (P=0.025). Use of rescue medication: 29% *vs.* 43% (P=0.125)	Only 1 patient in the placebo arm developed grade 3 abdominal pain, otherwise there was no difference in toxicities between the 2 arms and no other toxicities greater than grade 2

Table 1 (*continued*)

Table 1 (*continued*)

Study	Study design	Sample size	Intervention	Radiotherapy details	Outcome	Toxicity
Spitzer *et al.* 2000 (16)	Double-blind RCT with extra historical control	34 patients, additional 90 patients as historical control	Oral ondansetron 8 mg 1.5 h before each fraction of RT or oral granisetron 2 mg 1 hour prior to first daily fraction of RT; unspecified in the historical control	TBI 13.2 Gy in 11 fractions over 4 days	Complete control of vomiting: granisetron group 33%; ondansetron group 26.7%; historical control 0%. Complete control of nausea: granisetron group 11.1%; ondansetron group 13.3%; historical control 0%.	Headache 18.8% *vs.* 27.8%. Diarrhoea 6.3% *vs.* 22.2%. Asthenia 0% *vs.* 11.1%.
Lanciano *et al.* 2001 (28)	Multi-center, placebo-controlled, double-blind RCT	260 patients with cancer	Oral granisetron 2 mg daily or placebo, 1 hour before RT on each scheduled treatment day	10–30 fractions of RT to upper abdomen (T11–L3 with a field size at least 100 cm^2)	Complete prophylaxis of emesis: 57.5% *vs.* 42.1% (P=0.0047). Complete prophylaxis of nausea: 30.6% *vs.* 16.7% (P=0.0042)	The most commonly reported adverse events in patients treated with granisetron were diarrhea (27.6%), asthenia (25.4%) and constipation (19.4%), in patients treated with placebo were diarrhea (33.8%), asthenia (19.2%), and headache (11.5%). Most were mild to moderate
Martin *et al.* 2002 (29)	Placebo-controlled, double-blind RCT	56 patients receiving adjuvant pelvic irradiation after curative surgery	Enzyme group: 3×4 capsules containing papain, trypsin and chymotrypsin daily. Placebo group: placebo capsules	Pelvic irradiation using box-technique, 50.4 Gy/28 Fr/5.5 weeks	None/mild nausea: 93% *vs.* 93%. Moderate/severe nausea: 7% *vs.* 7%. None/mild vomiting: 100% *vs.* 97%	NA
Wong *et al.* 2006 (30)	Multi-center, placebo-controlled, double-blind RCT	211 patients receiving RT	Oral ondansetron 8 mg BID with dexamethasone 4 mg daily or placebo during fractions 1 to 5	Radiotherapy to the upper abdomen T11–L3, area ≥80 cm^2, total dose ≥20 Gy, at least 15 fractions	Fractions 1–5 (prophylactic period): complete control of nausea: 50% *vs.* 38% (P=0.06); complete control of emesis: 78% *vs.* 71% (P=0.14); average nausea score (maximum =4): 0.24 *vs.* 0.2 (P=0.08); use of rescue medication: 10% *vs.* 15% (P=0.2). Fractions 1–15: complete control of nausea: 15% *vs.* 9% (P=0.14); complete control of emesis: 23% *vs.* 12% (P=0.02); average nausea score: 0.28 *vs.* 0.39 (P=0.03); use of rescue medication: 70% *vs.* 80% (P=0.09)	Overall: 50% *vs.* 57%. Constipation: 27% *vs.* 20%. Headache: 18% *vs.* 12%. Dyspepsia: 16% *vs.* 17%. One patient in the dexamethasone group experienced grade 3 gastric ulcer

tds, three times a day; tid, three times a day; bid, twice a day; Fr, fraction; RT, radiotherapy; NA, not available; SF, single fraction; IV, intravenous; hr, hour; RCT, randomized controlled trial.

