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Additional dexamethasone in chemotherapies with carboplatin and paclitaxel could reduce the impaired glycometabolism in rat models

Yanxiu Guo^{1†}, Haoxia Zeng^{2†}, Xiaohong Chang¹, Chaohua Wang^{3*} and Heng Cui^{1*}

Abstract

Background: Side-effects have been considered as the limitation of the chemotherapy agents' administration and life quality in patients with ovarian cancers. In order to explore the influence of the chemotherapy agents commonly used in ovarian cancer patients on the blood glucose metabolism in rat models, we conducted this study which simulated the conditions of clinical protocols.

Methods: Eighty clean-grade female Wistar rats were randomized into 8 groups: Group 1 (Negative control), Group 1' (Dexamethasone), Group 2 (Carboplatin), Group 2' (Carboplatin-plus-dexamethasone), Group 3 (Paclitaxel), Group 3' (Paclitaxel-plus-dexamethasone), Group 4 (Combined therapy), Group 4' (Combined-therapy-plus-dexamethasone). On day 0, 4, 7 and 14, after fasted for 12 h, the rats in all groups underwent a glucose load and their blood glucose, glucagon and insulin levels were measured.

Results: The glucose levels in group 2, 3 and 4 at 1 h after the loading on day 4 significantly increased ($P = 0.190$, 0.008 and 0.025 , respectively). The glucagon levels in group 3 and 4 showed a similar trend and the increase was not suppressed by the glucose loading ($P < 0.001$). A significant decrease of insulin levels in group 2, 3 and 4 were observed on day 14 after treatment ($P = 0.043$, 0.019 and 0.019 , respectively). The change of HOMA2 %B, an index reflects the ability of insulin secretion was negatively corresponded to the glucose levels, and the trends of HOMA2 IR, an index shows insulin resistance, were positively correlated to the glucose levels. The application of dexamethasone could reduce the degree of increased glucose levels significantly in group 2, 3 and 4. There were no differences in overall survival between the 8 groups. Edema in the stroma of pancreases was observed in group 3, 3', 4 and 4' on day 4 after treatment ($P = 0.002$, 0.002 , 0.000 and 0.000 respectively) and lasted until day 14.

Conclusions: Carboplatin and paclitaxel administration could cause a transient hyperglycemia in rats. This effect might occur by the combination of glucagon accumulation due to the decrease in islet cell secretion. The additional dexamethasone in the combination protocol of carboplatin and paclitaxel seemed to reduce the impaired blood glucose metabolism.

Keywords: Glycometabolism, Chemotherapy, Dexamethasone, Carboplatin, Paclitaxel

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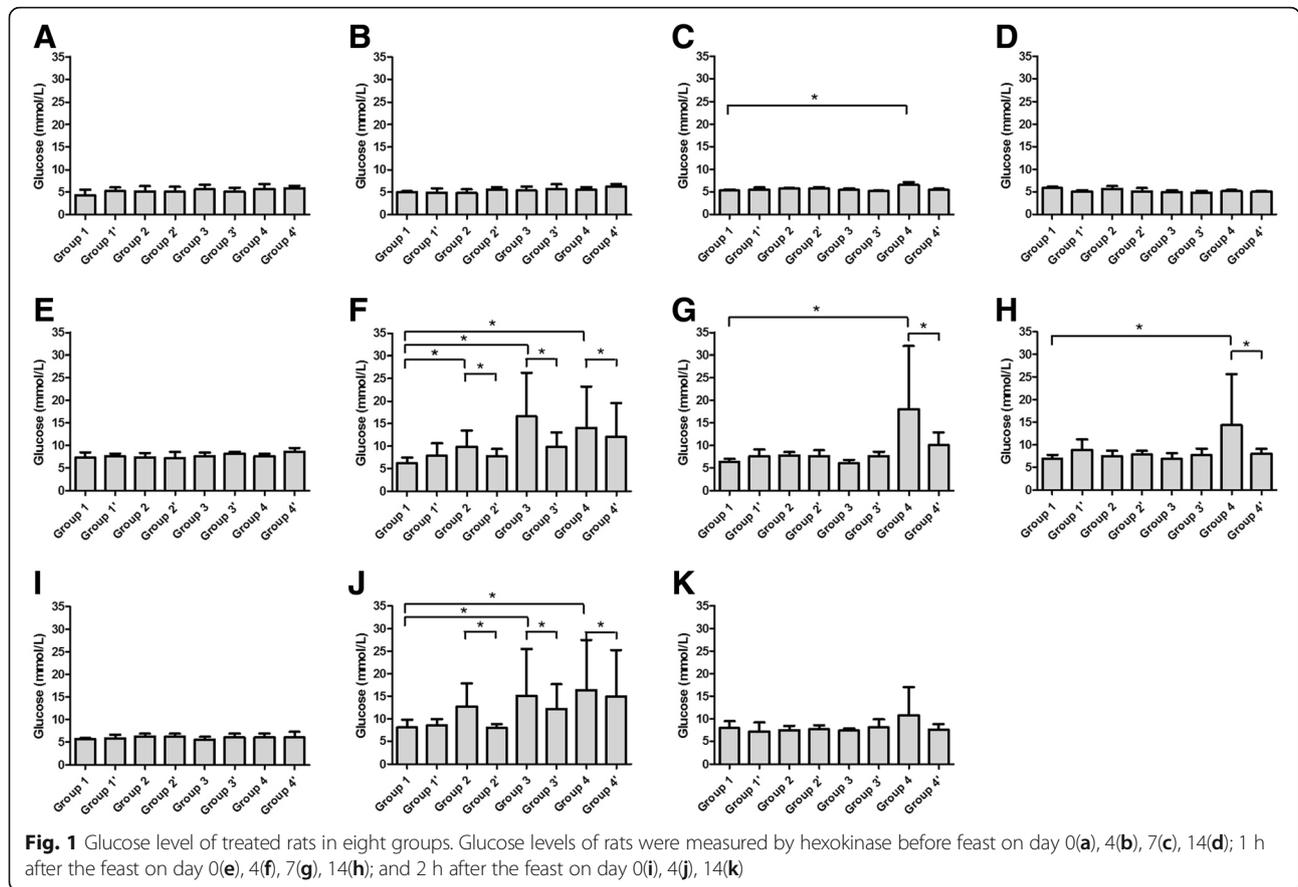
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Background

