



Effects of Different Doses of Dexamethasone on Blood Glucose Concentration in Patients Undergoing Elective Abdominal Surgery: A Double-Blind Randomized Clinical Trial

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Received: 15 Dec 2020

Published: 28 Dec 2021

Abstract

Background: Various studies have shown the benefits of using glucocorticoids following surgery. However, side effects associated with drug administration have been investigated sufficiently. We aimed to evaluate the effects of different doses of dexamethasone on blood glucose concentration in patients undergoing elective abdominal surgery.

Methods: This double-blind clinical trial design study was conducted among 90 candidates of elective abdominal surgery referred to RasoolAkram Medical Complex in Tehran, Iran, 2017-2018. Patients included two groups of intervention: group I, received 4 mg dexamethasone; group II, received 8-10 mg dexamethasone; and group III (control group), received ondansetron after induction of general anesthesia. Data were analyzed using ANOVA, Kruskal-Wallis test, and repeated measures. $\alpha=0.05$ was considered as a statistically significant level.

Results: The highest increase in blood glucose concentrations in all three groups occurred in the first 6 hours after the surgery. The lowest intensity of pain in all the groups occurred in the first 24 hours after the surgery. All the groups showed statistically significant changes in blood glucose concentration and pain intensity. Comparing among the mean blood glucose concentrations over time, there were statistically significant changes in time and group/time ($p<0.001$). Comparing the mean intensity of pain over time, statistically, significant changes were observed in time and group / time ($p<0.001$).

Conclusion: In general, change trends in blood glucose concentration and pain intensity could be dependent on the medication used and its dose, as well as the time of drug administration. Changes in blood glucose levels in the control group can be attributed to metabolic changes caused by surgical trauma.

Keywords: Dexamethasone, Blood Glucose, Pain, Nausea, Abdominal Surgery

Conflicts of Interest: None declared

Funding: None

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Cite this article as: Rahimzadeh P, Nikoubakht N, Faiz SHR, Khodabandeh M. Effects of Different Doses of Dexamethasone on Blood Glucose Concentration in Patients Undergoing Elective Abdominal Surgery: A Double-Blind Randomized Clinical Trial. *Med J Islam Repub Iran.* 2021 (28 Dec);35:178. <https://doi.org/10.47176/mjiri.35.178>

Introduction

Dexamethasone is a potent corticosteroid that is commonly administered in low doses (<10mg) while the pa-

tient is in care during and after surgery (1-3). Several studies have shown the benefits of using dexamethasone. In

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↑What is “already known” in this topic:

Administration of a single low dose of it to a patient in operating room can reduce the intensity of pain and use of narcotics, and accelerate postoperative recovery. However, side effects associated with drug administration have been investigated sufficiently mainly wound healing delay, surgical site infection, and its effect on glucose metabolism.

→What this article adds:

Based on our results, change trends in blood glucose concentration and pain intensity could be depended on medication used, dose and time of drug administration and metabolic changes caused by surgical trauma in the control group.

general, dexamethasone can regulate the neuroendocrine system and inflammatory response resulting from surgery (3). Moreover, other studies have demonstrated that the administration of a single low dose of dexamethasone to a patient in the operating room can reduce the intensity of pain and use of narcotics and accelerate postoperative recovery (1-3). Some studies have also suggested that an injection of 4-5 mg of intravenous dexamethasone is as effective as intravenous ondansetron for the prevention of postoperative nausea and vomiting (1-3).

In contrast with the studies investigating the benefits of dexamethasone, a number of studies have investigated the adverse effects of dexamethasone administration in surgery. The most important problems identified with dexamethasone administration include delay in wound healing, surgical site infection, and its effect on glucose metabolism (1-3). The results of research on the effect of dexamethasone on increasing postoperative blood glucose levels are somewhat controversial. According to some studies, administration of a single low dose of intravenous dexamethasone causes hyperglycemia during and after surgery (1-3). The results of a meta-analysis study performed in 2018 demonstrated that dexamethasone administration might lead to a mild increase in blood glucose concentration in nondiabetic patients within 12 hours and in diabetic patients 24 hours after intravenous dexamethasone administration (3). However, some studies have revealed that the increase in blood glucose concentrations in non-diabetic patients has not been significant nor dose-dependent (1).

