Therapeutic study of the nausea and vomiting caused by chemotherapy medications by olanzapine to triple antiemetic therapy in Iraqi cancer patients

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Abstract:

Background: Chemotherapy-caused nausea and vomiting is a health problem in cancer patients. Olanzapine is used with serotonin receptor antagonists plus dexamethasone post Neurokinin 1 receptor antagonists as the antiemetic.

Objective: The study aimed to determine the efficacy of (5 and 10) mg of olanzapine with antiemetic drugs against chemotherapy-induced nausea and vomiting.

Methods: The study groups are Group S: received triple antiemetic therapy aprepitant at (1-3) day, dexamethasone at (1-4) day, and ondansetron only on the first day. Group O5: received olanzapine 5 mg with triple antiemetic therapy aprepitant (1-3) days, dexamethasone (1-4) day, ondansetron the first day, and olanzapine 5 mg (1-4) days. Group O10: received (olanzapine 10 mg with triple antiemetic therapy) aprepitant (1-3) days, dexamethasone (1-4) days, ondansetron day 1, and olanzapine 10 mg (1-4) days. The cancer was diagnosed by mamograph; the MAT score was used to control chemotherapy-caused nausea and vomiting.

Results: Higher acute and delayed nausea was observed in group S than in groups O5 and O10. Overall, nausea control was increased in group S than in groups O5 and O10. There was no significant difference between the different study groups.

Conclusion: Olanzapine 5 mg and 10 mg could treat nausea more than triple antiemetic in patients with nausea.

Key words: chemotherapy induced nausea and vomiting (CINV), olanzapine, (MASCC) antiemetic tool.

دراسة علاجية للغثيان والقيء الناجمين عن أدوية العلاج الكيميائي بأولانزابين إلى العلاج الثلاثي المضاد للقيء في مرضى السرطان العراقيين

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الخلاصة

الخلفية العلمية: كان المرضى يعانون بشكل كبير من الغثيان والقيء الناجم عن العلاج الكيميائي (١). واعتمادا على الدليل الإرشادي للغثيان والقيء الناجم عن العلاج الكيميائي الذي وضعته الشبكة الوطنية الشاملة للسرطان فان أولانزابين يستخدم مع مضادات مستقبلات السيروتونين بالإضافة إلى مضادات مستقبلات ديكساميثازون بوست نيوروكينين للعلاج الكيميائي بمضادات القيء المرتفعة والمتوسطة ؛ لذلك يتم إعطاء عقار أولانزابين ٥ ملغ عن طريق الفم مرة واحدة يوميًا.

الهدف: أجريت هذه الدراسة لتقييم ملف فعالية ٥ ملغ أولانزابين مقابل ١٠ ملغ أولانزابين بالاشتراك مع الأدوية المضادة للقيء الروتينية للوقاية من الغثيان والقيء الناجم عن العلاج الكيميائي.

المواد والطرق: اشتملت الدراسة على ثلاث مجموعات على النحو التالي: المجموعة S: العلاج الثلاثي بمضادات القيء. شمل ٢٠ مريضًا بالسرطان تلقوا أبريبيتانت من الأيام ١ إلى ٣ ، والديكساميثازون من الأيام ١ إلى ٤ ، و ondansetron فقط في اليوم الأول. المجموعة O5: olanzapine 5 ملغ مضاف إلى العلاج الثلاثي المضاد للقيء ، بما في ذلك ٢٠ مريضًا بالسرطان عولجوا من الأيام الأولى إلى الثالثة ، والديكساميثازون في الأيام من ١ إلى ٤ ، والأوندانسيترون في اليوم الأول ، وأولانزابين ٥ ملغ في الأيام من ١ إلى ٤. المجموعة O10 (أولانزابين 10 ملغ مضافة إلى العلاج الثلاثي بمضادات القيء) تضمنت ٢٠ سرطانًا المرضى الذين عولجوا بالأيام ١ إلى ٣ ، ديكساميثازون من ١ إلى ٤ أيام ، أوندانسيترون يوم ١ ، وأولانزابين ١٠ ملغ في الأيام من ١ إلى ٤. وتلقى العلاج الكيميائي لعلاج السرطان ، باستخدام درجة MAT للسيطرة على CINV.