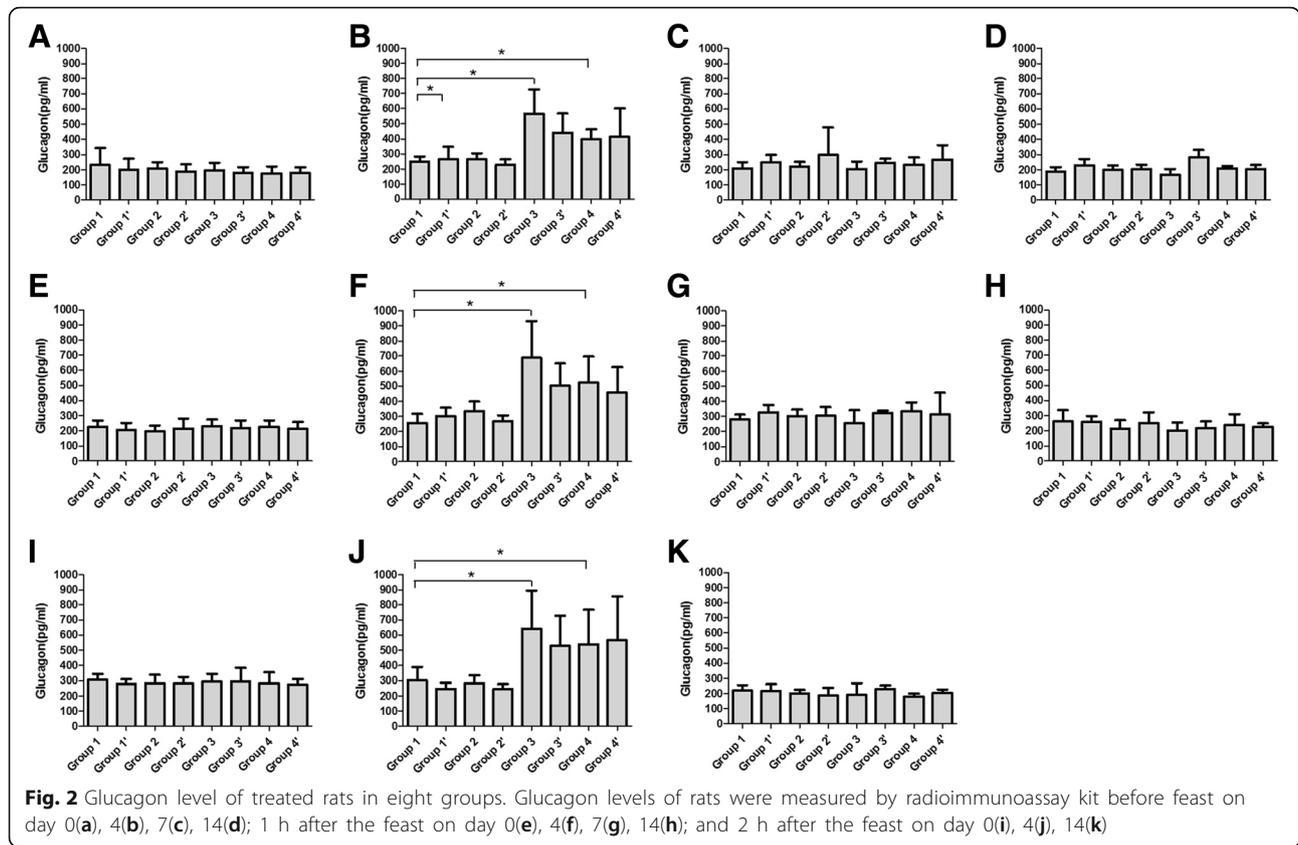
Hyperglycemia occurs in 7.9–37% of patients after combined chemotherapy [1–5]. Recently, the combination of carboplatin plus paclitaxel for the treatment of ovarian cancer has received considerable attention [1]. Typically, 6.4–27% of patients on a paclitaxel-containing regimen develop grade 3–4 hyperglycemia (sugar levels greater than 250 mg/dl) [1, 2]. We have discovered that 12.4% of patients with hyperglycemia and 14.9% of patients who first diagnosed diabetes mellitus after 3–9 cycles of chemotherapy among ovarian cancer patients [6]. We compared the different chemotherapy regimens our patients received. Among patients receiving coordinated chemotherapy with paclitaxel and cisplatin or carboplatin, the occurrence of DM was higher. In that study, we hypothesized that chemotherapy may induce diabetes mellitus among patients with malignant gynecological tumors and be one mechanism that interferes with insulin function [6].

Some of the side-effects of chemotherapy have been studied and understood. Hyperglycemia, as one of side-effects of many chemotherapy treatment, becomes more common these days. Little is known about the mechanisms of it. Most reports did not discuss with the mechanism of hyperglycemia after chemotherapy. Some

authors concluded part of adjuvant chemotherapy regimens produced an appreciable incidence of hyperglycemia [7].

In 1982, Goldstein et al. elucidated the effects of cisplatin on carbohydrate tolerance and insulin and glucagon secretion in rats [8]. They found the appropriate immunoreactive insulin response to a glucose stimulus was absent in the high-dose chemotherapy group. Basal plasma glucagon concentrations in this group were approximately 3–4 times greater than those of control and were not suppressed following a glucose load. They suggested that cisplatin induces marked glucose intolerance, in association with an impaired insulin response, and an abnormal glucagon response to a glucose stimulus.

