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Attenuation of metabolic stress response during spinal surgery under general anaesthesia - A comparison between preoperative carbohydrate drink or no carbohydrate load

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ABSTRACT

Background: Surgery is a stress which stimulates the increase of counter regulatory hormones. Pre-operative prolonged fasting increases stress further. Although a pre-operative carbohydrate (CHO) drink has been variably reported to yield benefit in reducing the perioperative stress and is being used frequently for elective surgeries, some recent reports also reports that preoperative CHO loading did not result in increase or decrease in the post-operative complication rates when compared with placebo or fasting group. **Aims and Objectives:** The present study was designed to determine the stress response in the postoperative period at 24 h in terms of changes in the levels of cortisol and other biomarkers. **Materials and Methods:** This randomized, parallel group, and double-blind study was conducted in 75 patients aged 18–65 years, of American Society of Anesthesiologists Physical Status Classes I and II, scheduled for elective lumbar spine surgery under general anesthesia. The patients were randomly allocated to receive 300 ml plain water at 9 pm on the day before surgery and 2 h before operation (Group C, control, n=25), or 300 ml plain water at 9 pm on the day before surgery and solution containing 75 grams of glucose dissolved in 300 ml water in the morning 2 h before surgery (Group CHO-1, n=25), or to receive 75 grams of glucose dissolved in 300 ml water at 9 pm in the night before the surgery and again in the morning at 2 h before surgery (Group CHO-2, n=25). In all the three groups, the levels of insulin (C-peptide), lactate, glucose, and cortisol were determined preoperatively (before the induction of anesthesia) and 24 h postoperatively. **Results:** There was considerable difference between post-operative blood cortisol level among the three groups (583.9 vs. 462.3 vs. 389.6 nMol/L, Control vs., CHO load once or twice, respectively, $P<0.0001$). A significant difference in post-operative values was also seen with other parameters such as serum lactate, glucose, and C-peptide. Considerable differences were seen in both preoperative and postoperative period in case of cortisol and lactate whereas it was limited to postoperative values in case of glucose and C-peptide. **Conclusion:** Pre-operative glucose loading showed better efficacy in suppressing perioperative stress response in terms of less rise of serum cortisol and lactate as compared to no CHO load.

Key words: Carbohydrate drink; Cortisol; C-Peptide; Perioperative; Stress

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INTRODUCTION

Surgery is a stress with combination of anesthesia, tissue trauma, blood loss, temperature changes, etc., – all of which can stimulate metabolic changes and subsequent alteration in various organ function.[1,2] Surgery stimulates the increase of counter regulatory hormones such as catecholamines, glucagon, and cortisol.[3] Cortisol works by

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increasing blood sugar levels through the mechanism of gluconeogenesis, suppression of the immune system and increases the metabolism of fat, protein, and carbohydrates (CHOs).[4] Levels of the cortisol hormone in circulation are a very strong predictor of an increased insulin resistance as a result of post-surgical stress response.[2] The increased cortisol level causes insulin resistance and hyperglycemia which have a significant effect on the healing process and leads to increased morbidity and mortality in patients undergoing surgery.[3,5]

Prolonged fasting before surgery increases perioperative discomfort such as hunger, thirst, dehydration, anxiety, dry mouth, fatigue, and headache in patients. Pre-operative fasting is routinely advised in elective surgery to reduce the risk of intraoperative pulmonary aspiration. However, fasting for more than 4 h can lead to a change in the ratio of insulin and glucagon,[3] causing a stress response to surgical trauma, which, in turn, has a major influence on glycemic control and insulin resistance.[2]

In the last few years, the duration of fasting before elective surgery is being revised throughout the world including India. It is recommended that reducing the duration of pre-operative fasting with provision of water or glucose solution for a few hours prior to elective surgery can improve the patient comfort and safety.[6,7] This fasting period actually relates to gastric emptying of solid food. Gastric emptying of fluid occurs within 2–3 h. Literature[5-8] in this arena put emphasis on allowing consumption of clear fluids to the extent of total 1 l up to 2 h pre-operatively. This has showed a subjective improvement of patient comfort with no increase in morbidity in the post-operative period. A recent meta-analysis[9] also consolidates this novel concept that pre-operative intake of a CHO drink shortens the length of hospital stay by reducing the post-operative endocrine catabolic responses and improving the insulin resistance.