النتائج: لوحظ غثيان حاد ومتأخر أعلى بشكل ملحوظ في المجموعة S مقارنة بالمجموعتين O5 و O10. بالإضافة إلى ذلك ، تمت زيادة السيطرة على الغثيان بشكل عام في المجموعة S مقارنة بكلتا المجموعتين O5 و O10. وفقًا لمراحل التقيؤ الحاد والمتأخر والشامل، لم يكن هناك فرق كبير بين مجموعات الدراسة المختلفة.

الاستنتاجات : كان أولانزابين ٥ مجم و ١٠ مجم أكثر فعالية في تقليل مراحل الغثيان والقيء الحاد والمتأخر والشامل مقارنة بالعلاج الكيميائي القياسي الثلاثي المضاد للقيء في المرضى الذين تلقوا علاجًا كيميائيًا مع وجود مخاطر عالية من الغثيان والقيء.

الكلمات المفتاحية: الغثيان والقيء الناجم عن العلاج الكيميائي (CINV) ، أولانزابين ، (MASCC) أداة مضادة للقيء.

Introduction

In cancer patients receiving higher emetogenic chemotherapy that results in developing nausea and vomiting (CINV) [1][2], this is considered the main side effect in the management of their cancer that leads to a bad effect on patient quality of life [3]. Nausea is the subjective sensation or feeling of an unsettled stomach in the epigastrium and/or throat. It is associated with a feeling that vomiting is imminent and occurs more frequently during cancer chemotherapy. Vomiting is the physical ejection of stomach contents through the mouth as a separate effect [4]. There are many mechanisms responsible for the development of CINV, and the mechanisms appear to be different for CINV, which starts in the first 24 hours after chemotherapy versus that which develops 1–5 days after chemotherapy. Five categories are used to classify CINV in order to differentiate these mechanisms: acute, delayed, anticipatory, breakthrough, and refractory. The incidence of acute CINV (occurrence within 24 hours of administration of chemotherapy) was found to be 36%, and for delayed CINV, it was 59% (2–5 days after the administration of chemotherapy) [5]. The combination of aprepitant, 5-HT3 receptor antagonist (5-HT3RA), and dexamethasone (DXM) has reduced the development of CINV [6].

54.7% patients continue to suffer from nausea after using these medications. The FDA recently approved the antipsychotic medication olanzapine, which inhibits 1 adrenergic receptor, serotonin receptors, and muscarinic receptors [7]. It has been demonstrated through randomized controlled trials (RCTs) [8,9] and meta-analyses that the use of olanzapine in cancer patients who are getting chemotherapy is beneficial for reducing the risk of CINV [10,11]. The 2016 guidelines published by MASCC and ESMO propose olanzapine together with 5-HT3 RA and dexamethasone for the prevention of CINV [12], but the degree of recommendation was rated as low.

RCTs [13,14] demonstrated that olanzapine 5 mg PO once daily was successful in treating CINV. On the other hand, a randomized phase study advised using olanzapine 5 mg, which had a higher level of complete control in delayed CINV compared with 10 mg (83.1% vs. 77.6%) [15]. In addition, the results of the meta-analysis showed that the efficacy of olanzapine at doses of 5 mg and 10 mg was similar [16]. In spite of this, neither triple therapy (olanzapine and dexamethasone) or quadruple therapy

(olanzapine, 5-HT3 RA, NK-1 RA, and dexamethasone) was employed, and the degree of CINV was not noted in any of the patients.

The present study planned to assess the effecacy of olanzapine after added to triple antiemetic therapy [apprepitant, dexamethasone and ondansetron] for management of CINV in highly and moderately emetogenic chemotherapy.

Methods

Study design and Patients selection:

Prospective randomized, single-blinded comparative three-arm clinical trial(group S, group O5 and group O10) that involved 60 patients selected through their visit to Al-Anbar oncology Centre in Anbar, all patients were diagnosed with active Cancer (All types of cancer involved in this study) and will receive chemotherapy for treating their cancer, (males and females) (one cycle) for five days after taking the chemotherapy directly except patients with heart disease, diabetic mellitus, and hyperlipidemia, those excluded from the study.