Some authors have concluded a fraction of adjuvant chemotherapy regimens produce an appreciable incidence of hyperglycemia [9–13]. To explore this issue, we conducted this study to simulate conditions of a clinical protocol. Chemicals involved in this study included carboplatin (carboplatin group, group 2), paclitaxel (paclitaxel group, group 3), and a combination of carboplatin and paclitaxel (carboplatin-paclitaxel group, group 4). Saline (0.9%) was used as a negative control (group 1). Taking into consideration that some studies [14, 15] have cast



doubt on whether dexamethasone contributes to the increased glucose level, as an additional part of the chemotherapy protocol, we set up 4 additional groups, each including dexamethasone plus any of the 4 groups (groups 1', 2', 3' and 4', respectively).

Methods

Animal groups

Eighty clean-grade female Wistar rats, weighing 220 to 280 g, were purchased from the Department of Science of Experimental Animals, Peking University Health Science Center. All animals were housed in static microisolator cage and allowed free access to laboratory chow and distilled water. The 80 rats were weighed and numbered, then were randomized into the following 8 groups: Group 1 (Negative control), Group 1' (Dexamethasone), Group 2 (Carboplatin), Group 2' (Carboplatin-plus-dexamethasone), Group 3 (Paclitaxel), Group 3' (Paclitaxel-plus-dexamethasone), Group 4 (Combined therapy), Group 4' (Combined-therapy-plus-dexamethasone). Each group comprised 10 rats.

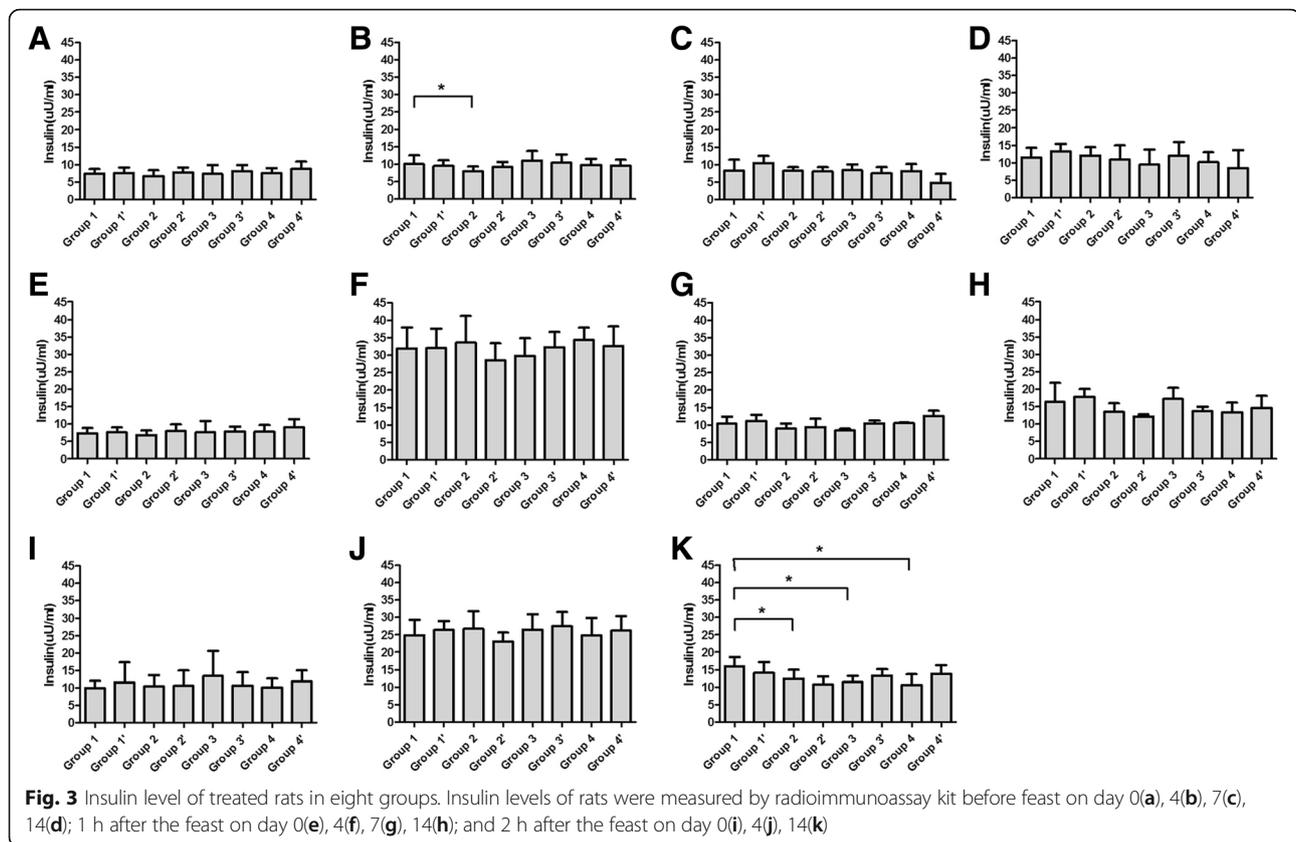
Chemotherapy

On day 0, the rats in group 1 were treated with 0.9% saline (Beijing Fresenius Cub Medical Co. Ltd., China PR) 2 mg/kg i.v.; group 1' were treated with

dexamethasone (Qilu Pharmacy Co., Ltd., China PR) 1.8 mg/kg i.v.; group 2 were treated with carboplatin (Bristol-Myers Squibb Company, USA) 45 mg/kg i.v.; group 2' were treated with carboplatin 45 mg/kg and dexamethasone 1.8 mg/kg i.v.; group 3 were treated with paclitaxel (Bristol-Myers Squibb Company, USA) 16 mg/kg i.p.; group 3' were treated with paclitaxel 16 mg/kg i.p. and dexamethasone 1.8 mg/kg i.v.; group 4 were treated with carboplatin 45 mg/kg i.v. and paclitaxel 16 mg/kg i.p.; group 4' were treated with carboplatin 45 mg/kg i.v., paclitaxel 16 mg/kg i.p and dexamethasone 1.8 mg/kg i.v.. To imitate chemotherapy in clinic, all doses above were made by formula $D\text{-rats} = D\text{-human} \times 0.018$ [16]. To mimic the special considerations for the use of paclitaxel, the drug was administered by peritoneal injection twice, each containing half the dose.