A major component of the enhanced recovery after surgery (ERAS) program is the use of pre-operative CHO drink. The concept of giving a preoperative CHO drink in the ERAS protocol originates from its first use in the setting of major open abdominal surgery.[3] In the recent past, one study[8] has highlighted that patient undergoing elective major abdominal surgery the rise of cortisol concentration was found to be significantly lower in those receiving CHO drink in the evening of day before surgery and at 2 h before surgery, compared with those receiving placebo drink. Some studies[7,9] indicate that a pre-operative CHO drink may be beneficial in terms of reducing the catabolic response to surgery, improving insulin resistance and preventing the post-operative hyperglycemia. However, another recent study[10] found that although the pre-operative CHO drink yielded a small reduction in the length of hospital stay, such pre-operative CHO loading did not result in increase or decrease in the post-operative complication rates when compared with placebo or fasting group. Thus, the quality of evidence to support the effects of CHO supplements on post-operative complication rate was low owing to varied results with different studies. Besides, there were issues with non-uniformity of study designs and hence the results could not be compared simply across the studies.[10] The potential role of nutritional intervention to optimize surgical outcome is yet to be fully realized. Moreover, the pre-operative nutritional energy support is clearly underutilized in low-resource settings. Thus, it appears that there is a paucity of relevant literature on the beneficial role of pre-operative CHO loading on post-operative metabolic response in patients undergoing non-abdominal surgeries. This was identified as a major lacuna in the existing literature.

Aims and objectives

The present study was designed to determine the stress response of surgery in terms of changes in cortisol levels in the post-operative period at 24 h and to compare them between the groups (Primary outcome), during elective lumbar spine surgery under general anesthesia among the patients receiving either preoperative CHO load-once or twice or not receiving at all. Thus, it was hypothesized that there would be considerably lower rise of serum cortisol in those receiving CHO load compared with those receiving placebo. In addition, the glucose, lactate, and C-peptide levels (secondary outcomes) were also measured at the same time points and were compared.

MATERIALS AND METHODS

This randomized, parallel group, and double-blind study was conducted in Neurosurgery OT in a tertiary care hospital. Seventy-five patients aged between 18 and 65 years, scheduled for elective lumbar spine surgery under general anesthesia without personal or family history of diabetes and under physiological score for pre-operative assessment of health, American Society of Anesthesiologists physical status (ASA-PS) Class I and Class II. Patient having other endocrine disorder or receiving steroids or other hormonal therapy was excluded from this study. The patients belonging to ASA-PS Classes III and IV, or those having inability to consume fluids, or undergoing surgeries with anticipated bleeding more than 30% of estimated blood volume and duration of surgery more than 5 h — all were excluded from the study.

Sample size for the study was calculated on the basis of duration of variation in serum cortisol level as the primary outcome measure. It was estimated that 25 subjects were required per group to detect a difference of 20 nMol/L. In this parameter between groups, with 80% power and 5% probability of type I error. This calculation assumes standard deviation of serum cortisol to be 25 nMol/L on the basis of an earlier study and two-sided testing. Sample size calculation was done with nMaster 2.0 (Department of Biostatistics, Christian Medical College, Vellore, 2011) software. We had extrapolated the same number of subjects to the control group. Therefore, there was 75 subjects in the study equally distributed between three study groups.

After approval of the Institutional Ethical Committee, 75 adult patients undergoing lumbar spine surgery were recruited for the study, over a period of 18 months. At the pre-operative visit, each patient was examined and was explained about the study. A written informed consent was obtained from each patient. Patients were selected according to inclusion and exclusion criteria. Visual Analog Scale (VAS) score (0-10 cm) for pain was explained to each patient.