Fewer studies have been performed on non-diabetic patients undergoing abdominal surgery. Most studies have been performed on diabetic patients, while fewer studies have investigated the effect of both different doses of dexamethasone on blood sugar and postoperative pain.

One of the features of our current research is the use of corticosteroids during surgery that may exacerbate metabolic changes such as an increase in blood glucose concentration caused by surgical trauma. Another design directive that motivated us to conduct the current study was inconsistencies in various studies on the increase in blood glucose concentration following different doses of dexamethasone, as well as its effect on other indicators such as pain and nausea after the surgery.

In this study, we aimed to evaluate the effects of different doses of dexamethasone on blood glucose concentration in patients undergoing elective abdominal surgery.

Methods

A double-blind clinical trial was conducted on 96 patients referred to RasoolAkram Medical Complex who were candidates for elective abdominal surgery from December 2017 to April 2018 that 6 of them were excluded (Fig. 1), so 90 candidates were included in the study. The study was approved by the ethics Committee of Iran University of Medical Sciences; trial ID: 28011 and the IRCT code for this study is IRCT20120814010599N13; all patients involved in the study signed informed consent. Based on mean \pm standard deviation of blood glucose concentrations and pain in similar studies (1-5) and taking

into account the error rate of $\alpha=5\%$ and $\beta=80\%$, a sample size of 30 was decided for each group (6).

The study inclusion criteria were as follows: ASA (American Society of Anesthesiologists) II patients (A patient with mild systemic disease) and ASA I patients (A normal healthy patient) who were a candidate for the abdominal surgery under general anesthesia, and aged between 18–65 years old. The study exclusion criteria were heart disease, pulmonary, liver, and renal diseases, diabetes, a history of steroid use in the recent year, and allergy to each drug used in the study. Demographic data were collected using a researcher-made questionnaire. The patients were randomized to three groups based on the block randomization using a random number table. Before the intervention, the patients' blood glucose concentrations were checked. In the intervention group (group I), 4mg dexamethasone was injected, in the intervention group (group II) 8mg dexamethasone, and in the control group (group III) ondansetron was injected. Both patients' segmentation and type of drug used for the patients were blinded, and all the patients, doctors and nurses were unaware of applying dexamethasone or ondansetron. Three groups had the same drugs which were in the same color and volume, and the drugs had already been taken by someone else who was not in this trial.

General anesthesia was applied to all three groups. After the surgery, patients' blood glucose concentrations were measured and recorded by the nurse with a glucometer during recovery, as well as in the first 6 hours and 24th hour after the administration of dexamethasone or ondansetron. Pain score in the patients under-recovery at 6 and 24 hours after administration of the drugs was measured using the visual analogue scale (VAS) device. The VAS is a pain ruler with a horizontal line that is scaled from zero to ten, that zero represents pain-free and 10 is the worst pain imaginable (3). In the operating room, the drugs were injected to the patients, and then in the ward as well; they were visited by a person who was not aware of the study group nor the patients' blood glucose concentrations. Pain, nausea and vomiting scores were then recorded. The patients included in the records were analyzed (Fig. 1). The data obtained from the checklist, which resulted from assessing 30 samples in each group during this period.

Statistical analysis: For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 19.0 (IBM Corp. Released 2010, Armonk, New York) was used. In this study, the data were analyzed by descriptive and inferential statistics. ANOVA and Kruskal-Wallis tests were applied to compare the mean and standard deviation of each group, and repeated measures test was used for comparison of the means of blood glucose concentrations and pain intensity of the three groups studied over a specified period of time, according to the correlation of observations; and Tokey Post-Hoc test was used for pairwise comparison. The equation of variance (sphericity assumption) was assessed using Mauchly's test of sphericity. Due to the lack of this assumption, the difference between the means at different times was assessed using the Greenhouse-Geisser correction (7, 8). P-value <0.05 was