Glucose load

On day 0 (before the chemotherapy), 4, 7 and 14, after fasted for 12 h, the rats in all groups were anesthetized with 2% sodium pentobarbital (Beijing chemical reagent company, Co. Ltd., China PR, 25 ml/kg, i.p.) and treated with 50% glucose, 2 g/kg i.p.. Blood was sampled before and 1 and 2 hours (except day 7 for the poor condition of the rats) after the glucose loading, then reserved for subsequent analysis.



Blood sample collection

Rats were anesthetized with 2% sodium pentobarbital (25 ml/kg, i.p.), and blood was sampled (0.8–1 ml) from the vena orbitalis posterior. Blood samples were collected in chilled sterilized test tubes containing EDTA (25 μ l/ml blood) as an anticoagulant, paclitaxel (5000 U/ml of blood) to inhibit proteolytic degradation of glucagon, and sodium fluoride (4%, 50 μ l/ml of blood) as an inhibitor of glycolysis. The samples were preserved at 4 °C for subsequent analysis.

Blood glucose, glucagon and insulin measurement

Each blood sample was separated into three subgroups for the analysis of glucose, insulin and glucagon through Glucose assay kit (Roche Diagnostics GmbH, Shanghai Company, China PR), Insulin radioimmunoassay kit (Beijing Atom High-Tech Nuclear Technique Utilization Corporation Co. Ltd., China PR) and Glucagon radioimmunoassay kit (Beijing Atom High-Tech Nuclear Technique Utilization Corporation Co. Ltd., China PR) respectively.

Pathology of pancreas

The Rats in all groups were executed after day 7 or 14, pancreatic tissues were fixed in 4% paraformaldehyde, and paraffin sections were stained with hematoxylin and

eosin. Edema, necrosis, inflammation and hemorrhage conditions were measured by Schmidt J score [17].

Statistics analyze

Homeostatic model assessment (HOMA) indices which shows insulin resistance (HOMA2 IR) and beta cell function percent (HOMA2 %B) were calculated by HOMA-2 calculator [18–20].

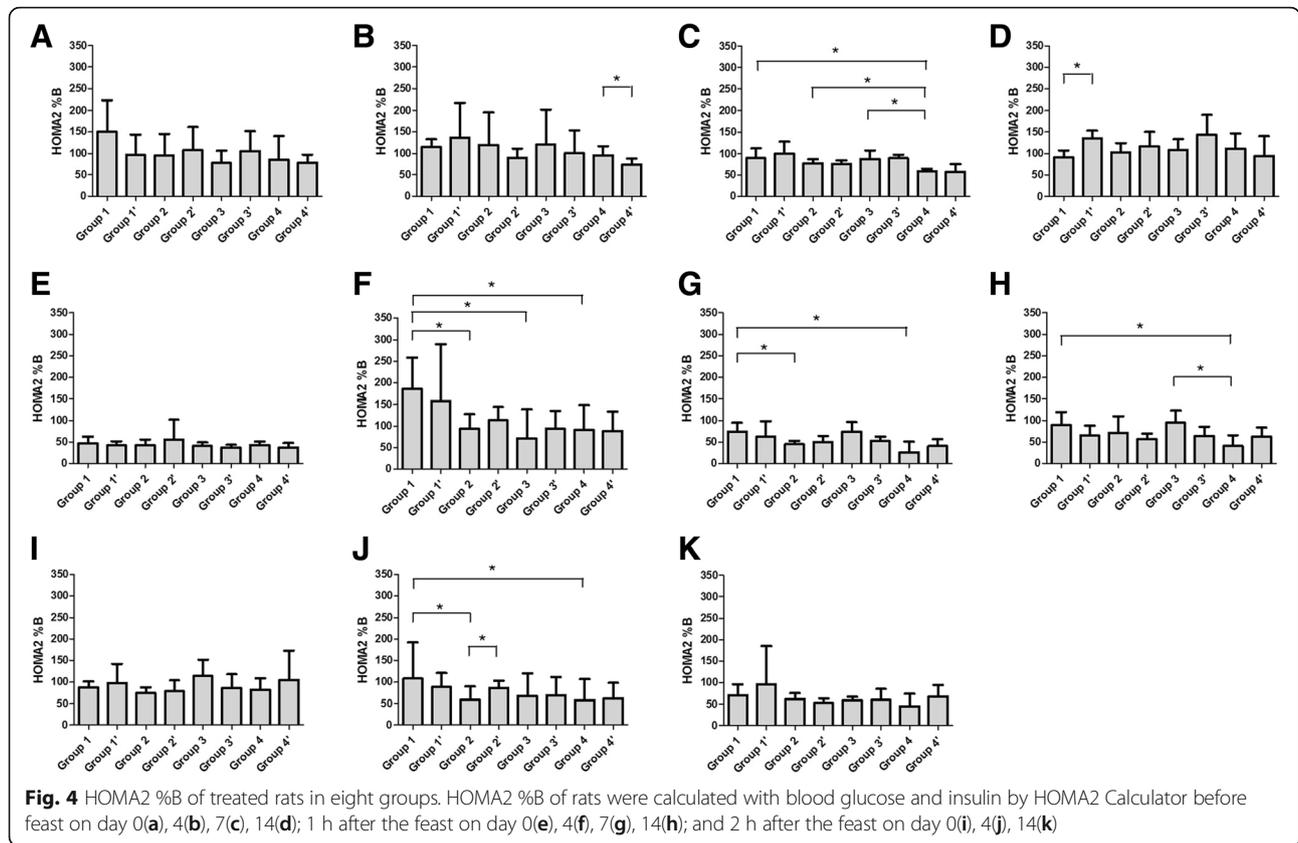
Data in the tables and text are expressed as the mean \pm standard deviation unless specified otherwise. Between-group comparisons were performed using Kruskal-Wallis one-way analysis. Differences were considered statistically significant at $P < 0.05$. All statistical analyses were conducted using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and Prism 5 (GraphPad Software, Inc., USA).

