ORIGINAL ARTICLE:

Combination of palonosetron-dexamethasone is more effective than ondansetron-dexamethasone as single cisplatin antiemetic chemotherapy

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ABSTRACT

Objective: To know the efficacy differences between two groups of drug combination ondansetron-dexamethasone (A) and ondansetron-dexamethasone (B) to prevent emetic rsponses after chemotherapy cisplatin administration (CINV).
Materials and Methods: A prospective double blind randomized clinical trial study held in Dr. Soetomo General Hospital involving 66 subjects, devide into two groups randomly 33 patients each. One group receive palonosetron-dexamethasone combination therapy compare to ondansetron-dexamethasone combination as standart therapy in gynecologic oncology Dr. Soetomo Hospital in a control group as cisplatin chemotharapy CINV prophylaxis. The research was conducted from June till October 2014 in the Dr. Soetomo General Hospital-Surabaya. Assessment and measurement of the response of nausea and frequency of vomiting according Gralla scale, changes in plasma density and electrolyte serum (Na, K, and Cl) as a result of dehydration caused by nausea and vomiting, as well as counting the onset of nausea and vomiting occur.
Results: There was significant differences between the results of the combination therapy compared ondansetron-dexamethasone to palonosetron-dexamethasone for nausea and vomiting (p=0,001). 31 subjects suffers nausea in ondansetron group, while 9 subjects suffers nausea in palonosetron group. Vomiting occurs in 17 subjects from ondansetron group, and only 1 subject from palonosetron group during study. Changes in plasma density significant in palonosetron group, and natrium in ondansetron group. For K and Cl not significantly difference in both groups before and after cisplatin chemotherapy administration.
Conclusion: Palonosetron-dexamethasone combination is superior as cisplatin CINV prophylaxis in response to nausea and vomiting frequency, and also give longer protection compare to ondansetron-dexamethasone significantly. The plasma density and electrolyte serum changes are varied in numbers and also influenced by many factors including physical status and nutrition, also intake of each patients.

Keywords:Palonosetron; dexamethasone; ondansetron; CINV; cisplatin.

ABSTRAK

Tujuan: Untuk mengetahui perbedaan efikasi antara dua kelompok kombinasi obat ondansetron-dexamethasone (A) dan ondansetron-dexamethasone (B) untuk mencegah rimpons emetik setelah pemberian cisplatin kemoterapi (CINV).
Bahan dan Metode: Penelitian klinis prospektif acak buta ganda yang diadakan di Rumah Sakit Umum Dr. Soetomo yang melibatkan 66 subjek, dibagi menjadi dua kelompok secara acak 33 pasien masing-masing. Satu kelompok menerima terapi kombinasi palonosetron-dexamethasone dibandingkan dengan kombinasi ondansetron-dexamethasone sebagai terapi standart dalam onkologi ginekologi Rumah Sakit Dr. Soetomo dalam kelompok kontrol sebagai cisplatin chemotharapy CINV prophylaxis. Penelitian dilakukan mulai Juni hingga Oktober 2014 di Rumah Sakit Umum Dr. Soetomo-Surabaya. Penilaian dan pengukuran respon mual dan frekuensi muntah menurut skala Gralla, perubahan densitas plasma dan serum elektrolit (Na, K, dan Cl) sebagai akibat dari dehidrasi yang disebabkan oleh mual dan muntah, serta menghitung onset mual dan muntah terjadi.
Hasil: Ada perbedaan yang signifikan antara hasil terapi kombinasi dibandingkan ondansetron-dexamethasone dengan palonosetron-dexamethasone untuk mual dan muntah (p=0,001). 31 subjek menderita mual pada kelompok ondansetron, sedangkan 9 subjek mengalami mual pada kelompok palonosetron. Muntah terjadi pada 17 subjek dari kelompok ondansetron, dan hanya 1 subjek dari kelompok palonosetron selama penelitian. Perubahan kerapatan plasma signifikan pada kelompok palonosetron, dan natrium pada kelompok ondansetron. Untuk K dan Cl tidak ada perbedaan signifikan pada kedua kelompok sebelum dan sesudah pemberian kemoterapi cisplatin.
Simpulan: Kombinasi palonosetron-dexamethasone lebih unggul sebagai profilaksis CINV cinplatin sebagai respons terhadap frekuensi mual dan muntah, dan juga memberikan perlindungan yang lebih lama dibandingkan dengan ondansetron-dexamethasone secara signifikan. Kerapatan plasma dan perubahan serum elektrolit bervariasi dalam jumlah dan juga dipengaruhi oleh banyak faktor termasuk status fisik dan nutrisi, juga asupan setiap pasien.