Data Collection and Measurements

In the present study, the research team uses specific sheets (to collect important personal information) and some data for the patients (females and males) with Cancer (All types of cancer involved in this study) regarding their sociodemographic data, history of comorbid diseases, and history of medication used measurement of weight, height, and body surface area based on (MASCC).

Definition of Variables

The number of times that patients reported feeling significant acute nausea and vomiting (as indicated by the MAT score) and the frequency of these symptoms. The Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT) of an eight-question score is used to evaluate acute and delayed nausea and vomiting, that done once after each cycle of chemotherapy; this means it is possible to reduce the need for repetitive daily assessments, which, in turn, reduce the amount of stress experienced by both the patient and the physician [10].

There are a total of eight questions on the MAT: The incidence, length, and frequency of acute nausea and vomiting are each addressed in four of these bullet points, whereas the occurrence, duration, and frequency of delayed nausea and vomiting are each addressed in four of these bullet points. The ratings for dichotomous items are either "0" ("no") or "1" ("yes"), while the ratings for continuous variables are on a scale from 0 to 10.

Statistical Analysis:

Collected data was introduced into Microsoft Excel 2016 and loaded into SPSS software (21) for statistical analysis. Categorical variables were presented as percentages. Continuous variables were presented as (Means ± SD). Sample normality was tested using a Shapiro-Wilk test, and visual inspection of their histograms and normal Q-Q plots and box plots showed that all tested variables were normally distributed. A chi-square test was used to detect the association between the categorical variables. Student t-tests and ANOVA were used to compare means within the same group; one-way ANOVA and the Bonferroni post hoc test were used to find out differences between groups. Odds ratios (OR) were estimated using multinomial logistic regression. A p-value of < 0.05 was considered significant, and $p<0.01$ was considered highly significant.

Result

Demographics and Medical History of Participants

Sociodemographic data

There does not appear to be a statistically significant variation in mean age, mean body surface area, gender distribution, education level distribution, and marital status distribution between the various study groups; also, the groups don't show differences among them in the occupations that their participants at p-value <0.05, as shown in table (1).

Table (1): Assessment of sociodemographic variables, number, gender, income, marital status, Employment, and Education

	Group S	Group O5	Group O10	p-value
Number	20	20	20	-
Age (y), mean ± SD	46.8±12.6	46.0±11.7	47.2±9.6	0.944
BSA	1.8±0.2	1.7±0.2	1.8±0.2	0.115
Gender				
Female	17 (85.0%)	15 (75.0%)	14 (70.0%)	0.638
Male	3 (15.0%)	5 (25.0%)	6 (30.0%)	
Income				
Low	0 (0.0%)	3 (15.0%)	1 (5.0%)	0.419
Middle	9 (45.0%)	10 (50.0%)	9 (45.0%)	
High	11 (55.0%)	7 (35.0%)	10 (50.0%)	
Marital status				
Single	2 (10.0%)	3 (15.0%)	2 (10.0%)	0.784
Married	18 (90.0%)	16 (80.0%)	18 (90.0%)	
Divorced	0 (0.0%)	1 (5.0%)	0 (0.0%)	
Employment				
Employed	1 (5.0%)	6 (30.0%)	2 (10.0%)	0.104
Seasonal employed	1 (5.0%)	0 (0.0%)	3 (15.0%)	
Retired	1 (5.0%)	1 (5.0%)	0 (0.0%)	
Housewife	17 (85.0%)	13 (65.0%)	15 (75.0%)	
Education				
Illiterate	14 (70.0%)	9 (45.0%)	10 (50.0%)	0.049
Primary	4 (20.0%)	3 (15.0%)	5 (25.0%)	
Secondary	0 (0.0%)	3 (15.0%)	5 (25.0%)	
College	2 (10.0%)	5 (25.0%)	0 (0.0%)	

Both acute and delayed nausea was significantly higher in group S, compared to both group O5 and O10 at p-value <0.05; additionally, overall nausea control was significantly higher in group S, compared to both groups O5 and O10, as shown in table (2) and figures (1) (2) and (3).