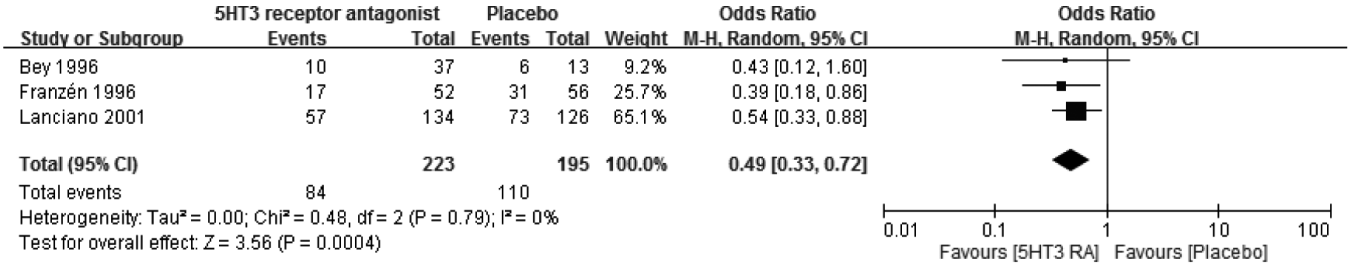

Figure 2 5HT3 receptor antagonist versus placebo, outcome: vomiting during acute phase.

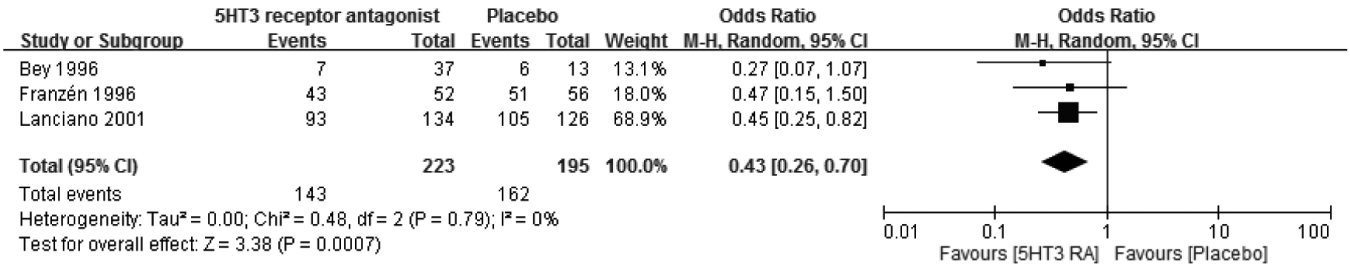

Figure 3 5HT3 receptor antagonist versus placebo, outcome: nausea during acute phase.

and one other study (27) compared dexamethasone against placebo. The remaining four studies (17-19,30) investigated other agents including thiethylperazine (an antiemetic of phenothiazine group acting as a dopamine receptor antagonist), pyridoxine, ibuprofen [non-steroidal anti-inflammatory drug (NSAID)], levonatradol (cannabinoid) and enzyme capsules (containing papain, trypsin and chymotrypsin). Beyond abdominal and/or pelvic radiation, the other three RCTs (15,16,21) included patients receiving TBI. Among these three, one compared a 5HT3 RA against placebo (21), one compared a 5HT3 RA with the combination of metoclopramide, dexamethasone and lorazepam (15), and the remaining study (16) compared two 5HT3 RAs, ondansetron versus granisetron, against each other.

Complete control of RINV in the acute phase

Radiotherapy to the abdomen and/or pelvic regions

A meta-analysis was not performed for all studies that compared a 5HT3 RA against another antiemetic in view of the high degree of clinical heterogeneity among all studies that compared a 5HT3 RA with different therapy groups. To facilitate the comparison of 5HT3 RAs with different antiemetics, the analysis was separated by comparison groups.

5HT3 RA versus placebo

Meta-analysis of three RCTs (22,23,28) showed a significant benefit of 5HT3 RA over placebo in both complete control of vomiting (OR 0.49; 95% CI: 0.33–0.72, *Figure 2*) and complete control of nausea (OR 0.43; 95% CI: 0.26–0.70, *Figure 3*).

5HT3RA versus dopamine receptor antagonist

Meta-analysis of three RCTs (13,20,24) demonstrated a significant benefit of 5HT3 RA over dopamine receptor antagonists (metoclopramide, prochlorperazine) in complete control of vomiting (OR 0.17; 95% CI: 0.05–0.58, *Figure 4*). 5HT3 RA was also superior to dopamine receptor antagonists in complete control of nausea in two RCTs (13,20) (OR 0.46; 95% CI: 0.24–0.88, *Figure 5*). One study (24) was excluded from the meta-analysis of complete control of nausea because it did not report the proportion of patients that had no nausea during the study period. Instead, it reported a higher mean score of nausea [based on daily visual analogue scale (VAS)] and more patients suffered from significant nausea (defined by a score of >25 mm on the VAS) in the metoclopramide group compared with the tropisetron group.

