

Research Article

Granisetron was more Effective than Ondansetron as Antiemetic in Ovarian Cancer Patients: a Randomized Controlled Trial**Granisetron Lebih Efektif Dibandingkan Ondansetron Sebagai Antiemetik Pada Pasien Kanker Ovarium: Penelitian Uji Acak Terkendali**Hanif Reza¹, Shinta Prawitasari², Ardhanu Kusumanto²

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Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta**Abstract**

Objective: To determine the effectiveness of intravenous injection of granisetron compared to ondansetron in preventing nausea and vomiting, we used the MASCC Antiemesis Tool (MAT) in ovarian cancer patients undergoing paclitaxel-carboplatin chemotherapy

Methods: This study was conducted as a double-blind, randomized controlled trial. The treatment group received 1 mg of granisetron, whereas the control group received 8 mg of ondansetron intravenously. Nausea and vomiting were assessed using the MAT scale at 12 hours, 24 hours, and 48 hours after chemotherapy. The differences in MAT scores between the groups were analyzed using the Mann-Whitney test.

Results: A total of 60 participants were enrolled in this study. The results indicated that the MAT score at the 12-hour mark significantly differed from the 24-hour and 48-hour MAT scores ($p = 0.00$, $p = 0.00$). The MAT scores in the granisetron group at 12 hours, 24 hours, and 48 hours were statistically lower compared to the ondansetron group ($p = 0.00$, $p = 0.00$, $p = 0.00$).

Conclusions: In conclusion, intravenous granisetron proved to be more effective than intravenous ondansetron in preventing nausea and vomiting among patients with ovarian cancer undergoing paclitaxel-carboplatin chemotherapy.

Keywords: chemotherapy, granisetron, MAT score, ondansetron, ovarian cancer.

Abstrak

Tujuan: Mengetahui efektivitas perbandingan pemberian injeksi intravena antara granisetron dan ondansetron dalam mencegah mual dan muntah dengan menggunakan MAT pada pasien dengan kanker ovarium yang mendapat kemoterapi dengan regimen paclitaxel-carboplatin.

Metode: Penelitian ini merupakan double blind randomized controlled trial dengan kelompok perlakuan diberikan granisetron 1 mg dan kelompok kontrol yang diberikan injeksi ondansetron 8mg. Kemudian dilakukan penilaian terhadap mual dan muntah dengan menggunakan skor MAT pada 12 jam, 24 jam, dan 48 jam setelah diberikan kemoterapi dengan menggunakan Mann-Whitney test karena distribusi data tidak normal.

Hasil: Total sampel pada penelitian ini adalah 60 subjek. Hasil skor MAT pada 12 jam berbeda bermakna dengan skor MAT 24 jam dan skor MAT 48 jam ($p = 0,00$, $p = 0,00$). Terdapat perbedaan bermakna secara statistik pada pengaruh terapi granisetron dan ondansetron terhadap skor MAT 12 jam, 24 jam, dan 48 jam ($p = 0,00$, $p = 0,00$, $p = 0,00$).

Kesimpulan: Pemberian injeksi granisetron intravena lebih efektif mencegah mual dan muntah dengan menggunakan MAT dibandingkan dengan injeksi ondansetron intravena pada pasien dengan kanker ovarium yang mendapat kemoterapi paclitaxel-carboplatin.

Kata kunci: kemoterapi, granisetron, kanker ovarium, ondansetron, skor MAT.

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INTRODUCTION

Globally, in 2018, more than 295,000 women were diagnosed with ovarian cancer¹. Data from the International Society of Gynecologic Oncology reveals that ovarian cancer is the second most common cancer following cervical cancer. The most prevalent type of ovarian cancer is the epithelial type, accounting for 90% of primary ovarian tumors². Chemotherapy, particularly for stage IC or IIIC epithelial ovarian cancer, involves platinum-based combinations like carboplatin and paclitaxel every 3 weeks for 6 cycles³.

Nausea and vomiting occurring after chemotherapy is known as chemotherapy-induced nausea and vomiting (CINV). Chemotherapy's side effects affect patients' quality of life^{3,4}. Nausea and vomiting top the list of chemotherapy-related side effects affecting daily life and causing anxiety [4]. The severity of these symptoms can lead to dose adjustments, potentially reducing chemotherapy dosage. Uncontrolled nausea and vomiting might even prompt patients to refuse further chemotherapy, underscoring their significance in cancer treatment [5].

Ondansetron and granisetron, both anti-vomiting 5-HT₃ antagonists, are often used to mitigate chemotherapy-induced nausea. These drugs have different pharmacodynamics and pharmacokinetics mechanisms for reducing nausea and vomiting. Ondansetron has a half-life of 6 hours, with 70% protein binding, hepatic metabolism, and 5% elimination through feces and urine. Granisetron, on the other hand, has a half-life of 9½ hours, 65% protein binding, hepatic metabolism, and elimination via urine and feces [6]. In terms of pharmacodynamics, granisetron selectively binds to 5-HT₃ receptors, while ondansetron also binds to 5-HT_{1b}, 5-HT_{1C}, 1-adrenergic, and -opioid receptors. Both drugs are cost-effective [7].