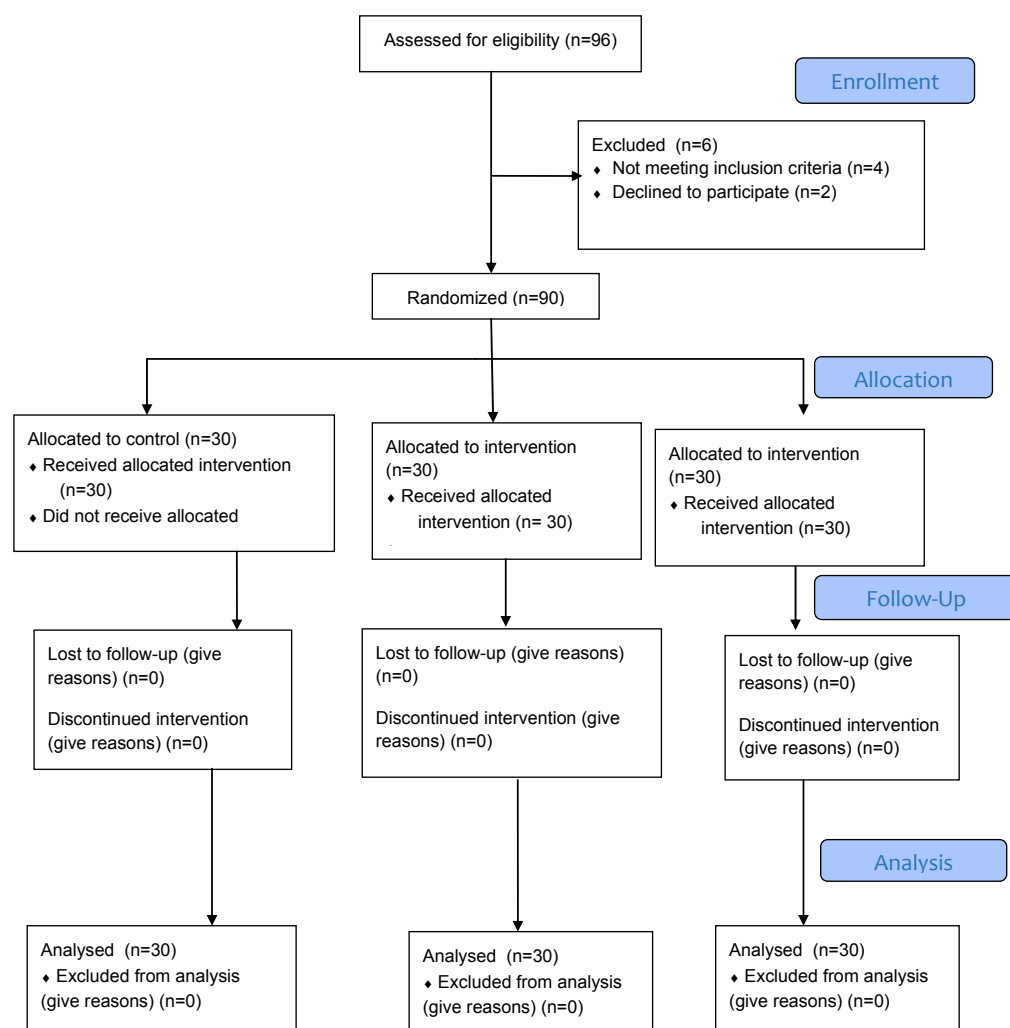


Fig. 1. CONSORT diagram

considered statistically significant.

Results

The present study was conducted in order to evaluate and compare the effects of different doses of dexamethasone on blood glucose concentration in patients who underwent elective abdominal surgery in RasoolAkram Medical Complex. The demographic characteristics of the study patients in the three groups are presented in Table 1.

In this study, the mean and standard deviation of blood glucose concentration (primary outcome) (Table 2) and pain intensity (secondary outcome) (Table 3) were compared at different times within each group and between the groups. Dexamethasone was an independent variable. The highest increase in blood glucose level in all three groups occurred in the first 6 hours after the surgery. The highest mean blood glucose level changes were in group II: 150.67 SD 7.87, in group I: 130.93SD 7.51, and in group III: 116.67SD 8.17, respectively. No statistically significant difference was found in the mean blood glucose levels in the three groups before the surgery ($p=0.542$), but there were statistically significant differences in the means of blood glucose concentration and pain intensity among

the groups at specified times ($p<0.001$). There was a statistically significant difference in the mean blood glucose concentrations among the groups at different times, except before the surgery ($p<0.001$). The lowest intensity of pain in all three groups occurred in the first 24 hours after the surgery. The lowest mean intensity of pain in group II was: VAS = 1.55 SD 0.50, in group I: VAS = 2.23± 0.56 and in group III: VAS = 2.73 SD 0.44, respectively. Also, there was a statistically significant difference in the mean pain intensity among the groups and at different times in each group ($p<0.001$).