5HT3 RA versus rescue therapy

Only one study was identified. In patients receiving multiple-fraction dog-leg or para-aortic radiotherapy, Khoo *et al.* (25) showed that prophylactic oral ondansetron

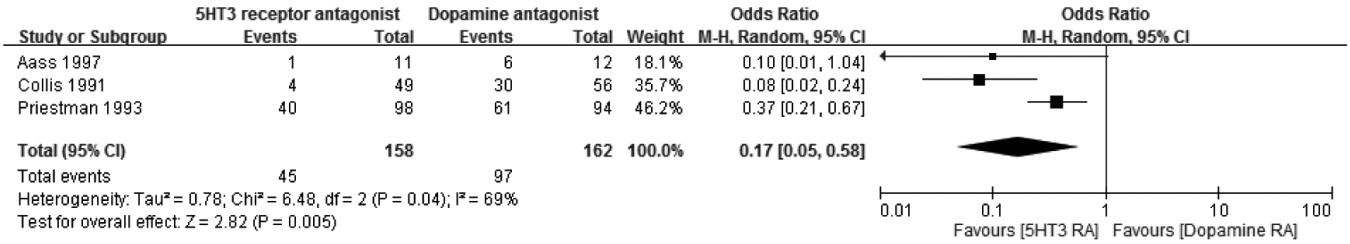

Figure 4 5HT3 receptor antagonist versus dopamine receptor antagonist, outcome: vomiting during acute phase.

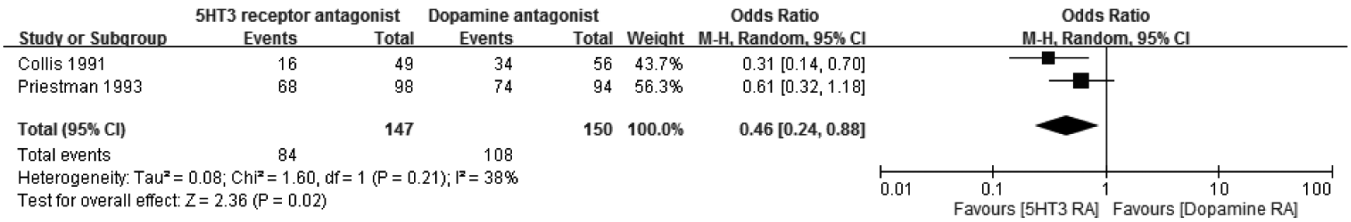

Figure 5 5HT3 receptor antagonist versus dopamine receptor antagonist, outcome: nausea during acute phase.

was better than rescue therapy with metoclopramide in complete control of nausea (67% *vs.* 34%, P=0.02). There was a trend towards better complete control of vomiting (80% *vs.* 30%, P=0.06)

5HT3 RA versus dopamine receptor antagonist plus dexamethasone

The single study by Sykes *et al.* (26) demonstrated that oral ondansetron was more effective in complete or major control (0–2 emetic episodes) of vomiting (93.9% *vs.* 34.4%, P<0.001) and complete control of nausea (70% *vs.* 28% P<0.001) than the combination therapy of chlorpromazine and dexamethasone in patients undergoing single fraction radiotherapy to upper abdomen or lower HBI.

5HT3 RA plus dexamethasone versus 5HT3 RA plus placebo

Wong *et al.* (30) investigated the addition of a short course of dexamethasone (fractions 1–5) to ondansetron in patients receiving radiotherapy (≥15 fractions) to the upper abdomen. During the prophylactic period (fractions 1–5), the dexamethasone arm showed a trend of better complete control of nausea (50% *vs.* 38%, P=0.06), while complete control of vomiting was similar (78% *vs.* 71%, P=0.14). During the overall study period (fractions 1–15), complete control of vomiting was better (23% *vs.* 12%, P=0.02) and the average nausea score (using a 4-point scale) was lower (0.28 *vs.* 0.39, P=0.03) in the dexamethasone arm, while complete control of nausea was similar (15% *vs.* 9%, P=0.14).

Dexamethasone versus placebo

Kirkbride *et al.* (27) reported better complete control of vomiting (70% *vs.* 49%, P=0.025) in patients receiving dexamethasone prophylaxis during multiple-fraction radiotherapy to the upper abdomen.