Table (2): Assessment of nausea depending on Number, Acute nausea, Frequency, Delayed nausea, Frequency, and Overall nausea control

	Group S	Group O5	Group O10	p-value
Number	20	20	20	-
Acute nausea	2.5 (1 – 3.75)	0 (0 – 2)	0 (0 – 2)	0.001
Frequency	16 (80%)	9 (45%)	8 (40%)	0.022
Delayed nausea	2 (1.25 – 4)	0.5 (0 – 1.75)	0 (0 – 1)	<0.001
Frequency	18 (90%)	10 (50%)	8 (40%)	0.003
Overall nausea control	20 (100%)	14 (70%)	11 (55%)	0.004

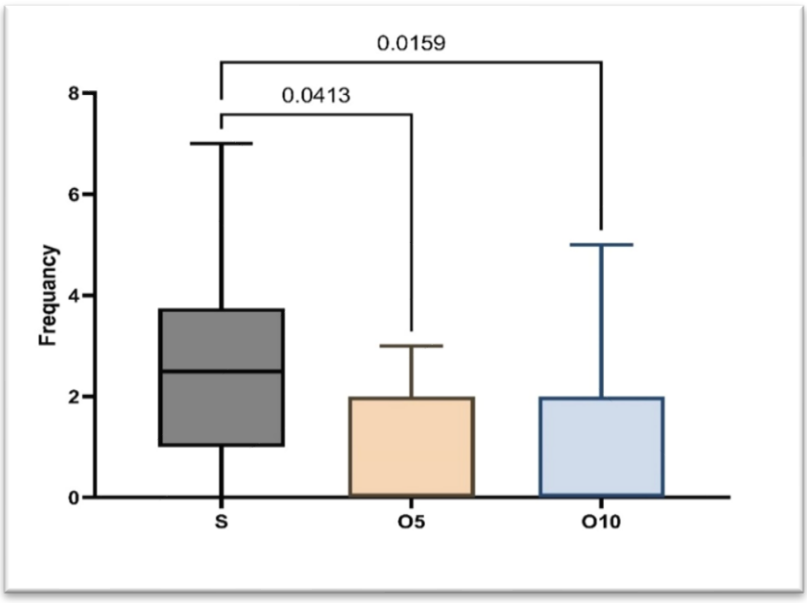

Figure (1): Boxplot of acute nausea according to MAT score

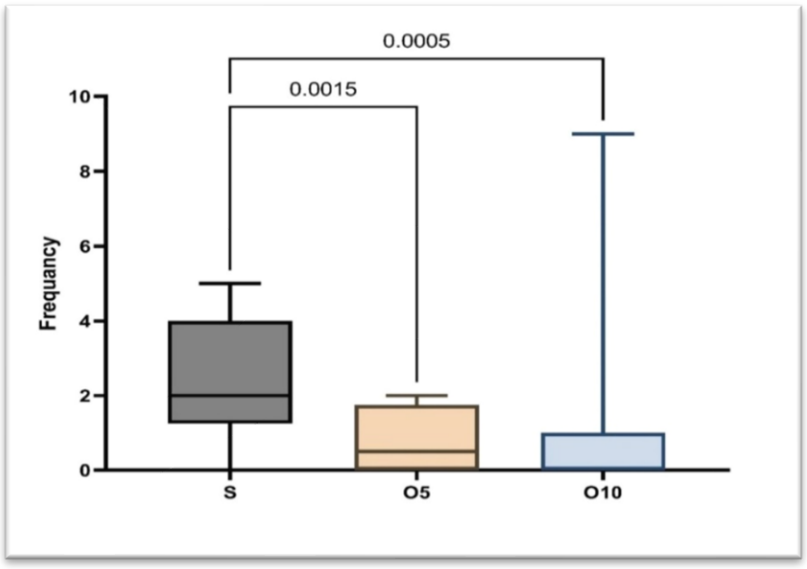

Figure (2): Boxplot of delayed nausea according to MAT score

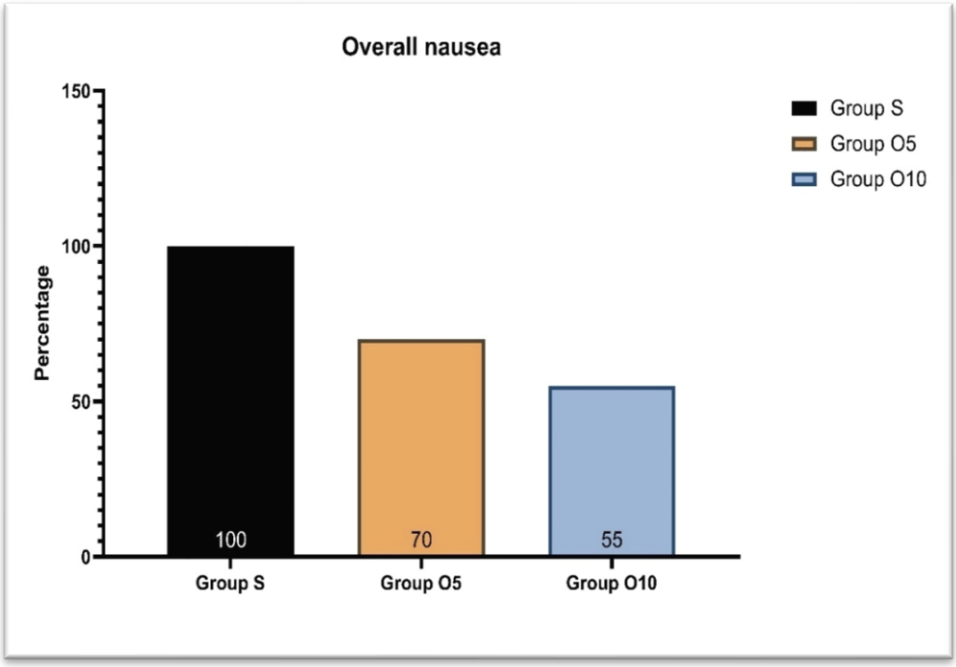

Figure (3): Histogram of overall nausea control

As shown in table (3) and figure (4), there was not a significant difference between the study groups in terms of either acute or delayed vomiting and total vomiting control.