Computer generated randomization technique was followed to divide the patients into three groups: Group C (control group, n=25), Group receiving CHO drink once (CHO-1) (n=25) and Group receiving CHO drink twice (CHO-2) (n=25). Group C received 300 ml plain water at night 9 pm on the day before surgery and 2 h before operation. Group CHO-1 received 300 ml plain water at night 9 pm the day before surgery and solution containing 75 g of glucose anhydrate dissolved in 300 ml water in the morning 2 h before surgery. Group CHO-2 received 75 g of glucose anhydrate dissolved in 300 ml water at night before the surgery at 9 pm and in the next morning 2 h before surgery. To make the study blind pharmacist prepared the solution. The nursing staff gave the solution to all patients.

All patients in three groups received standard general anesthesia during the surgical procedure. In the OR, monitors were attached and intravenous (i.v.) line was secured. Baseline parameters (heart rate [HR]; electrocardiography; non-invasive blood pressure [NIBP]; SpO_2, oxygen saturation, and temperature) were monitored continuously. Patients were pre-oxygenated with 100% O_2 for 3 min. Injection (inj.) propofol (2.5 mg/kg body weight) and inj. fentanyl (2 mcg/kg) were used for induction. Following administration of inj. rocuronium (1 mg/kg) i.v bolus, airway was secured with appropriate size of flexometallic endotracheal tube. The maintenance of the anesthesia was with sevoflurane 1.0–1.2 MAC with 50% nitrous oxide and 50% O_2. Muscle relaxation was maintained with intermittent bolus inj. rocuronium (0.3 mg/kg). For intraoperative analgesia inj. fentanyl (1 mcg/kg) was injected when HR and BP were ≥20% of baseline. For the reversal of neuromuscular blockade, inj. neostigmine (0.05 mg/kg) along with glycopyrrolate (0.01 mg/kg) was used.

After reversal from anesthesia, the patients were monitored in the post anesthesia care unit and were subsequently transferred to their respective wards. For post-operative analgesia, Inj. paracetamol 1 g i.v. infusion was administered to the patients thrice daily. If the VAS score is ≥4, inj., tramadol was given at a dose of 2 mg/kg i.v. slowly.

This study was designed and evaluated to find the efficacy of metabolic stress response attenuation by oral glucose pre-operatively in patients undergoing major spine surgery under general anesthesia, in terms of blood parameters (Cortisol, Lactate, Glucose, and C-peptide). In all the three groups, the levels of insulin (C-peptide), lactate, glucose, and cortisol were determined preoperatively (before the induction of anesthesia) and 24 h postoperatively.

Statistical analysis

Data were analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. One-way analysis of variance (one-way ANOVA) was used to compare means of three or more samples for numerical data (using the F distribution). Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. P≤0.05 was considered for statistically significant.

RESULTS

The study spanned between January 2020 and June 2021 approximately over 18 months. Data from all patients from the three groups were available for analysis. Data were checked and found to have a normal distribution. Continuous parameters such as age, BMI, and serum cortisol level were analyzed using ANOVA test. Categorical data such as distribution of gender and number of patients having different ASA physical status are analyzed using Chi-square test. Considering the practical utility of measuring units of observed values, the data were approximated to two points or three points after the decimal, as appropriate.

The demographic parameters of the three groups were comparable except the BMI which was considerably lower in the CHO-1 group (Table 1). Duration of surgery was comparable with in the three groups. The rise of pre-operative and post-operative markers of stress (Cortisol, Glucose, Lactate, and C-peptide) was found considerably less in those patients receiving CHO load once or twice compared with those no receiving CHO load (control). It should be noted that for estimation of the pre-operative markers the blood sampling was done immediately before induction while the patients already received CHO load or placebo (CHO free drink) in the pre-operative fasting phase. However, the pre-operative glucose and C-peptide were found comparable between the groups (Table 2, Figure 1a and b).