The MASCC Antiemesis Tool (MAT) was developed to assist patients and oncologists in preventing and controlling chemotherapy-induced nausea and vomiting. MAT is an easy-to-use tool applicable in individual patient care [8]. There is still controversy regarding the effectiveness of granisetron compared to ondansetron in preventing nausea and vomiting. Hence, this study aims to compare the anti-emetic effects of granisetron and ondansetron using the MASCC Antiemesis Tool (MAT) in ovarian cancer patients who recently received

paclitaxel-carboplatin chemotherapy.

METHODS

Globally, in 2018, more than 295,000 women were diagnosed with ovarian cancer [1]. Data from the International Society of Gynecologic Oncology reveals that ovarian cancer is the second most common cancer following cervical cancer. The most prevalent type of ovarian cancer is the epithelial type, accounting for 90% of primary ovarian tumors [2]. Chemotherapy, particularly for stage IC or IIIC epithelial ovarian cancer, involves platinum-based combinations like carboplatin and paclitaxel every 3 weeks for 6 cycles [3].

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RESULTS

This study was performed at Dr. Sardjito Hospital from July 2020 to March 2021. The number of study participants was 60 patients divided into two groups: 30 patients in the control group received 8 mg intravenous ondansetron injection, and 30 patients in the treatment group received intravenous granisetron (Granon®) 1 mg (Figure 1).

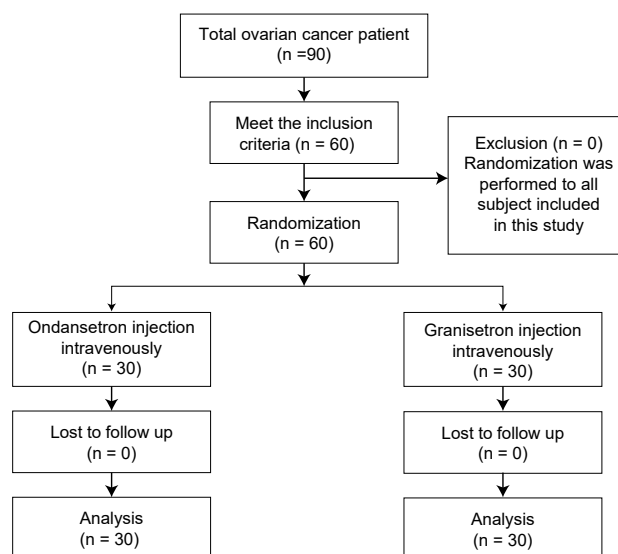


Figure 1. CONSORT Diagram

Table 1. Subject Characteristics

Variabel	Treatment		n	P-value
	Granisetron	Ondansetron		
Age (y o)				
< 50	18 (56.2)	14 43.8	32 53.3	0.31
> 50	12 (42.8)	16 57.2	28 46.7	
BMI (kg/m²)				
< 27.5	27 (50)	27 50	54 90	1.00
> 27.5	3 (50)	3 50	6 10	
History of nausea and vomiting				
Yes	5 (62.5)	3 37.5	8 13.3	0.70
No	25 (48)	27 52	52 86.7	
Cancer stage				
Early	16 (47)	18 53	34 56.7	0.60
Late	14 (53.8)	12 46.2	26 43.3	
Residual tumour (cm)				
<2	28 (54.9)	23 45.1	51 85	0.14
>2	2 (22.2)	7 77.8	9 15	
Chemotherapy dose				
Paclitaxel (Median (Min-Max))	230 (180-230)	230 (180-230)		0.29
Carboplatin (Median (Min-Max))	450 (450-600)	450 (450-600)		0.30

Table 1 displays the subject characteristics of the two groups. In the age group < 50 years old, there were 32 cases (53.3%), while for the age group > 50 years old, there were 28 cases (46.7%). For the BMI < 27.5 kg/m² group, there were 54 cases (90%), and BMI > 27.5 kg/m² group had 6 cases (10%). Fifty-two subjects (86.7%) had a previous history of nausea and vomiting, with 26 subjects (43.3%) having advanced tumor stage, and 51 subjects (85%) having residual tumor < 2cm.

There was no significant difference in the dose of paclitaxel and carboplatin in the granisetron and ondansetron groups. The Friedman test

was then performed to assess the differences in MAT scores at 12-hour, 24-hour, and 48-hour intervals. Friedman test results showed that the highest average MAT score was at 48-hour (2.28), followed by 24-hour (2.19), and 12-hour (1.53). The p-value < 0.05 indicates differences in MAT scores across measurements at 12-hour, 24-hour, and 48-hour intervals. Wilcoxon test (post hoc analysis for Friedman test) was performed to evaluate the differences between MAT scores.

