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RESEARCH ARTICLE

OLANZAPINE ONDANSETRON DEXAMETHASONE REGIME VERSUS APREPITANT PALONOSETRON DEXAMETHASONE REGIME FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING: RCC STUDY

Vishnu H Lal, *Rajesh Kumar, Beniwal, S., Akanksha solanki, Trupti Kothari, Murali Paramanandan, Kumar, H.S., Neeti Sharma and Jhakar, S.L

Acharya Tulsi, Regional Cancer Centre, Bikaner Rajasthan

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ABSTRACT

Background: At the outset of olanzapine gaining popularity as a drug for Chemotherapy induced nausea and vomiting(CINV). Study was conducted with the aim to compare to antiemetic regimes Olanzapine, Ondansetron, Dexamethasone (OOD) with Aprepitant, Palonosetron, Dexamethasone (APD) in patients receiving highly emetogenic chemotherapy.

Method: A double bind randomized control study was performed to compare the two antiemetic regimes in patients receiving HEC (Cisplatin>70mg/m2 or Doxorubicin>50mg/m2 and Cyclophosphamide>500mg/m2) with complete response (CR) defined as no vomiting and no rescue (till 5 days post chemotherapy) as the primary endpoint. 270 patients initially allotted to the study of which finally 230 were available for evaluation

Results: The primary endpoint of CR was 75% for overall period (92% early period and 75% delayed period) for the OOD arm whereas overall was 70% (81% early period and 70% delayed period) for the APD arm where early period is defined as first 24 hours and delayed as day 2 to day 5 .Nausea control as per MD Anderson Symptom Inventory (MDASI) based questionnaire was better in OOD (60%) vs APD (53%) arm. There was no statistically significant difference between the arms (P>0.05).hence OOD was comparable with APD for prevention of CINV

Discussion: study points out an significantly cheaper yet effective option in managing CINV which is a major adverse effect of chemotherapy with repercussions in quality of life and adherence to treatment. The cost factor is of greater significance for a developing country like ours.

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INTRODUCTION

CINV is a major adverse effect of chemotherapy with repercussions in quality of life and adherence to treatment. The science of antiemetic drugs for CINV is ever evolving. The journey from the first generation antiemetics to the multi-drug cocktail was at par with the evolution of anti-cancer therapy. Guidelines have placed the combo regime of 2nd generation 5-HT3 receptor antagonist with neurokinin receptor antagonist (NK-1) and oral steroids as standard of care for prevention of CINV. The discovery of antiemetic potentials of antipsychotic agent olanzapine (multiple neurotransmitter blockade) has generated renewed interest in CINV management. Each agent of the combo regime has its well defined roles, in the widely prescribed APD regime. Aprepitant crosses blood brain barrier and binds to NK-1 receptors, thereby preventing substance P from exerting its action on the vomiting centre. Aprepitant has control over both acute and delayed emesis induced by anticancer drugs. Amidst these salient features the cost of the drug is an inhibitory factor in a developing nation like ours. Palonosetron is a 2nd generation 5-HT3 antagonist which prevents serotonin from binding to peripheral serotonin receptors on intestinal vagal afferents. it also has central action. Dexamethasone is a time tested agent in CINV with action at various levels both central and peripheral. It is into this fray that olanzapine as antiemetic is introduced .Olanzapine is an atypical antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, and D4 brain receptors; serotonin at 5-HT2a, 5-HT2c, 5-HT3, and 5-HT6 receptors; catecholamines at alpha-1-adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H1 receptors. Olanzapine's activity at multiple receptors, particularly at the D2, 5-HT2c, and 5-HT3 receptors, which appear to be involved in nausea and emesis, suggests that it may have significant antiemetic properties.

Corresponding author: **Rajesh Kumar,**
Acharya Tulsi, Regional Cancer Centre, Bikaner Rajasthan

This theoretical possibility was proved by a phase III trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and palonosetron, was very effective at controlling acute and delayed CINV in patients receiving HEC. The toxicity profiles of these antiemetic agents are also significant as they are repeated over many cycles and for many days during a cycle. Aprepitant is seen to cause headache, fatigue GI-disturbances, hiccups and insomnia. Palonosetron shares a similar profile with headache, fatigue.GI-disturbance, anxiety and QT prolongation as the main adverse effects. Dexamethasone is known to cause insomnia, hyperglycaemia, indigestion–epigastric discomfort, agitation, increased appetite, weight gain, and acne. Hence it can be observed that toxicity profile of these agent do overlap with the risk of insomnia, diabetes and headache being the most significant especially in a geriatric population. Olanzapine on the other hand causes sedation as a side effect which is likely to improve the sleep profile when given others which cause insomnia. The study thus aims to see if a regime of Olanzapine Ondansetron and dexamethasone (OOD) is comparable with Aprepitant, Palonosetron, Dexamethasone, combination (APD).

MATERIALS AND METHODS

A double blind randomized control study was performed to compare the two antiemetic regimes in patients receiving HEC (Cisplatin>70mg/m2 or Doxorubicin>50mg/m2 and Cyclopho sphamide>500mg/m2), with complete response (CR) defined as no vomiting and no rescue (till 5 days post chemotherapy) as the primary endpoint.270 patients initially allotted to the study of which finally 230 were available for evaluation. The OLN, OND, DEX (OOD) regimen was 10 mg of oral OLN, 8 mg of IV OND, and 20 mg of IV DEX prechemotherapy, day 1, and 10 mg/day of oral OLN alone on days 2-4 postchemotherapy. The APR, PAL, DEX (APD) regimen was 125 mg of oral APR, o.25 mg of IV PAL, and 12 mg of IV DEX, day 1, and 80 mg of oral APR, days 2 and 3, and 4 mg of DEX BID, days 2-4. Demographic and medical data were collected and MDASI (MD Anderson Symptom Inventory) based questionnaire was used to collect data regarding intensity of symptoms and patients were asked to record the number of episodes of vomiting, retching, nausea and use of rescue therapy.