Kata kunci: Palonosetron; deksametason; ondansetron; CINV; cisplatin

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INTRODUCTION

The main strategy of cancer prevention now include surgery, radiotherapy and chemotherapy. Chemotherapy has great benefits, it can even give a total cure in the stadium and certain types of cancer. The problem that often arises after the administration of chemotherapy is the frequent occurrence of severe side effects although given in therapeutic doses.[1] Nausea and vomiting that occurs after chemotherapy (chemotherapy-induced nausea and vomiting, CINV) is a major problem in 70-90% of patients, especially those receiving high and moderate emetogenic chemotherapy. Accompanying accompanying problems, in the form of anorexia, complications of gastrointestinal diseases, electrolyte imbalances, dehydration, even malnutrition, will ultimately increase the cost of care, time and work volume of health workers and losses due to prolonged treatment time. Reduced oral intake and excessive vomiting can disrupt the gradient of water and minerals rapidly in plasma. In addition, a decrease in adherence to planned chemotherapy schedules and increased rates of chemotherapy failure are other disadvantages.[2]

Based on the consensus of international oncology institutions, such as MASCC and ASCO, the emetogenic level of chemotherapy agents is classified into 5 categories: high, moderately high, moderate, moderate low, and low.[3] Cisplatin is a high emetogenic chemotherapy drug that is widely used in the field of gynecological oncology for patients with ovarian, cervical and endometrial carcinoma. In addition to the side effects of nausea and vomiting, cisplatin is also nephrotoxic and affects the absorption of water and minerals in the proximal tubule.[4] Some international oncology bodies have been updating regular prophylactic standards of CINV procedures. For CINV protection, after the administration of high emetogenic chemotherapy drugs (HEC), 3 classes of drugs are used: serotonin receptor antagonists (5HT3), neurokinin-1 receptor antagonists (NK1) and corticosteroids (dexamethasone). Metoclopramide is used in resuscitation therapy because of recurrent vomiting.[5] However, to date the class of neurokinin-1 receptor antagonists has not been readily available and the price is very expensive.

The development of serotonin receptor antagonist groups (5-HT3) in recent years provides good results for CINV prevention. This contributes significantly to improving the quality of life of cancer survivors with chemotherapy. Giving antiemetic injections provides a sense of comfort for patients while undergoing chemotherapy.[5] The combination of palonosetron-dexamethasone prevents nausea and vomiting after cisplatin chemotherapy 81.8%, versus 50% when given with ondansetron-dexamethasone.[6,7] In the Division of Gynecology Oncology, Dr. Soetomo Hospital, Surabaya, prophylaxis after chemotherapy (CINV) provided for HEC and MEC is a combination of ondansetron-dexamethasone.

This study aims to determine the effectiveness difference of combination of antiemetic therapy ondansetron-dexamethasone from the combination of palonosetron-dexamethasone as anti-emetic prophylaxis of patients who received single cisplatin chemotherapy at the Department of Obstetrics and Gynecology, Dr. Soetomo Hospital, Surabaya, Indonesia. This study used Gralla scale to measure the weight of response nausea and frequency of vomiting that arise. We also examined serum electrolytes (Na, K, & Cl) and specific gravity (BJ) of blood plasma to assess post-nausea dehydration and vomiting. We also get a description of the time of the onset of nausea and vomiting.