Results

Glycometabolism in rats treated with chemotherapy

Blood glucose level

Before the treatment there were no significant difference among 8 groups ($P = 0.72$ for 0 h, $P = 0.644$ for 1 h and $P = 0.153$ for 2hs, Fig. 1a–i). After treatment most of the groups showed a slightly increase of basic glucose level including the negative control. This may be associated with stress induced hyperglycemia during operation (Fig. 1a–d).



There were significant increases in the 0 h glucose level in group 4 on day 7 ($P = 0.035$) after treatment (Fig. 1d).

At 1 h after the loading, increases of glucose levels were observed on day 4 after treatment in group 2, 3 and 4 ($P = 0.190, 0.008$ and 0.025 , respectively, Fig. 1f). Increase in group 4 could still be observed on day 7 and day 14 ($P = 0.045$ and 0.278 , respectively, Fig. 1g-h).

Changes in glucose level were more aggravated 2 h after loading on day 4 after treatment (Fig. 1j). But all of the changes recovered on day 14, except group 4 (Fig. 1h, k).

The addition of dexamethasone into the chemotherapy protocols was protective, although a slight increase in glucose levels was observed in group 1' compared with group 1 (Fig. 1f). When used together with chemo drugs, significant decreases were observed in all treatment groups, especially when there was a significant increase in glucose levels after glucose loading (Fig. 1f, j).

Plasma glucagon level

Basal plasma glucagon concentrations in group 3 were increased on day 4 after treatment ($P < 0.001$, Fig. 2b). This increase was not suppressed following glucose loading (Fig. 2f, j). The increased glucagon level in group 4 was only significantly observed at 1 h on day 4 ($P < 0.001$, Fig. 2f), and these changes just remained for a short

period, there was no significance observed on day 7 and 14 after treatment (Fig. G-H, K).

The use of dexamethasone did not increase the levels of glucagon. In contrast, when there was a significant increase in glucagon, such as group 3, the use of dexamethasone seemed to reverse the changes, but not significantly (Fig. 2b-j).

To explore if the increases of glucose level were due to higher level of Glucagon after chemotherapy, we compared these two values simultaneously. In group 1 and 1', both levels of glucagon and glucose maintain stable with little fluctuation. On day 4, in group 3 and 4, both glucose and glucagon levels increased synchronously, but on day 7 and 14, the synchronization disappeared. This implies that another factor insulin may also plays an important role in the increases of glucose level.

Plasma insulin level and HOMA2

The insulin levels without glucose loading before treatment were similar between the groups ($P = 0.376$, Fig. 3a). After treatment, there was a decrease in 0 h insulin levels in group 2 on day 4 ($P = 0.029$, Fig. 3b). There were no differences in 2 h insulin levels between the groups prior to treatment ($P = 0.726$, Fig. 3i). On day 4 after treatment, the 2 h insulin levels of all the 8 groups were increased compared with day 0, but there