Other agents

Sicher *et al.* (17) investigated the efficacy of thiethylperazine against pyridoxine in patients undergoing ovarian ablation (group 1) or radiotherapy to whole abdomen and pelvis (group 2). It was shown that thiethylperazine was more effective in the complete control of RINV (78.3% *vs.* 50%, P<0.01 in group 1 and 71.4% *vs.* 0%, P<0.01 in group 2) than pyridoxine. In patients receiving whole pelvic irradiation, Stryker *et al.* (18) reported that patients on oral ibuprofen had better complete control of vomiting (100% *vs.* 73%, P<0.05) but similar complete control of nausea (65% *vs.* 60%) compared to the control group with no prophylactic treatment. In the study by Lucraft *et al.* (19), levonantradol had no advantage over chlorpromazine in the complete control of vomiting [41.4% *vs.* 50%, P value not reported (NR)] in patients receiving single fraction palliative radiotherapy to the upper abdomen. Finally, Martin *et al.* (29) compared enzyme capsules (containing papain, trypsin and chymotrypsin) with placebo in patients receiving pelvic irradiation. There was no difference in the control of vomiting (none/mild vomiting) (100% *vs.* 97%, P value NR) or the control of nausea (none/mild nausea) (93% *vs.* 93%) between the two groups.

TBI

A pooled analysis was not performed because the three RCTs compared 5HT RAs with different agents.

5HT3 RA versus placebo

Spitzer *et al.* (21) showed that patients in the ondansetron arm had better control of vomiting (≤2 episodes) (50% *vs.* 0%, P=0.012) during four days of TBI.

5HT3 RA versus the combination of metoclopramide, dexamethasone and lorazepam

Prentice *et al.* (15) demonstrated better complete control of vomiting (53% *vs.* 13.3%, P=0.001) during the acute phase in the granisetron arm relative to combination treatment.

Granisetron versus ondansetron

Complete control of vomiting (33% *vs.* 26.7%) and complete control of nausea (11.1% *vs.* 13.3%) were similar between the two groups as reported in the study by Spitzer *et al.* (16).

Complete control of RINV in the delayed phase

Only three studies evaluated control of delayed nausea and vomiting. Collis *et al.* (13) reported that ondansetron resulted in better complete or major control (≤2 episodes) of vomiting (day 2 98% *vs.* 86%; day 3 100% *vs.* 93%; day 4 98% *vs.* 91%; day 5 98% *vs.* 96%) yet similar control of (none or mild) nausea (day 2 82% *vs.* 76%; day 3 75% *vs.* 75%; day 4 79% *vs.* 84%; day 5 74% *vs.* 83%) when compared with metoclopramide in patients receiving single fraction radiotherapy to the upper abdomen. Sykes *et al.* (26) showed better complete or major control (0–2 episodes) of vomiting on days 2–4 (day 2: 96.2% *vs.* 42.9%; day 3 96.2% *vs.* 39.3%; day 4 96% *vs.* 37%, P<0.001) with ondansetron relative to chlorpromazine plus dexamethasone in patients receiving single fraction HBI or radiotherapy to the upper lumbar spine. Finally, Prentice *et al.* (15) showed that granisetron was only slightly better than the combination therapy of metoclopramide, dexamethasone and lorazepam in complete control of vomiting over 7 days (13.3% *vs.* 6.7%, P=0.004) after TBI on day 1.

Use of rescue medication

Five RCTs investigated the use of rescue medication (15,16,24,27,30). Aass *et al.* (24) reported a similar proportion of patients (18.2% *vs.* 25%, P value NR) requiring rescue medication in both tropisetron and metoclopramide groups. Wong *et al.* (30) demonstrated a trend towards less use of rescue medications (70% *vs.* 80%, P=0.09) with addition of dexamethasone to ondansetron. In the study by Kirkbride *et al.* (27), it appeared that less patients in the dexamethasone group required rescue medication than those in the placebo group (29% *vs.* 43%, P=0.125). In patients receiving TBI, Spitzer *et al.* (16) reported that fewer patients in the ondansetron group required additional rescue medication than those in the placebo group (40% *vs.* 0%, P value NR). Prentice *et al.* (15) also showed that significantly fewer patients receiving TBI in the granisetron group required additional rescue medication compared with the combination therapy of metoclopramide, dexamethasone and lorazepam (46.7% *vs.* 93.3%, P=0.05).