MATERIALS AND METHODS

This study was a prospective, double-blind randomized clinical trial study that compared the effectiveness of antiemetic prophylaxis therapy consisting of two combinations of drug regimens in patients exposed to single cisplatin chemotherapy. The group that followed the antiemetic prophylaxis CIMV used in RSUD Dr. Soetomo Hospital, Surabaya, (ondansetron-dexamethasone) was considered a control compared to a novel therapeutic regimen (palonosetron-dexamethasone). The study was conducted in all wards of Obstetrics and Gynecology and randomization was carried out at the pharmacy of Gynecology Oncology wards. Examination of plasma density and serum electrolyte was done in Clinical Pathology Section, Graha Amerta Laboratory, Dr. Soetomo Hospital, Surabaya, Indonesia. The study was conducted from July to October 2014.

The sample population was patients who received HEC, with the study subjects comprising patients who received the first single cisplatin chemotherapy. Sampling was done by consecutive random sampling with total sample 66, divided randomly and evenly in 2 groups of the same size. Patient identities and drugs were disguised. Random sampling allocation was done by pharmacists based on arrival time with prescription. Each sample group amounted to 33 subjects. Groupings were performed by the pharmacy section of the treatment wards randomly based on the arrival of the patient to the pharmacy carrying chemotherapy prescriptions and ani informed consent form to participate in the study.

The inclusion criteria were: willing to follow the study, aged 30-65 years, get the first single cisplatin chemotherapy schedule, and cooperate and compliant to the therapeutic instructions. The exclusion criteria were medical complications during observation, nausea and vomiting before chemotherapy is given, alcoholic beverages consumption, radiotherapy, medicament therapy that stimulates or suppresses the effects of nausea and vomiting, history of laparotomy surgery, known to have a history of disease: chronic dyspepsia, severe renal function disorders, hyperemesis gravidarum, impaired movement and balance such as vertigo, and suffering from severe anxiety disorders. Patients were declared as disqualified if they could not continue treatment, the questionnaire is lost or damaged so that it cannot be identified, and dies before the observation period is complete.

The variables measured were nausea response and vomiting frequency based on Gralla scale. The impact of dehydration caused by nausea and vomiting was measured by assessing the change of plasma density and serum electrolyte (SE) ie: Na, K, and Cl. Plasma density and SE (Na, K, & Cl) samples were taken the day before and 24 hours after chemotherapy. Antiemetic therapy was given by paramedics 60 minutes before cisplatin was administered. Observations were made for 1 x 24 hours. The results of the study in the form of questionnaires and laboratory results were collected and processed using SPSS 20 computer program.

RESULTS AND DISCUSSION

The labels of the therapy group was divided by Roman alphabet A and B and the label was opened after the management of the drug. Label A for the ondansetron-dexamethasone and label B for palonosetron-dexamethasone. Characteristics of the sample based on diagnosis, age, and dose of cisplatin received by the patients are presented in Tables 1 and 2. A statistical test were used in each group (KS: Kolmogorov-Smirnov) to test the distribution of the subjects. Age and dose of cisplatin were uniformly distributed (both homogeneous) in both treatment groups (p> 0.05), and did not confounding factors for the outcomes of the two treatment groups.

Table 3 shows changes in plasma density in both treatment groups after cisplatin chemotherapy, in which group A showed a decrease (p=0.758) and group B showed an increase (p=0.002). The comparison of changes that occurred in both groups had p=0.008. There was a change in serum electrolyte during the study as shown in the table.

Table 1. Diagnosis of samples

Diagnosis	Group A		Group B	
Cervical Cancer				
Stage IB1	0	-	1	3%
Stage IIA	0	-	1	3%
Stage IIB	14	42.4%	10	30.4%
Stage IIIB	9	57.6%	21	63.6%
Total	33	100%	33	100%

Table 2. Distribution of age and dose of cisplatin

Group of Therapy	Min.	Max.	Mean	SD	Distribution test
					KS
Ages.					
A	31	57	46.6970	6.74761	0.602
B	31	62	48.2121	7.34744	0.554
Cisplatin Dose					
A	61.04	116.53	80.1400	11.50121	0.799
B	64.36	130.78	82.1739	11.67355	0.490

Table 3. Comparison of plasma density and SE (Na, K, & Cl)