According to the results, the greatest changes in blood glucose concentrations and pain intensity were related to the dexamethasone 8mg (group II) both in terms of elevated blood glucose levels especially in the first 6 hours after the surgery, and reduced pain intensity in the first 24 hours after the surgery.

In the next step, repeated-measures ANOVA was used to analyze changes in the blood glucose level in the three groups at the above-mentioned times. In this model, the sphericity assumption was not confirmed for assessing the equation of variance and covariance of observations using Mauchly's test of sphericity ($p<0.05$), and thus the Green-

Table 1. Frequency distribution for sex and mean and standard deviation of demographic characteristics of the subjects

Variable	Group I	Group II	Group III	P value
	Ondansetron	Dexamethasone 4 mg	Dexamethasone 8 mg	
Sex				
Man	12 (%40.0)	18 (%60.0)	16 (%53.3)	
Woman	18 (%60.0)	12 (%40.0)	14 (%46.7)	0.288*
Age (years)	37.66 ±5.50	33.46 ±5.59	37.58 ±5.86	0.991**
Height (cms)	169.30±8.27	170.73±10.75	171.20±9.71	0.729**
Weight (kg)	132.37±8.83	131.77±9.26	133.23±8.73	0.821**
BMI (kg/m ²)	46.28±8.26	60.42±8.26	60.42±8.26	

*Chi-square test ** ANOVA

Table 2. Comparison of the mean blood glucose concentrations with respect to time in each group and between groups

Variable	Time	Group I (ondansetron) mean± SD	Group II (dexamethasone 4 mg) mean±SD	Group III (dexamethasone 8 mg) mean±SD	P-Value*
blood glucose concentration	Before surgery	81.16± 5.21	80.99±6.13	79.77±7.92	0.442
	During recovery	90.53±4.98	94.13±4.73	104.52±5.41	<0.001
	In the first 24 h aftersurgery	116.67±8.17	130.93±7.51	150.67±7.87	<0.001
	In the first 24 h after surgery	101.72±7.13	109.37±5.42	124.93±6.61	<0.001
P-value**		<0.001*	<0.001*	<0.001 ^{b*}	-

Values are expressed as mean ± SD or No. (%)

^bSignificant at P < 0.05.

* Comparison of the mean blood glucose concentrations between groups

** Comparison of the mean blood glucose concentration in each group with respect to time

house-Geisser test was applied. This test showed statistically significant differences among the three groups with respect to the mean blood glucose levels before the surgery, during recovery, and in the first 6 and 24 hours after the surgery (p<0.001) (Table 3). Also, changes in the level of blood glucose concentrations and pain intensity with respect to time and group/time were significant (p<0.001). Moreover, considering the significant effect of the mean blood glucose levels in the three groups over time (p<0.001), it can be concluded that change trends in blood glucose concentration and pain intensity could be depended on the medication used and its dose, as well as the time of the drug administration. In other words, changes in the mean blood glucose level were not the same in the three groups over time.

Repeated measures ANOVA was applied to analyze changes in pain intensity. In this test, the sphericity assumption was confirmed by using Mauchly's test of sphericity (p>0.05), and the results were evaluated by the assumed sphericity test. Based on the results (time/sphericity assumed test), there was a significant trend in the mean pain intensity over time. Also, considering the significant

effect of the mean pain intensity in the intervention and control groups, it can be concluded that the current trend of the mean pain intensity was dependent on the drug used and its dose, as well as the time of the drug administration. In other words, the mean pain changes were not the same in the three groups over time (p<0.001).

In the above tests, pairwise comparisons were performed in terms of the mean blood glucose levels and the intensity of postoperative pain. All comparisons were statistically significant (p<0.001). The results are summarized in Table 4.

In the final step, the following results were obtained:

All patients received 20mg pethidine during the recovery. Also, regarding nausea, 4 patients had nausea in group I and 2 patients in group II; there was no significant difference between the groups (Table 5).

Discussion

The present study attempted to answer the question of whether different doses of dexamethasone and a single dose of ondansetron have different effects on blood glucose in patients undergoing elective abdominal surgery.