RESULTS

The primary endpoint of CR was 75% for overall period(92% early period and 75% delayed period) for the OOD arm whereas Overall was 70% (81% early period and 70% delayed period) for the APD arm where early period is defined as first 24 hours and delayed as day 2 to day 5. Nausea control as per MD Anderson Symptom Inventory (MDASI) based questionnaire was better in OOD (60%) vs APD (53%) arm. There was no statistically significant difference between the arms (P>0.05), hence OOD was comparable with APD for prevention of CINV. The toxicity profile of both regimes were comparable with statistically significant improvement in sleep and appetite in the OOD arm (P<0.05). The hyperglycaemia concern of the APD arm was also non existent in the OOD arm

DISCUSSION

It can be inferred from the study that the OOD regime is comparable to the APD regime which finds place in many established guidelines. The CR rate achieved in acute and delayed period is no statistically different in both the groups.

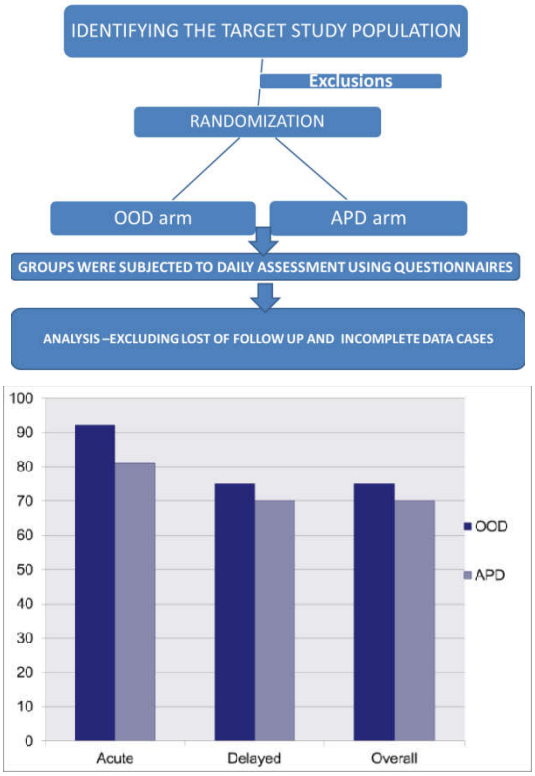

Chart 1. Comparison between Complete response in two arms in acute, delayed and overall scenarios

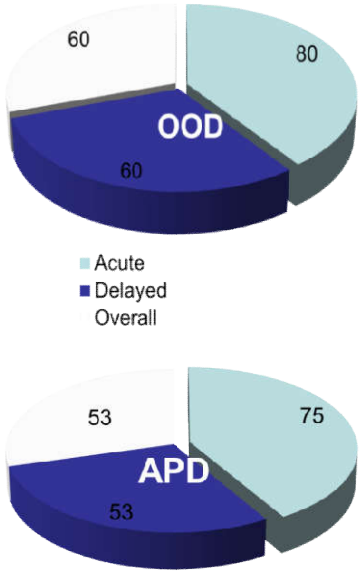

Chart 1. Comparison between "NO NAUSEA" in two arms in acute , delayed and overall scenarios

SYMPTOM	OOD		APD	
	DAY I	DAY 5	DAY 1	DAY5
FATIGUE	1.5	1.7	1.4	1.6
DISTURBED SLEEP	4.1	1.3	3.8	4.3
REMEBERING ISSUES	1.8	1.9	1.5	1.9
LACK OF APPETITE	4.5	1.9	4.3	4.1
FEELING DROWSY	1.9	2.3	1.7	1.8
GLUCOSE ELEVATION >	8		23	

The CR rates were similar to previous studies[4] which compared Olanzapine Aprepitant if not better. It can be seen that OOD

fares better in Nausea control especially in the delayed phase than the APD regime. This advantage of olanzapine is in line with the findings of a recent phase III study [5]. The reduced dose of dexamethasone in the OOD regime is of significant benefit especially in the diabetic geriatric population. The toxicity profile of both the arms were comparable and there were no grade 3 or 4 toxicities. Disturbed sleep a common adverse effect of APD was better in the OOD arm though statistically not significant (P>0.05). This can perhaps be attributed to the low dose of steroid used and the drowsiness attributed to olanzapine. Hyperglycaemia profile was also better in the OOD arm, as steroid dose was reduced and Aprepitant was taken off. The notorious adverse effects of olanzapine as an antipsychotic are weight gain and drowsiness, they were not observed in the OOD arm. This might be attributed to the fact that the dose used is lesser than the typical antipsychotic dose and the duration is significantly shorter. The economic factor should also be discussed with special reference to Indian scenario, the OOD regime roughly costs just 1/10 th that of APD regime with equal or better efficacy. All these points add evidence towards favouring the implementation of OOD regime into the various institutional protocols.

Conclusion

The study points to the fact that OOD is a highly economical yet effective antiemetic regimen with better toxicity profile in reference to the diabetic and cachexic patients .In a developing nation like ours replacing the existing institutional protocols with this more economical alternative would be boon to the needy patients without compromising on quality of care.

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