PD & SE	Group of Ther.	Mean Pre Chemo	Mean Post Chemo	Mean of change	T Test Group	T Test Comp.
Plasma density	A	1.02203	1.02194	-0.00009	0.758	
	B	1.02130	1.02242	0.00112	0.002	0.008
Na	A	139.2727	137.3636	-1.9091	0.001	
	B	140.7879	140.4848	-0.3031	0.520	0.008
K	A	3.9364	3.9727	0.0363	0.618	
	B	3.7333	3.9152	0.1819	0.001	0.910
Cl	A	104.8788	104.7273	-0.1515	0.604	
	B	105.4545	105.7576	0.3031	0.443	0.353

In Table 4 the difference in nausea response in both treatment groups showed 31 subjects experiencing nausea in group A and 9 subjects in group B. Statistically this difference was significant (p=0.001), either the comparison of nausea or the comparison of severity of nausea between the two groups

Table 4. Comparison of nausea responses

Nausea Response Rate	Group of Therapy A	Group of Therapy B	Result	Mann-Whitney U
A (No Nausea)	2 (6.1%)	24 (72.7%)	26 (39.4%)	Cross Tabulation
B (Nausea. appetite is not impaired)	23 (69.7%)	9 (27.3%)	32 (48.5%)	
C (Nausea. appetite is impaired)	6 (18.2%)	0 -	6 (9.1%)	
D (Nausea & Can not Eat)	2 (6.1%)	0 -	2 (6.1%)	
Result :	33 (100.0%)	33 (100.0%)	66 (100.0%)	p = 0.001

Table 5 shows the differences in vomiting frequency of the two groups, 17 subjects in group A and 1 subject in group B. Statistical tests showed significant numbers (p=0.001) for differences in vomiting frequency and severity of vomiting in both treatment groups.

Table 5. Comparison of frequency of vomiting

Vomiting Frequency Rate	Group of Therapy		Result	Mann-Whitney U
	A	B		
No vomiting *(Complete Response)*	16 (48.4%)	32 (97%)	48 (72.7%)	p = 0.001
Vomiting 1 - 2 x/ 24 hours *(Mayor Response)*	12 (36.4%)	1 (3%)	13 (19.8%)	
Vomiting 3 – 5 x/ 24 hours *(Minor Response)*	3 (9.1%)	0 -	3 (4.5%)	
Vomiting > 5 x/24 hours *(Failure Response)*	2 (6.1%)	0 -	2 (3%)	
Total patients	33 (100%)	33 (100%)	66 (100%)	

The onset of nausea and vomiting varied by individual. Without the administration of anti-emetic drugs, in the first 2-3 hours after administration of chemotherapy the patients had severe nausea and vomiting. In this study we divided the onset of nausea and vomiting according to the acute (early and late onset) and delayed phase.

Table 6. Onset of nausea

Nausea Onset	Group of Therapy		Result
	A	B	
Acute on Early *(0 – 12 hours)*	15 (48.4%)	0 -	15 (37.5%)
Acute on Late *(13 – 24 hours)*	15 (48.4%)	4 (44.4%)	19 (47.5%)
Delayed *(> 24 hours)*	1 (3.2%)	5 (55.6%)	6 (15%)
Total patients	31 (100%)	9 (100%)	40 (100%)

The onset of nausea and vomiting was highest in the second 12-hour half (13th to 24th hour), mainly found in the drug A group. There were 6 subjects in all nauseated samples and 3 subjects experienced first vomiting more than 24 hours after chemotherapy.

Table 7. Onset of vomiting

Vomiting Onset	Group of Therapy		Result
	A	B	
Acute on Early *(0 – 12 hours)*	0 -	0 -	15 (37.5%)
Acute on Late *(13 – 24 hours)*	15 (88.2%)	0 -	19 (47.5%)
Delayed *(> 24 hours)*	2 (11.8%)	1 (100%)	6 (15%)
Total patients	17 (100%)	1 (100%)	18 (100%)

Monitoring and prevention of adverse effects on moderate to high emetogenic chemotherapy should be done early and be prepared as best as possible to determine the accompanying series of complications. One of the successes of antiemetic therapy in chemotherapy is the success of preventing nausea and vomiting in the acute phase (first 24 hours after chemotherapy). The main complications of nausea and vomiting due to chemotherapy that lasts several days can lead to dehydration, electrolyte balance disorders, and malnutrition.[9] Some predisposing factors that often affect the onset of nausea and vomiting side effects in chemotherapy include: emetogenic nature of chemotherapy drugs, chemotherapy doses, frequency of administration, duration of chemotherapy exposure, drug delivery pathway, sex, history of alcohol consumption, age, history of hyperemesis gravidarum, disease or disorder in GIT, metabolic disease disorder and psychological disorders.[10,11,12,13] In this study both treatment groups had age distribution and received a dose of cisplatin and other influencing factors filtered through inclusion and exclusion criteria, so that a homogeneous sample subject was obtained.