QoL

Four trials evaluated QoL in patients receiving antiemetics during the study period. Franzén *et al.* (23) used the EORTC QLQ-C30 questionnaire for evaluation before the start of treatment, at two weeks and at the end of treatment. Patients in the ondansetron group reported better functioning, global QoL and lower symptom levels at week 2 than those in the placebo group. Wong *et al.* (30) evaluated QoL using the EORTC QLQ-C30 questionnaire as well. With the addition of dexamethasone to ondansetron, there were significant benefits in appetite, nausea and vomiting and a trend favouring global QoL improvement. However, there were marginally worse outcomes in the sleep and constipation scales. Sykes *et al.* (26) used the Functional Living Index Cancer (FLIC) and Functional Living Index Emesis (ELIE) QoL questionnaires before treatment and at the end of study. There was no difference for the FLIC questionnaire, but there was a difference in favour of the ondansetron group over the chlorpromazine plus dexamethasone group for the FLIE questionnaire. Kirkbride *et al.* (27) also utilized the EORTC QLQ-C30 questionnaire for evaluating QoL outcomes. There was no difference in global QoL between the two arms, but patients in the dexamethasone group had better scores in the domains of nausea/vomiting and appetite but a lower score in the domain of sleep when compared with patients in the placebo group.

Adverse events

The adverse events of various agents are summarized in *Table 1*. A pooled analysis could not be performed among the clinical studies as the results were reported in different

ways. Two studies reported a higher overall rate of adverse events in the 5HT3 RA group over the placebo group [43.2% *vs.* 7.6%, P value NR in the study by Bey *et al.* (22) and 82.1% *vs.* 69.2%, P value NR in the study by Lanciano *et al.* (28)]. In general, the adverse events were usually mild to moderate in severity. There was no grade 5 or serious toxicity reported. The more commonly reported side-effects of 5HT3 RAs include headache (2.7–53.3%) and constipation (11.2–20%). Other less commonly reported adverse events are abdominal pain (8.1%), asthenia (11.1–25.4%), drowsiness (33.3%), and tachycardia (5.4%). The side effect of constipation with 5HT RAs could be advantageous in patients receiving radiotherapy to the abdomen /pelvic region, where diarrhea can be a side effect from radiation. Khoo *et al.* (25) reported a trend of reduced diarrhea with ondansetron in patients receiving para-aortic field radiotherapy.

Discussion

Our systematic review demonstrated that 5HT3 RA was significantly more efficacious than all other therapy groups (placebo, dopamine receptor antagonist, rescue therapy and dopamine receptor antagonist plus dexamethasone) in the prevention of acute RINV among patients receiving single or multiple fraction radiotherapy to the abdomen/pelvis. Limited data showed that 5HT3 RA was also better than dopamine receptor antagonist or dopamine receptor antagonist plus dexamethasone in the prophylaxis of radiation induced vomiting during the delayed phase among patients receiving single fraction radiotherapy to the upper abdomen.

The addition of dexamethasone to 5HT3 RA gives a slight benefit in the prophylaxis of RINV when compared with 5HT3 RA plus placebo. One study (30) showed better complete control of nausea during the prophylactic period with dexamethasone and better complete control of vomiting during the overall study period in patients receiving multiple-fraction radiotherapy to the upper abdomen.

Among patients receiving TBI, 5HT3 RA was also more efficacious than other agents (placebo, combination of metoclopramide, dexamethasone and lorazepam) in the prevention of RT induced vomiting during the acute phase (15,21). During the delayed phase, one study (15) showed that 5HT3 RA was better than the combination of metoclopramide, dexamethasone and lorazepam in the complete control of vomiting.

There appears to be a higher incidence of overall adverse events in patients receiving 5HT3 RA than the placebo arm, as reported in two studies (22,28). However, the reported side-effects of 5HT3 RA are mostly mild to moderate in severity only.

Among the four studies that investigated QoL, two reported better QoL in the 5HT3 RA arm over placebo or dopamine receptor antagonist plus dexamethasone (23,26). QoL was also more favourable in patients receiving 5HT3 RA plus dexamethasone compared with 5HT3 RA plus placebo (30) and dexamethasone compared with placebo (27).