Pre-operative VAS scores were high in all the three groups; however, it was comparable among the three groups. Post-operative VAS scores were relatively lower values compared with its preoperative values. On analysis, it was comparable between the three groups (Table 3 and Figure 2). Intraoperatively and postoperatively, there was no significant changes in clinical parameters (HR, NIBP, temperature, etc.) among three groups.

DISCUSSION

Surgical trauma produces metabolic, hormonal as well as hemodynamic responses in the body.[11] Hormonal and metabolic stress response increase serum concentration of cortisol, lactate, glucose, and C-peptide postoperatively.[12] The present study was performed to evaluate the attenuation of metabolic stress response by pre-operative oral glucose loading in patients scheduled for spinal surgery under general anesthesia. The present study finds that the rise of pre-operative and post-operative markers of stress (Cortisol, Glucose, Lactate, and C-peptide) was found considerably less in those patients receiving CHO load once or twice compared with those not receiving CHO load (control). It should be noted that for estimation of the pre-operative markers the blood sampling was done immediately before induction while the patients already received CHO load or placebo (CHO free drink) in the pre-operative fasting phase. Hence, in both the groups CHO-1 and CHO-2 the patients received CHO load either once or twice before the blood sampling. Probably this provision of drink has reduced the amount of stress and thus the rise of stress markers has been attenuated.

In the present study, there was considerable difference between post-operative blood cortisol level among the three groups. Similar trend was also observed in a recent study[9] where the authors found that administration of oral glucose solution preoperatively reduced the markers of stress responses. The Gill and Miller in that study[9] explained that the preoperative glucose drink might have triggered the insulin secretion, thereby have changed the patient's metabolic status from "fasted state" to "fed state."

In the present study, the pre-operative glucose and C-peptide levels (for insulin levels) were found comparable between the three groups. One explanation may be that less stringent duration of fasting was followed in the current study as per revised fasting guidelines and thereby the stress response was not mounted to a considerable amount even in the control group. However, no further

Table 1: Demographic parameters

Parameters	Control (n=25)	CHO-1 (n=25)	CHO-2 (n=25)	P-value
Age (years)	43.5±9.75	44.08±11.40	48.64±9.17	0.152
Gender (M/F)	9/16	12/13	9/16	0.606
BMI (kg/m^2)	24.52±2.16	22.87±2.91	24.44±2.23	0.033
ASA (I/II)	12/13	9/16	12/13	0.614
Duration of Surgery (Minutes)	106.68±24.13	107.92±25.69	109.64±27.91	0.921

CHO-1: Patients receiving carbohydrate load once only in the preoperative period, CHO-2: Patients receiving carbohydrate load twice in the preoperative period, M/F: Male and Female, BMI: Body mass index, ASA: The American Society of Anaesthesiologist

Table 2: Pre-operative and post-operative blood levels of markers of stress response

Parameters (Markers of stress response of Surgery)	Control (n=25)	CHO-1 (n=25)	CHO-2 (n=25)	P value
Serum Cortisol levels				
Pre-op CORT (nMol/L)	439.99±70.84	389.7±65.15	338.16±51.11	<0.0001
Post-op CORT (nMol/L)	583.92±63.67	462.32±81.38	389.61±66.54	<0.0001
Blood glucose levels				
Pre-op GLU (mg/dL)	112.0±20.48	116.96±14.51	119.8±14.79	0.259
Post-op GLU (mg/dL)	171.32±25.45	134.92±20.06	129.04±14.35	<0.0001
Serum lactate levels				
Pre-op Lactate (mMol/L)	3.42±0.96	2.85±0.69	1.99±0.54	<0.0001
Post-op Lactate (mMol/L)	5.87±1.46	3.55±0.55	2.42±0.57	<0.0001
Serum C-peptide levels				
Pre-op C-peptide (pMol/L)	1.33±0.34	1.37±0.33	1.46±0.31	0.357
Post-op C-peptide (pMol/L)	2.71±0.67	2.16±0.31	1.83±0.23	<0.0001

Pre-op: Pre-operative, Post-op: Post-operative, CORT: Cortisol, GLU: Glucose, CHO-1: Patients receiving carbohydrate load once only in the pre-operative period, CHO-2: Patients receiving carbohydrate load twice in the pre-operative period, P<0.05 was considered as statistically significant strong conclusion can be drawn from the observation of this study.