Decreasing levels of electrolytes (Na, K, and Cl) after cisplatin chemotherapy is in accordance with the results of a study conducted by Arunkumar et al. in 2011, which showed a decrease in magnesium, calcium, potassium and serum phosphate, as well as an increase in plasma density and a decrease in urine osmolarity. This can be caused by acute tubular response to cisplatin toxicity in the form of diuresis.[14] Increased plasma density occurred in group B was in accordance to the low incidence of nausea and vomiting in the group, while group A had the decrease of plasma density. This was due to the high incidence of nausea and vomiting, which affected plasma density regulation. A significant reduction in Na levels in group A was probably related to the high incidence of nausea and vomiting in the group, whereas a significant increase in K levels in group B was due to the control of anti-emetic drugs in the group. Other serum electrolyte changes were not significant in both drug therapy groups. The differences between the two groups were not significant and also did not match the proportion of the incidence of nausea and vomiting in both groups. Increased plasma density and decreased serum electrolytes (sodium, potassium and chlorine) in this study were not only caused by dehydration due to the lack of oral intake resulting from the effects of nausea and vomiting, but also due to the nephrotoxic effect of cisplatin which can interfere with electrolyte balance.

We found a significant difference in the response of nausea and vomiting frequency in both therapy groups. According to a systematic review and meta-analysis by

Sert NP et al, the effect of ondansetron protection on CINV cisplatin of 5-10 mg/kgBW in experimental animals ranged from 70%, if ondansetron was given 30 minutes before chemotherapy with a repeat dose 2x daily. Ithimakin's clinical study found that the complete response (CR) ondansetron-dexamethasone antiemetic combination was 50% in cisplatin chemotherapy,[6] whereas Maemondo et al. said the complete protection of the palonosetron-dexamethasone antiemetic therapy combination was 81.8%.[7] The results of statistical analysis on all levels of nausea and vomiting response according to Gralla classification in this study showed significant advantages of palonosetron-dexamethasone combinations.

Many studies have revealed the superiority of palonosetron for the protection of nausea and vomiting after administration of chemotherapy compared to other groups of 5-HT3 RA. This is consistent with the finding that the degree of affinity attributed to the 5HT-3 receptor that palonosetron has is stronger (potent) than ondansetron. The affinity of ondansetron binding to 5-HT3 receptors is 8.39 pKi,[12] whereas palonosetron is >10 pKi. In addition, the long half-life of palonosetron (> 40 hours) is another advantage.[16]

The difference in protection time in the two treatment groups was caused by differences in half-life (t½). The main cause of failure of vomiting protection in the ondansetron-dexamethasone therapy group at the late onset of the acute emetic phase was the result of decreased drug concentration in the blood. The half-life (t½) of ondansetron is only about 4 hours, while the half-life of palonosetron is much longer (t½=40 hours).[16] In accordance with the vomiting incidence chart, an ondansetron repeat dose should be given to reduce or prevent the effects of nausea and vomiting from entering the acute emetic phase late onset. In terms of cost, the administration of palonosetron is indeed more expensive. However, if we take into account the losses caused by prolonged nausea and vomiting, such as longer treatment, not being able to work, let alone fear of further treatment, palonosetron has better effectiveness.

CONCLUSION

The combination of palonosetron-dexamethasone therapy is more effective than the combination of ondansetron-dexamethasone as CINV cisplatin prophylaxis. Advantages based on nausea response, vomiting frequency, plasma density and Na change were statistically significant, whereas K and Cl changes were not statistically significant. The superiority of the palonosetron-dexamethasone combination is due to its strong binding to receptor, in addition to its very long protective time.

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