Our systematic review supports the recommendation of current guidelines (3,9). 5HT3 RA is the antiemetic of choice in the prophylaxis of RINV in patients receiving radiotherapy at high and moderate emetogenic risk. The addition of a short course of dexamethasone to a 5-HT3 RA provides extra benefit in patients receiving radiotherapy to the upper abdomen. Based upon evidence from the moderate emetogenic risk group, patients at high emetogenic risk should also receive a 5-HT3 RA plus dexamethasone as prophylaxis.

Moreover, there is concrete evidence that prophylaxis of RINV was more effective than placebo (21-23,27,28) or rescue therapy (25) among patients receiving radiotherapy to the upper abdomen or TBI. Therefore, radiation oncologists are encouraged to be aware of current guidelines on RINV and follow the recommendations in daily practice, in order to maximize the control of RINV and preserve the QoL of patients.

Despite the use of 5HT3 RA in the prophylaxis of RINV, the complete control of nausea and vomiting is still suboptimal, especially in patients receiving multiple-fraction radiotherapy to the upper abdomen (complete control of nausea 9–30.6%; complete control of vomiting 12–67%) (20,23,28) and TBI (complete control of acute vomiting 26.7–53%; complete control of delayed vomiting 13.3%) (15,16).

Recent studies have shown that aprepitant, a substance P neurokinin 1 receptor antagonist, has a promising effect in the prophylaxis of RINV when combined with a 5HT3 RA. Dennis *et al.* (31) showed that the combination of aprepitant and granisetron was efficacious and safe for the prophylaxis of both acute and delayed RINV in patients receiving moderately emetogenic radiotherapy for thoracolumbar bone metastases (100% complete control of RINV in single fraction and 67% complete control of RINV in multiple fractions during acute phase). In a recent RCT, Emami

et al. (32) reported that the combination of ondansetron and aprepitant was significantly better than ondansetron alone in the prevention of RINV among patients receiving radiotherapy to the abdomen (OR =0.13; P<0.05). This trial was not included in our systematic review as some of the patients received concurrent chemotherapy with radiation. Therefore, future RCTs should investigate the benefit of adding aprepitant to 5HT3 RAs in the prophylaxis of RINV.

More recently, Wong *et al.* (33) reported ondansetron rapidly dissolving film was effective for the prophylaxis of RINV. This new formulation of ondansetron is bioequivalent to oral ondansetron formulations. It may be particularly useful for secondary prophylaxis in patients who have pre-existing nausea or vomiting, when swallowing of oral pills could be difficult. The study showed that the rates of overall control of nausea and vomiting for primary prophylaxis were 88% and 93% during the acute phase and 73% and 75% during the delayed phase, respectively. The rates of overall control of nausea and vomiting for secondary prophylaxis were both 100% during the acute phase and 50% during the delayed phase. Future trials could also investigate whether ondansetron rapidly dissolving film is more effective than the oral formulation in the prevention of RINV.

Our systematic review has some limitations. There is a potential publication bias since we included results from published papers only. Also, inclusion of articles written in English only could lead to selection bias. There is heterogeneity among the RCTs including variations in the definition of study endpoints, radiation treatment details (dose fractionation, total dose and radiation volume) and patient population (various types of cancer and extent of involvement). This heterogeneity limited our ability to perform a meta-analysis on certain endpoints. Further, some of the studies had small sample sizes (n=15–30) while other studies dated back to the 1970s and 1980s. There is also a chance of ecological fallacy since individual patient data was not available in performing the meta-analysis.

Conclusions

5HT3 RA is superior to placebo and other agents in the prevention of RINV among patients receiving single fraction or multiple-fraction radiotherapy to the abdomen and pelvis. The addition of dexamethasone to 5HT3 RA gives a modest improvement in the prophylaxis of RINV. During TBI, 5HT3 RA is also more efficacious than other agents such as dopamine receptor antagonists alone, dopamine receptor antagonists plus dexamethasone, lorazepam in the prevention of radiation-induced vomiting. However, there is still room for improvement in the complete control of nausea and vomiting, especially in patients receiving multiple-fraction radiotherapy to the upper abdomen and TBI. Future RCTs should investigate the efficacy and safety of substance P neurokinin 1 receptor antagonist in addition to 5HT3 RA for the prophylaxis of RINV during both acute and delayed phases.

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Footnote

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