In the present study, the rise of post-operative glucose level in those receiving CHO load once or twice was lesser than the increase in postoperative glucose level of control group from the base line values. This is in line with the observations of Widnyana et al.,[13] who also found a lower amount of rise in blood glucose level lower in those receiving oral glucose solution at night before the day of surgery and in the morning of surgery compared with those receiving a placebo drink (control group).

In the present study, the mean post-operative C-peptide of patients was found to be considerably higher in the control group compared with those receiving CHO drinks once or twice (2.71 vs. 2.16 vs. 1.83 pMol/L, P<0.0001). Perrone et al.,[14] observed a significant drop in insulin levels and insulin resistance in patients who received combined CHO-protein solution preoperatively. Preoperative administration of amino acids to patients with minor surgical trauma has been found to show a strong insulin-tropic effect.[3] It is speculated that caloric intake stimulates the secretion of

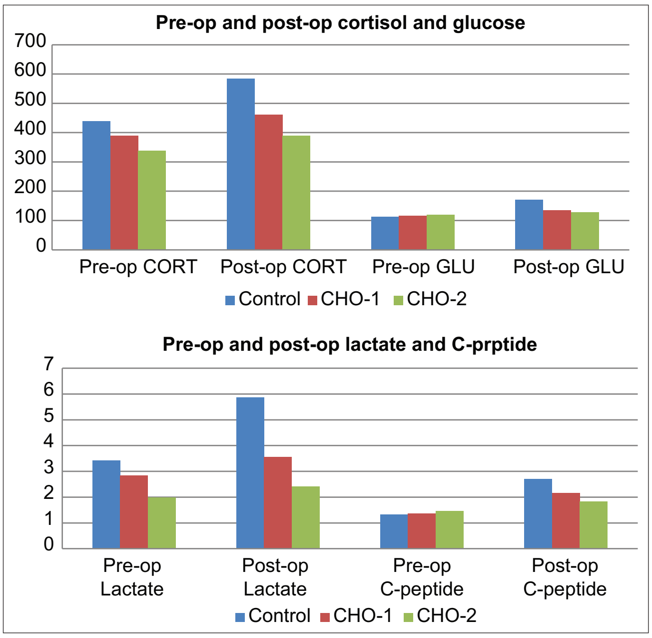

Figure 1: (a) Pre-operative and post-operative stress markers (cortisol and glucose) among the three groups, (b) Pre-operative and post-operative stress markers (lactate and C-peptide) among the three groups

insulin. However, a recent study[15] reported a contradictory observation that the use of pre-operative CHO in patients undergoing lumbar disk surgery does not attenuate the development of insulin resistance.

Preoperative consumption of high CHO drink has been found to decrease the insulin resistance and can enhance patient comfort leading to lesser sense of hunger and thirst in the preoperative period in open radical retropubic prostatectomies.[16] The Canbay et al.,[16] found both pre- and post-operative anxiety scores (measured with state-trait anxiety inventory test) to be comparable between the groups. The increase of procalcitonin levels was also found to be comparable in both the groups in the post-operative period. Other studies[17-21] have also examined the effect of preoperative CHO treatment on postoperative insulin resistance. A shortened pre-operative fasting and provision of preoperative CHO beverage have led to diminished insulin resistance. Pre-operative (3 h before induction) treatment with oral CHO supplementation was found to be associated with attenuation of the postoperative metabolic stress response.[19] The researchers have speculated that modulation of the inflammatory response can be one of the important mechanisms for that.