Table 3. Comparison of the mean pain intensity with respect to time in each group and between groups

Variable	Time	Group I (ondansetron) mean±SD	Group II (dexamethasone 4 mg) mean±SD	Group III (dexamethasone 8 mg) mean±SD	Comparison of the mean pain intensity between groups
Pain intensity	During recovery	5.55±0.50	4.83±0.59	3.83±0.59	P value <0.001*
	In the first 24 h aftersurgery	3.76±0.50	3.66±0.49	2.66±0.49	P value <0.001*
	In the first 24 h after surgery	2.73±0.44	2.23±0.56 ^a	1.55±0.50	P value ^b <0.001*
Comparison of the mean pain intensity in each group with respect to time		P value <0.001*	P value <0.001*	P value <0.001*	-

^avalues are expressed as mean ± SD or No. (%)

^bSignificant at P < 0.05.

* Kruskal- Wallis H test

Table 4. Comparison of the three groups in terms of blood glucose concentrations and pairwise comparisons in terms of pain intensity

Variable	Group	(J) Group	Mean Difference	P value*	95% Confidence Interval	
					Lower Bound	Upper Bound
Blood glucose concentration	Ondansetrone (Group I)	Dexamethasone 4 mg (group II)	-6.3167*	<0.001	-9.3602	-3.2731
		Dexamethasone 8 mg (Group III)	-17.4333*	<0.001	-20.4769	-14.3898
	Dexamethasone 4 mg (Group II)	Ondansetrone (Group I)	6.3167*	<0.001	3.2731	9.3602
		Dexamethasone 8 mg (Group III)	-11.1167*	<0.001	-14.1602	-8.0731
	Dexamethasone 8 mg (Group III)	Ondansetrone (Group I)	17.4333*	<0.001	14.3898	20.4769
		Dexamethasone 4 mg (Group II)	11.1167*	<0.001	8.0731	14.1602
Pain intensity	Ondansetrone (Group I)	Dexamethasone 4 mg (Group II)	0.44*	<0.001	0.22	0.67
		Dexamethasone 8 mg (Group III)	1.36*	<0.001	1.13	1.58
	Dexamethasone 4 mg (Group II)	Ondansetrone (Group I)	-0.44*	<0.001	-0.67	-0.22
		Dexamethasone 8 mg (Group III)	0.91*	<0.001	0.68	1.14
	Dexamethasone 8 mg (Group III)	Ondansetrone (Group I)	-1.36*	<0.001	-1.58	-1.13
		Dexamethasone 4 mg (Group II)	-0.91*	<0.001	-1.14	-0.68

* Tukey test

Table 5. Mean pethidine consumption and frequency distribution of nausea in the study patients

Variable	Dexamethasone 4 mg (n=30)	Dexamethasone 8 mg (n=30)	Ondansetrone	P value
Pethidine consumption (mg)	20.00 ±0.00	20.00 ±0.00	20.00 ±0.00	-----
Nausea	4 (%13.3)	2 (%6.66)	0 (%0.00)	0.362*

*ANOVA

To this end, the blood glucose concentrations of patients undergoing elective abdominal surgery were measured before the surgery, during recovery, and in the first 6 and 24 hours after the surgery. Results obtained from all three groups showed a significant increase in blood glucose concentrations compared with the day before the surgery, and the biggest changes were observed in group II. Also, there was a statistically significant difference in the mean blood glucose level in each group with respect to the specified time, as well as the mean blood glucose concentrations in the three groups ($p < 0.001$).

The above results are consistent with the findings of some studies (1, 3, 9-11), for example, a study which was conducted at the North Shore University Health System on 200 non-diabetic women candidates for elective hysterectomy in control and intervention groups (11). Results of the study showed that there was a statistically significant increase in blood glucose concentrations in both dexamethasone and control group after surgery (from the mean 94-102 mg/dl to max mean 141-161.5 mg/dl, $p < 0.001$) (11). A retrospective study conducted in the United States on 1037 patients with type II diabetes mellitus indicated that postoperative blood glucose levels were increased in both groups by administration of 4, 8 and 10mg dexamethasone (3). The results of the study were reported in two unmodified and multivariate models. In the unmodified model, a dose of dexamethasone 8mg had a significantly higher rise in blood glucose levels compared to a dose of 4 mg ($p < 0.0001$, 43 ± 45 mg / dL vs. 58 SD 50). In the multivariate model, the predictive factors for increased blood glucose levels were as follows: dexamethasone dosage, preoperative serum glucose, duration

of surgery, and total dose of insulin (3). However, unlike our study, the study population consisted of diabetic patients. Somehow contrary to our study, some studies have shown that there was no statistically significant increase in blood glucose levels. For example, a prospective, randomized study was conducted on 200 women who underwent gynecologic surgery, and the results did not show a statistically significant difference in postoperative blood glucose concentration after placebo or dexamethasone administration ($p = 0.807$) (11).