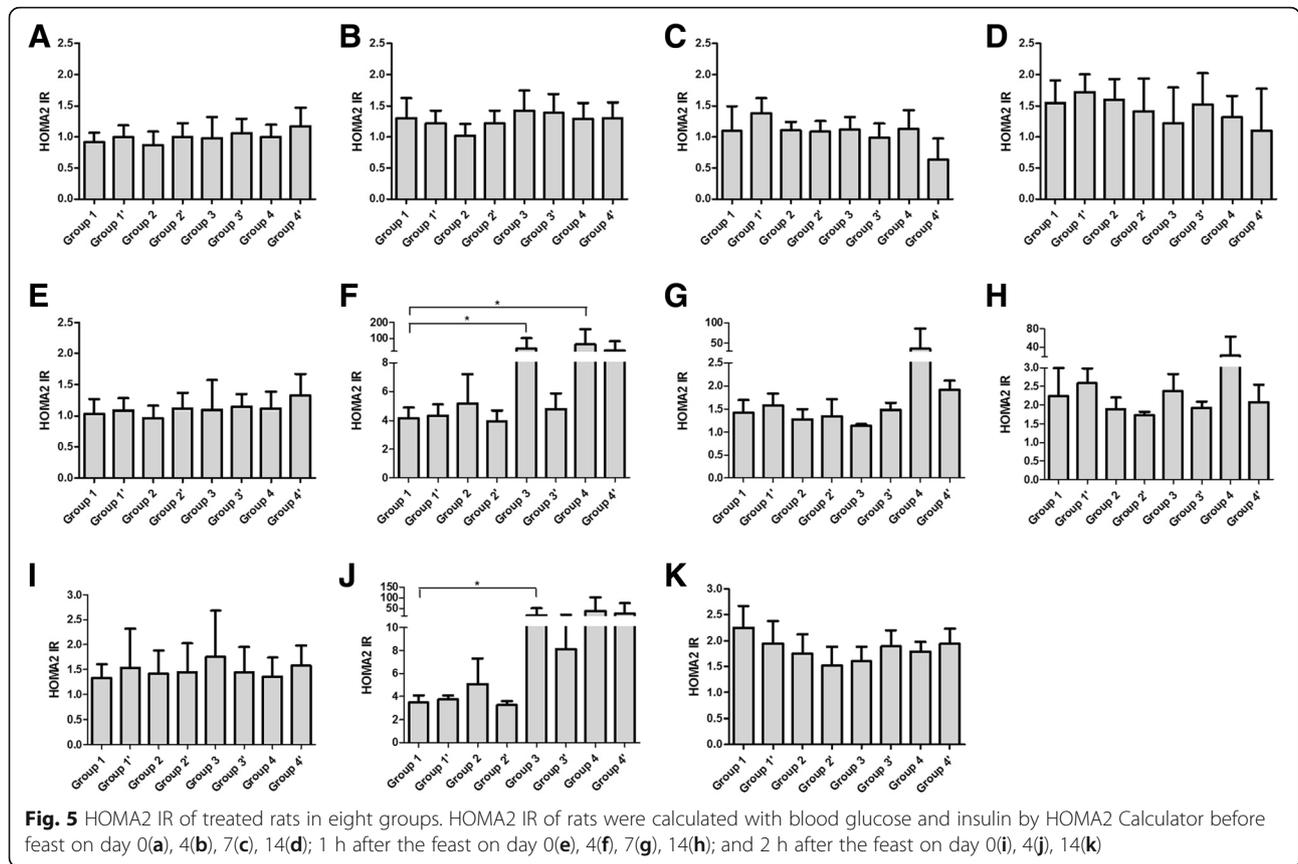


Fig. 5 HOMA2 IR of treated rats in eight groups. HOMA2 IR of rats were calculated with blood glucose and insulin by HOMA2 Calculator before feast on day 0(a), 4(b), 7(c), 14(d); 1 h after the feast on day 0(e), 4(f), 7(g), 14(h); and 2 h after the feast on day 0(i), 4(j), 14(k)

were no differences between the groups (Fig. 3i, j). On day 14 after treatment, decreases were observed in group 2, 3 and 4 ($P = 0.043$, 0.019 and 0.019 , respectively). With regard to 1 h insulin levels, the changes were not as clear as those observed at 2 h. Any differences between the treatment groups were lacking in significance.

The use of dexamethasone did not change the level of insulin significantly. However, when there was a decrease compared with the negative control, the additional use of dexamethasone appeared to eliminate the change.

Generally speaking, insulin level goes up and down as a result of glucose changing. But the Insulin levels of groups received chemotherapy seemed not to be correlated with their glucose levels directly (Figs. 1 & 3). Consequently, we observed the change of HOMA2 %B, an index reflects the ability of insulin secretion, in each group. At 1 h after the loading, decreases of HOMA2 %B were observed on day 4 after treatment in group 2, 3 and 4 ($P = 0.002$, 0.002 and 0.006 , respectively, Fig. 4f), which was negatively corresponded to the glucose levels (Fig. 1f). Similar trends were also observed at 2 h on day 4, 1 h on day 7 and 14 (Fig. 1g & 4g, Fig. 1h & 4h and Fig. 1j & 4j). HOMA2 IR, another index shows the insulin resistance of rats, significantly increased in group 3 and 4 at 1 h after the loading on day 4 ($P = 0.034$, 0.005

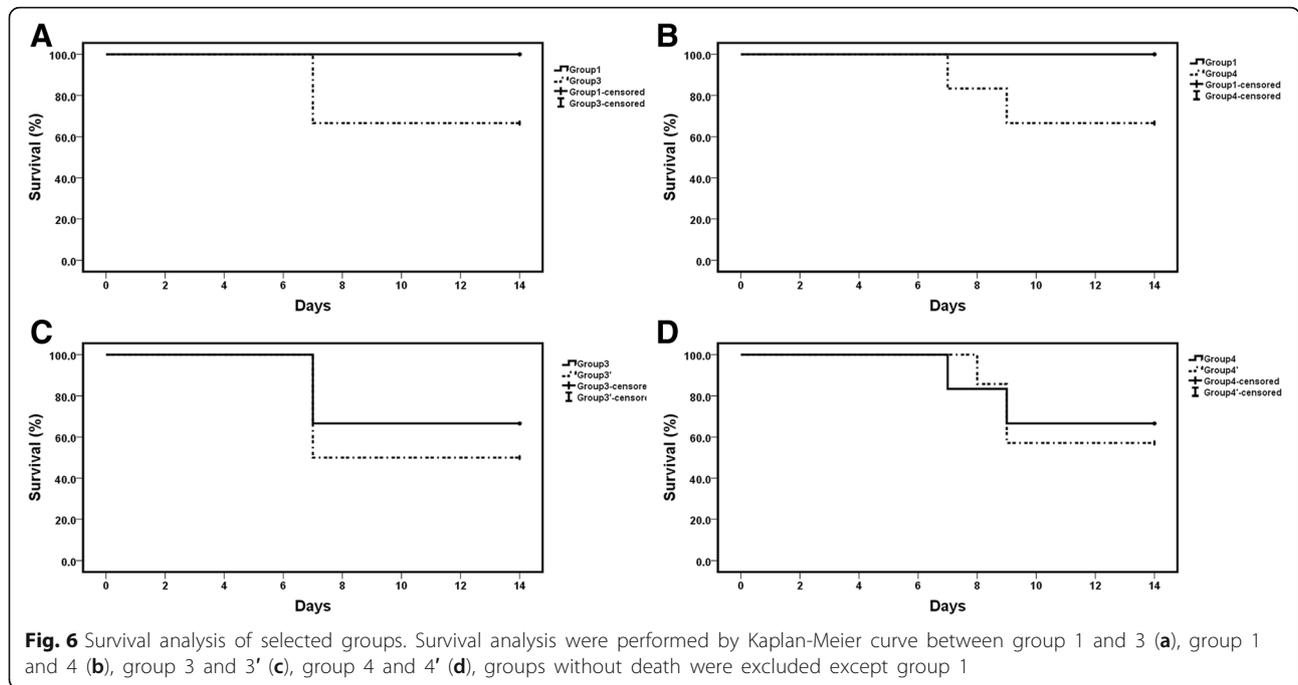
respectively, Fig. 5f). Trends of HOMA2 IR were positively correlated to the glucose levels (Fig. 1g & 5g, Fig. 1h & 5h and Fig. 1j & 4j).

Survival analysis

In all the 8 groups, the total death number was 10. Six were dead on day 7, one on day 8 and 3 on day 9. There was no dead case in group 1, group 1', group 2 or group 2', and death cases were evenly distributed among the other four groups (2 in group 3 and 4, 3 in group 3' and 4', respectively). However, as shown in Fig. 6, the overall survival of rats in group 3 was not significantly shorter than that in group 1 ($P = 0.138$), so was it in group 4 ($P = 0.138$). In addition, the use of dexamethasone did not reduce the overall survival in group 3' ($P = 0.575$, vs group 3) and group 4' ($P = 0.817$, vs group 4).