Table 2. Wilcoxon test results

MAT Score (hours)	Median (min-max)	P-value
12 – 24	0.00 (0-6)	0.001
12 – 48	2.00 (0-7)	0.001
24 – 48	2.00 (0-11)	0.211

Statistically, it can be concluded that the 12-hour MAT score was significantly different from the 24-hour MAT score and the 48-hour MAT score, but the 24-hour MAT score was not significantly different from the 48-hour MAT score.

Table 3. Effect of therapy on MAT scores at 12-hour, 24-hour, and 48-hour

MAT Score (hours)	Granisetron (n=30)	Ondansetron (n=30)	P-value
	Median (min-max)	Median (min-max)	
12	0.00 (0-5)	3.00 (0-6)	0.000
24	0.00 (0-4)	3.50 (0-7)	0.000
48	1.00 (0-4)	4.50 (0-11)	0.000

The Mann Whitney test was performed to determine the effect of therapy on 12-hour, 24-hour, and 48-hour MAT scores. The test results found that $p < 0.05$ and the difference in the median value between groups was 3, which means differences in MAT scores (12, 24, and 48 hours) between subjects receiving granisetron and ondansetron therapy. There is a relationship between MAT scores and treatment, both statistically and clinically. Granisetron is more effective in preventing nausea and vomiting (lower median value) than ondansetron.

cancer therapy. Our study demonstrates both clinical and statistical differences between the 12-hour MAT score and the 24-hour MAT score, as well as the 48-hour MAT score. However, the 24-hour MAT score was not significantly different from the 48-hour MAT score. This finding is attributed to the pharmacodynamics of the antiemetic drugs. The relatively short half-life of ondansetron, ranging from 3 to 6 hours, results in declining levels in the body within 24 hours. Similarly, granisetron's half-life is 5 to 9 hours, causing a decrease in systemic concentration after 24 hours.

Table 4. Multivariate Analysis between Therapy (granisetron and ondansetron) and Patient Age on MAT score.

	MAT Score (hours)	F	df	Error df	P-value
Antiemetic	12	17.806	1	56	0.000
	24	35.706	1	56	0.000
	48	24.853	1	56	0.000
Age	12	17.806	1	56	0.000
	24	35.706	1	56	0.000
	48	24.853	1	56	0.000

Our study also reveals differences in MAT scores (12, 24, and 48 hours) between subjects receiving granisetron and ondansetron therapy. Granisetron was more effective in preventing nausea and vomiting (lower median value) than ondansetron. This outcome contrasts with a previous study by Muhilrel et al., 2016, which found similar effectiveness between granisetron and ondansetron in controlling CINV, especially in the acute phase. These discrepancies may be attributed to variations in subject characteristics and the type of therapy administered.

MANOVA (Multivariate Analysis of Variance) test was performed to determine the effect of therapy (granisetron and ondansetron) and age on 12-hour, 24-hour, and 48-hour MAT scores, respectively. The test results found that there were differences in MAT scores (12, 24, and 48 hours) based on the given therapy and age ($p < 0.05$).

Our results align with studies demonstrating that 1 mg of granisetron is more effective than 8 mg of ondansetron in preventing acute CINV. Administering granisetron with dexamethasone in gynecologic cancer patients who received carboplatin chemotherapy also yielded positive responses. Prophylactic single antiemetic therapy is suitable for patients undergoing minimally emetogenic chemotherapy (such as Paclitaxel). Furthermore, another cohort study found that granisetron effectively prevents CINV in low emetogenic potential chemotherapy. Patients receiving granisetron exhibited better clinical responses to nausea and vomiting during the acute phase.

DISCUSSION

Chemotherapy-induced nausea and vomiting (CINV) is a significant side effect experienced by cancer therapy patients. Inadequate control of CINV can reduce patients' quality of life, leading to additional complications, increased hospital costs, and decreased patient compliance with

One limitation of this study was that MAT score assessments were conducted through indirect communication methods (telephone). Some subjects were difficult to contact due to inactive or unreachable phone numbers, resulting in imprecise timing of MAT score assessments at 12-hour, 24-hour, and 48-hour intervals.

CONCLUSION

In conclusion, our study demonstrated that intravenous injection of granisetron was more effective in preventing nausea and vomiting at 12 hours, 24 hours, and 48 hours compared to intravenous ondansetron injection in ovarian cancer patients undergoing paclitaxel-carboplatin chemotherapy

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CONFLICT of INTEREST

There is no apparent conflict of interest for the authors to declare in this report.

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AUTHOR CONTRIBUTION

This case report was written with equal contributions from all authors.

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