In the present study, the mean baseline pre-operative as well as the post-operative serum lactate values were found to be higher in patients not receiving any pre-operative CHO drink compared with those receiving that either once or twice. The post-operative lactate levels after elective major abdominal surgery have been evaluated for any prognostic value to predict about the postoperative complications, mortality and length of hospital stay.[22] The elevated serum lactate levels especially during the first 24 h in the post-operative period were found to be predictive of post-operative complications, mortality and surgical site infection after major abdominal surgery.[23]

Limitations of the study

In spite of every sincere effort, the present study has several lacunae. One limitation of the present study is that another extra sampling of stress markers before the time points of CHO drink or placebo drink should have been done to observe the existing baseline parameters of stress response. Moreover, the mean BMI of patients was considerably lower CHO-1 group compared with control group and CHO-2 group patients. This may be considered

Table 3: Pre-operative and post-operative VAS Scores (0-10)

Parameters	Control (n=25)	CHO-1 (n=25)	CHO-2 (n=25)	P value
Pre-op VAS	6.84±1.03	6.72±0.94	6.72±0.94	0.884
Post-op VAS	3.08±1.04	3.40±0.96	3.24±0.97	0.523

CHO-1: Patients receiving carbohydrate load once only in the pre-operative period, CHO-2: Patients receiving carbohydrate load twice in the pre-operative period, Pre-op: Pre-operative, Post-op: Post-operative, VAS: Visual analog scale, *P*<0.05 was considered as statistically significant

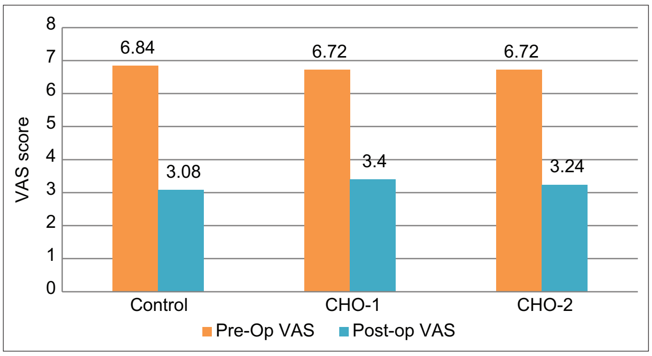

Figure 2: Pre-operative and post-operative VAS scores among the three groups

a chance value owing to sampling error and small sample size. To mention other short comings, the present study was a single center study, carried out in a tertiary care hospital, and observations were limited to only 24 h in the post-operative period. Moreover, the incidence of PONV and post-operative well-being (thirst, hunger, anxiety, mouth dryness, etc.) were not documented. These remains to be a future scope. Further study is needed involving larger sample with baseline estimation of stress markers is warranted to achieve a stronger conclusion.

CONCLUSION

It is concluded that the pre-operative glucose loading showed better efficacy in suppressing peri-operative stress response in terms of less rise of serum cortisol and lactate as compared to control placebo group. The rise of post-operative glucose and C-peptide levels in those receiving CHO loading – once or twice were lesser than that of control group (no CHO load) from the base line values. Therefore, the pre-operative glucose loading in patients undergoing spinal surgery can attenuate the metabolic and stress response.

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Authors Contribution:
AH - Participated in the concept of study design, conduct of study, data collection, and writing of first draft; **SM -** Helped in concept of study, subsequent designing, helped in data analysis, participated in the interpretation of result, review of literature and critically revising the first draft; **SC:** Participated during the concept of study design, time to time follow-up regarding progress of study, helped in statistical analysis and logical conclusion, participated in review of literature, contributed with critical revision of first draft, **MM -** Helped in concept of study, statistical analysis of data and logical conclusion of analyzed result, helped AH during first draft and subsequent revision of first draft; **AA -** Participated in the concept of the study, daily guidance regarding the conduct of the study, helped in data analysis and to arrive at logical conclusion, review of the literature, extensive revision of the first draft.

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