Table (3): Assessment of vomiting depending on Number, Acute vomiting, Frequency, Delayed vomiting, Frequency, and Overall vomiting control

	Group S	Group O5	Group O10	p-value
Number	20	20	20	-
Acute vomiting	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.221
Frequency	3 (15%)	2 (10%)	0 (0%)	0.352
Delayed vomiting	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.368
Frequency	0 (0%)	1 (5%)	0 (0%)	0.999
Overall vomiting control	3 (15%)	3 (15%)	0 (0%)	0.227

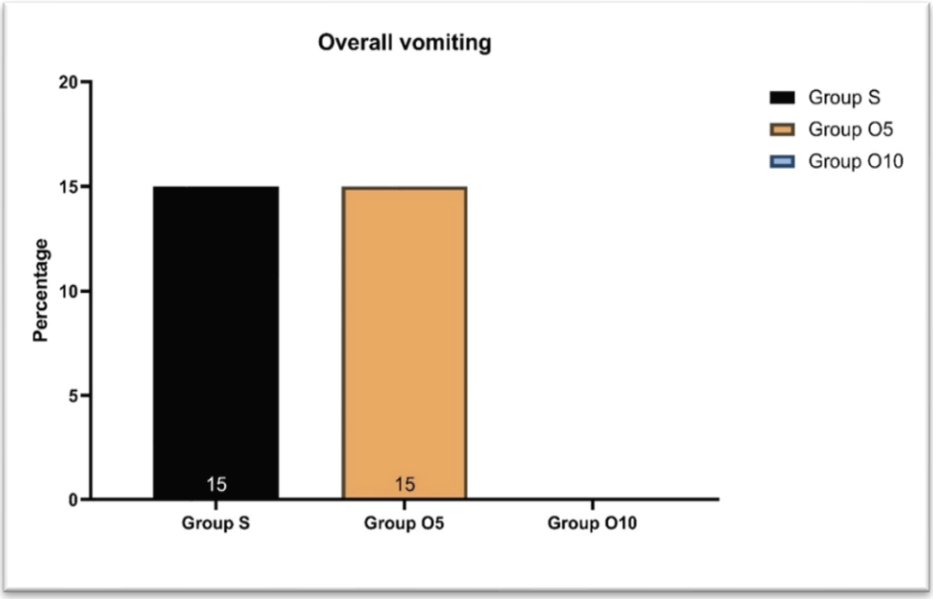

Figure (4): Histogram of overall vomiting control

Discussion

In the current research, there was no significant difference in the control of vomiting between the various groups examined. At the same time, in terms of nausea, olanzapine at both doses (5 mg and 10 mg) in addition to triple antiemetic medication (aprepitant, dexamethasone, and ondansetron) showed significantly lower rates of nausea compared to triple therapy alone in both acute (40, 45, and 80%, respectively) and delayed nausea (40, 50, and 90%, respectively).