Pathology of pancreases

Necrosis of pancreases cell is almost absent in all of the 8 groups. Hemorrhage and infiltration of inflammatory cells can be observed in every group, but there is no significance among the groups on day 4 ($P = 0.158$ and 0.367 respectively) and day 14 ($P = 0.073$ and 0.052 respectively). The relatively usual change is dropsy, which is localized only in the stroma. The dropsy is



more apparently in group 3, 3', 4 and 4' on day 4 after treatment ($P = 0.002, 0.002, 0.000$ and 0.000 respectively, vs group 1, Table 1). On day 14 after treatment the edema score decreased, but significant differences could still be observed in group 1', 2', 3' and 4 ($P = 0.047, 0.043, 0.021$ and 0.045 respectively, vs group 1, Table 2). The representative H&E images of the pancreas in all the groups are showed in Fig. 7.

Discussion

The side-effects of chemotherapy have been considered as the limitation of quality of life in patients with ovarian cancer. Hyperglycemia is one of the serious side-effects, of which the mechanism is still unclear. It had been demonstrated that cisplatin incorporating paclitaxel as the first-line therapy improves the duration of progress-free survival and of overall survival in women with incompletely resected

stage III and stage IV ovarian cancer [21]. Ozols [22] subsequently reported that the combination of carboplatin and paclitaxel could obtain a response equal to that of cisplatin and paclitaxel in the treatment of stage III and stage IV ovarian cancer, with less toxicity. The combination of carboplatin and paclitaxel provided a long-term control of the disease in a great many patients. However, in some cases, hyperglycemia was present during chemotherapy. Some patients even developed diabetes mellitus when treatment had concluded, which may have a negative effect on mortality and morbidity and represented an additional financial burden [23, 24].

The mechanism of hyperglycemia after chemotherapy is to be discovered. The major hypotheses include a defect in insulin secretion, accumulation of glucagon and adjuvant treatment in the chemotherapy protocols. Stress during therapy may also play a role.

Table 1 The pathology scores of pancreases in each group on day 4 after treatment

| Groups | Edema (Mean ± SD) | Necrosis (Mean ± SD) | Inflammation (Mean ± SD) | Hemorrhage (Mean ± SD) | Total (Mean ± SD) |
|---------|-------------------|----------------------|--------------------------|------------------------|-------------------|
| Group1 | 0.00 ± 0.00 | 0.50 ± 0.58 | 0.00 ± 0.00 | 0.25 ± 0.50 | 0.75 ± 0.50 |
| Group1' | 0.50 ± 0.41 | 0.00 ± 0.00 | 0.50 ± 0.58 | 0.00 ± 0.00 | 1.00 ± 0.91 |
| Group2 | 0.38 ± 0.25 | 0.00 ± 0.00 | 0.50 ± 0.58 | 0.50 ± 0.58 | 1.38 ± 1.03 |
| Group2' | 0.25 ± 0.29 | 0.25 ± 0.50 | 0.25 ± 0.50 | 0.50 ± 0.58 | 1.25 ± 1.19 |
| Group3 | 0.63 ± 0.63 * | 0.00 ± 0.00 | 1.00 ± 0.82 * | 0.25 ± 0.50 | 1.88 ± 1.80 |
| Group3' | 0.63 ± 0.48 * | 0.25 ± 0.50 | 1.25 ± 0.96 * | 0.25 ± 0.50 | 2.38 ± 1.25 * |
| Group4 | 0.88 ± 0.25 * | 0.00 ± 0.00 | 0.75 ± 0.50 | 0.25 ± 0.50 | 1.88 ± 0.85 |
| Group4' | 0.88 ± 0.25 * | 0.50 ± 0.58 | 1.75 ± 0.50 * | 0.00 ± 0.00 | 3.13 ± 0.63 * |

* $P < 0.05$, compared with group 1

Table 2 The pathology scores of pancreases in each group on day 14 after treatment

| Groups | Edema (Mean ± SD) | Necrosis (Mean ± SD) | Inflammation (Mean ± SD) | Hemorrhage (Mean ± SD) | Total (Mean ± SD) |
|---------|-------------------|----------------------|--------------------------|------------------------|-------------------|
| Group1 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.33 ± 0.52 | 0.33 ± 0.52 |
| Group1' | 0.42 ± 0.20 * | 0.50 ± 0.55 | 0.50 ± 0.55 * | 0.17 ± 0.41 | 1.58 ± 0.80 * |
| Group2 | 0.08 ± 0.20 | 0.00 ± 0.00 | 0.17 ± 0.41 | 0.67 ± 0.52 | 0.92 ± 0.49 |
| Group2' | 0.50 ± 0.32 * | 0.17 ± 0.41 | 0.33 ± 0.52 | 0.00 ± 0.00 | 1.00 ± 0.63 * |
| Group3 | 0.13 ± 0.25 | 0.00 ± 0.00 | 1.00 ± 0.00 * | 0.00 ± 0.00 | 1.13 ± 0.25 * |
| Group3' | 0.50 ± 0.00 * | 0.00 ± 0.00 | 1.00 ± 0.00 * | 0.33 ± 0.58 | 1.83 ± 0.58 * |
| Group4 | 0.38 ± 0.25 * | 0.00 ± 0.00 | 0.25 ± 0.50 | 0.00 ± 0.00 | 0.63 ± 0.25 |
| Group4' | 0.25 ± 0.29 | 0.00 ± 0.00 | 1.00 ± 0.00 * | 0.00 ± 0.00 | 1.25 ± 0.29 * |

*P < 0.05, compared with group 1

Some chemicals have been shown to be associated with beta-cell function damage [24–26]. Wang Y et al. [24] reported that hyperglycemia after cisplatin treatment may be caused by increases in somatostatin and inducible nitric oxide synthase (iNOS) in the pancreatic islets. Wang J et al. [26] demonstrated that increased apoptosis in vivo after chemotherapy and radiation treatment were associated with diabetes mellitus. Our results, in which the HOMA2 %B decreased and the edema score of pancreases increased after the chemotherapy,

supported the hypothesis directly, that the hyperglycemia might be caused by the decrease of insulin secretion in pancreatic islets.