It is worth noting that in surgical trauma, the catabolic stress response resulted in changes in endocrine function and increased blood glucose levels. Furthermore, by the consistency of our results along with the findings of studies that reported an increase in blood glucose levels after using corticosteroids during surgery, it may be assumed that corticosteroids could exacerbate metabolic changes such as an increase in blood glucose levels caused by surgical trauma, which in turn could be led to a significant increase in blood glucose levels in both the control and intervention groups; although such increase was significantly greater in the intervention group (12, 13).

Another important result from the present study was that the highest blood glucose concentrations in all three groups were observed in the first 6 hours after the surgery, and there was a statistically significant difference in changes in blood glucose level with respect to the time variable in the first 24 hours after the surgery in each group at different times ($p < 0.001$).

Regarding the evaluation of the effect of dexamethasone in terms of time, results from other studies were approximately similar to ours, for example, a randomized con-

trolled trial that was performed to evaluate the metabolic effects of a single dose of oral dexamethasone 8mg on women who underwent hysterectomy at five different times after the administration of the drug (approximately 2, 4, 6, 10, and 14 hours) (4). Results of the above study showed a higher increase in the dexamethasone group. In terms of time, similar to our study, the maximum increase was observed in the first 6 hours after the surgery, that is, approximately 10 hours after dexamethasone administration (3). In another study, the highest increase in blood glucose levels in non-diabetic patients was reported at 12 hours after the administration of intravenous dexamethasone. Results showed that hyperglycemia seems to be short-term after administration of intravenous single-dose dexamethasone; however, according to studies on the effect of glucocorticoid injection on diabetic patients or those with glucose intolerance, they should be used with more caution, especially in patients with risk factors for diabetes. In the next step, we compared the effects of different doses of dexamethasone and single-dose ondansetron on the pain scores of patients who underwent elective abdominal surgery during recovery and in the first 6 and 24 hours after the surgery. There was a significant difference in each group with respect to changes in pain intensity in the first 24 hours after the surgery ($p < 0.001$). Also, differences in the intensity of pain during recovery in the first 6 and 24 hours after the surgery and VAS changes among the three groups were statistically significant ($p < 0.001$). Similar to our study, in a systematic review (3, 5, 12), patients who received dexamethasone in the first 24 hours after surgery had significantly lower pain scores compared to the other analgesia [mean difference (MD) -0.48 (95% CI: $-0.62, -0.35$)] and less opioids were prescribed for them [MD -0.87 mg morphine equivalents (95% CI: -1.40 to -0.33)]. Therefore, it was concluded that patients who received a single dose of dexamethasone experienced lower pain and consumed less opioids. However, the relationship between a dose-response of dexamethasone and pain response was not investigated in the systematic review. Another point worth mentioning is that we found no report on the ineffectiveness of dexamethasone on pain control.

Finally, we compared the effects of different doses of dexamethasone on the incidence of nausea in patients who underwent elective abdominal surgery. We found no statistically significant difference between different doses of dexamethasone and single dose of ondansetron with respect to the evaluation of nausea and vomiting incidence in patients who underwent elective abdominal surgery. Also, in some studies, a lack of difference was confirmed (3), and some recommended administration of dexamethasone for patients (1-3, 11, 14-16). All these indicate that for developing better insights into the phenomena, more patients need to be assessed over a longer period of time.

Conclusion

In general, change trends in blood glucose concentration and pain intensity could be depended on the medication used and its dose, as well as the time of the drug admin-

istration (17-19). There were significant changes in blood glucose concentrations among the three groups over time, but changes in the control group might be due to metabolic changes caused by surgical trauma.

Given that corticosteroids are likely to exacerbate the metabolic changes caused by surgery, the latter should be used with more caution, especially in patients with risk factors for hyperglycemia. In this regard, it is recommended that more studies are needed in this area with larger sample size.

Acknowledgment

The authors wish to thank the RasoolAkram Medical Complex Clinical Research Development Center (RCRDC), Iran University of Medical Science, for its editorial assist.

Conflict of Interests

The authors declare that they have no competing interests.

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