In a randomized, double-blind, multiple-center study by Sommariva et al., that involved 218 patients were divided into two groups (105 were offered triple therapy alone, and 113 were offered triple therapy with 5 mg of olanzapine). With a mean age between 50 and 52 years, respectively, their median number of chemotherapy cycles was three, and all patients received highly emetogenic chemotherapy. In terms of vomiting, there was no significant difference between both groups in their acute vomiting (3.2 vs. 2.1%, p-value = 0.36), and there was also no significant difference in delayed vomiting between both groups (5.2 vs. 3.6%, p-value = 0.32). Overall vomiting control during the five days of follow-up post-chemotherapy showed no significant difference (7.5% vs. 4.2%, p-value = 0.066). In terms of nausea, acute nausea was significantly higher in the triple therapy alone group (28.3% vs. 19.6%, p-value<0.05) compared to quadrable therapy; the same findings were replicated for delayed nausea (32.4% vs. 21.9%, p-value <0.05) and overall nausea (41.3% vs. 27.7%, p-value <0.05) [2].

In one of the early published trials regarding the use of OLN 10 mg daily for three days with triple antiemetic therapy, Cohen L, et al. compared this quadrable therapy to metoclopramide (10 mg twice daily for three days) with standard triple antiemetic therapy (DEX, palonosetron, and fosaprepitant). The study included 108 patients (56 patients received OLN, and 52 patients received metoclopramide). The median age was 61–63 years; overall, most patients had good performance status. Emesis did not occur in any of the 39 out of 56 (70%) individuals who were taking olanzapine during the observation period that lasted for 72 hours. This is in comparison to 16 out of 52 (31% of patients) who did not experience emesis when taking metoclopramide (p = 0.01). Patients who were given olanzapine (68%) and metoclopramide (23%; p 0.01) were

the only ones who did not report experiencing any symptoms of nausea throughout the 72-hour observation period [5].

In another trial published 2015 (Phase III trial) to assess the benefits and safety of olanzapine in preventing nausea and vomiting induced by chemotherapy in addition to standard triple antiemetic therapy, Navari et al. published in the American journal of clinical oncology their findings in a double-blinded trial, in which 10 mg olanzapine compared to placebo in triple antiemetic therapy (APR, DEX, and ONS). The study included 401 patients (202 in the OLN group and 199 in the placebo group) [17].

In another study by Navari et al., in 2016, with the same design as its previous study [16], the study involved 380 patients (divided into two groups: OLN 10 mg with 192 patients and placebo with 188 patients in addition to triple therapy for both groups); the median age was 56 to 58 for both groups, and all patients received highly emetogenic chemotherapy with good performance status. OLN exhibited a greater decrease in nausea in the early phase (74% vs. 45%; P = 0.002), delayed phase (42% vs. 25%; P = 0.002), and overall phase (37% vs. 22%; P = 0.002) [18].

Patients and doctors alike will significantly benefit from the results of this study. This study not only confirms the significant anti-nausea benefits of olanzapine observed in previous studies at the 10 mg (PO OD, days 1 - 4) [19,20] and 5 mg doses, however, it also confirms them in a population of cancer patients identified as having a high personal risk of emesis using a validated risk-assessment model [21]

The extent of the gain in nausea control translated to fewer rescue drugs, a higher health-related quality of life, and more patients completing all of their treatment.

Conclusion:

Both 5 mg and 10 mg OLN were more effective in reducing acute, delayed, and total nausea compared to standard triple antiemetic chemotherapy in patients who received highly emetogenic chemotherapy [HEC]. So, in the setting of HEC, the effectiveness of a regimen that contains olanzapine has better efficacy for the prevention of CINV.

Conflict of interest: there is no conflict of interest

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