On the other hand, the hyperglucagonemia following chemotherapy, which may be related to decreased glucagon degradation associated with impaired renal function [27], contributed to the formation of the hyperglycemia in rats. In our results, the changes of glucagon and glucose before and after chemotherapies were roughly synchronized in group 2 (carboplatin) and 3 (paclitaxel),

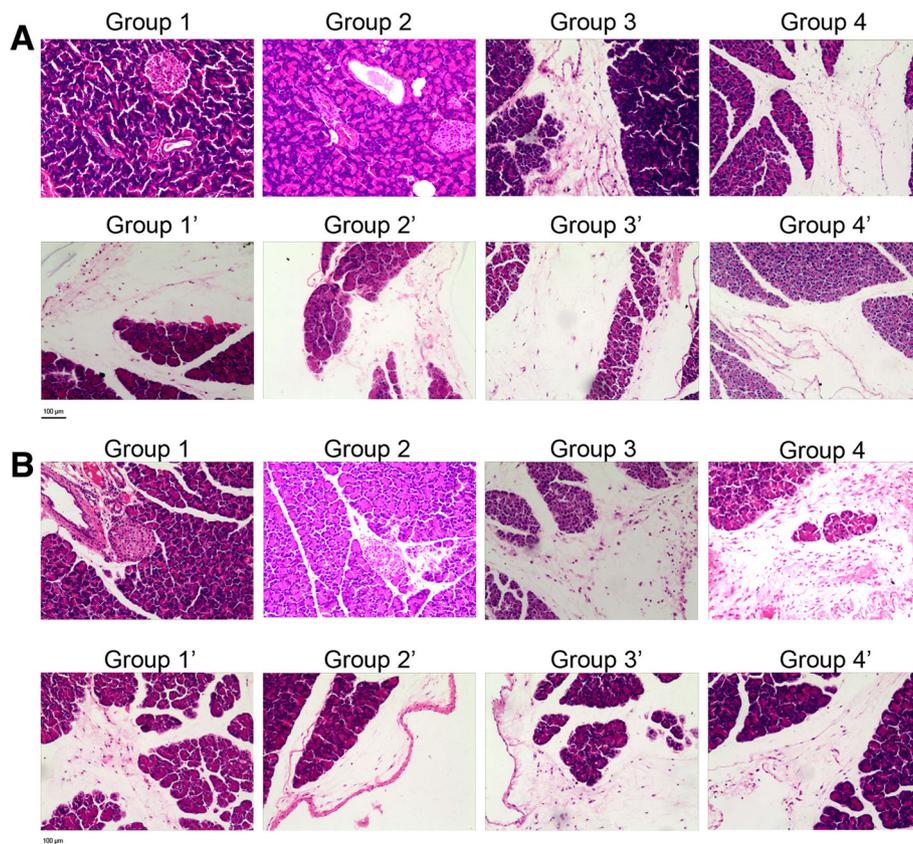


Fig. 7 The representative H&E images of the pancreas. **a** Pathology of the pancreas in group 1,1',2,2',3, 3', 4 and 4' on day 4. **b** Pathology of the pancreas in group 1,1',2,2',3, 3', 4 and 4' on day 14

which implied that the increased level of glucose after treatment could be explained by the decreased glucagon degradation. Furthermore, the changes of HOMA2 IR, an index shows the insulin resistance, were also synchronized with glucose, which indicated that the insulin resistance might be one of the cause of the hyperglycemia too.

Dexamethasone is widely used in chemotherapy; especially in protocols included Paclitaxel, to release side-effects and allergic reaction. Dexamethasone can induce hyperglycemia. But most studies tend to agree that this disorder is minor and temporarily [13, 15]. When treated with dexamethasone (group 1'), only a slim increase of glucose level can be observed compared with group 1 without significance. But in all of the 3 chemotherapy groups, that is group 2 with carboplatin, group 3 with Paclitaxel and group 4 with the combination protocol, the additional use of dexamethasone can reduce the degree of increased glucose levels significantly. The use of dexamethasone does not increase levels of glucagon; oppositely, glucagon levels decreased slightly, especially in group 3. The use of dexamethasone did not change the level of insulin significantly. The reason should be that neither carboplatin nor Paclitaxel induce severe damage on pancreases. These results shows that the protecting on insulin response is a part of the mechanism that dexamethasone could reduce the glucose side-effect of chemotherapy, but not the main one. Further studies are needed to explore this mechanism. The survival analysis shows no difference probably due to the limited use of the chemotherapies. The dose of the drugs was calculated and rats could tolerate it. As a result, the most rats did not die until the terminate day.

Conclusion

Our result indicates that carboplatin and paclitaxel administration could cause a transient hyperglycemia in rats. This effect may occur by the combination of glucagon accumulation due to the decrease in islet cell secretion. The additional dexamethasone in the combination protocol of carboplatin and paclitaxel does not increase the rats' blood glucose levels, on the contrary, it seems to reduce the impaired blood glucose metabolism caused by paclitaxel and carboplatin. Multicourse treatment of chemotherapy should be investigated in order to further determine the role of chemotherapy agents in glucose metabolism in rats.

Abbreviations

D-human: Dose of human; D-rats: Dose of rats; HOMA: Homeostatic model assessment; iNOS: Inducible nitric oxide synthase

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YG, HZ, CW and HC designed the study. CW, XC and CH organized the lecture. YG and HZ performed the study and analyzed the data. YG wrote the paper. All authors read and approved the final manuscript.

Ethics approval

The study was approved by the Institutional Ethics Review Boards of Peking University People's hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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