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Original Article

Evaluation of effects of a preoperative 2-hour fast with glutamine and carbohydrate rich drink on insulin resistance in maxillofacial surgery

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ABSTRACT

Introduction: The aim of this prospective, randomized, single-blinded study was to compare the effects of preoperative fast for clear fluids on insulin resistance and hemodynamic stability on patient undergoing maxillofacial surgery.

Method: In this study 20 patients undergoing maxillofacial surgery were randomized into four groups i.e. – group I patients with standard 08 h fasting before anesthesia, group-II patients were given 400 ml and 200 ml of water 08 h and 2 h respectively before anesthesia, group III patients were given 400 ml water with 50 gms of glucose and 40 gm of glutamine 08 h before anesthesia and 200 ml water with 25 gms of glucose and 10 gm of glutamine 2 h before anesthesia, group IV patients were given 400 ml water with 50 gms of glucose 08 h before anesthesia and 200 ml water with 25 gms of glucose 2 h before anesthesia. Blood samples were collected pre-operatively and post-operatively.

Results: Overall results suggest that Post-operative insulin resistance was greater in control patients (2.0 [0.3]) compared with the other 3 groups (placebo = 1.8 [0.9]); glutamine = (1.8 [0.6]); carbohydrate = (1.9 [0.6]).

Discussion: This study shows that shortening of pre-operative fasting time for clear fluids until 2- h prior to anesthesia may induce a favorable environment for the post-operative course. In conclusion, Glutamine with carbohydrate drink can be used safely in surgical patients.

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1. Introduction

"While it is desirable that there should be no solid matter in the stomach when chloroform is administered, it will be found very salutary to give a cup of tea or beef-tea about two hours previously"

Lord Lister, 1882.[1]

Retaining of food and fluids prior to surgery is a common practice due to concern regarding aspiration of acidic gastric contents during anesthesia. The traditional concept of 'fast from midnight' is a widespread accepted policy that is easy to apply, and is rarely challenged by staff and patients.[2] Standard fasting times are frequently longer than the expected 6–8 h, and may be as long as 10–16 h.[3] Fasting of prolonged duration is deleterious for the patient because the post-operative period is characterized by increased metabolic rate, hyper catabolism, gluconeogenesis and insulin resistance,[4] and is a key determinant of post-operative outcome and an independent predictor of the length of hospital stay after surgery.[5]

Enhanced Recovery after Surgery (ERAS) protocol has recently gained attention as an evidence-based method for peri-operative care used in hospitals worldwide to improve patient prognosis and this protocol recommends carbohydrate loading via oral administration before surgery, which reduces thirst, hunger, anxiety, and nausea, while preventing muscle wasting and loss of nitrogen and protein. Furthermore, the ERAS protocol has been shown to prevent the aggravation of insulin resistance that occurs as a result of surgery.[6]

Recently, several national anesthesia societies have revised their guidelines on preoperative fasting, recommending access to clear, non-particulate fluids up to 2 h prior to induction of anesthesia. These guidelines are supported by a Cochrane Collaboration review,[2] the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP)[7] and American society of Anesthesiologist task force on preoperative fasting.[8] The summary of fasting recommendations is as under:

Ingested material	Minimum fasting period (h)
Clear liquids	2
Breast milk	4
Infant formula	6
Non-human milk	6
Light meal	6

Glutamine is most abundant free amino acid and essential amino acid in extra-cellular and intra-cellular compartments with important role in carbohydrate metabolism. In humans, supplementation enriched with glutamine, increases serum insulin levels and patients treated with glutamine showed less decrease in glucose levels and decreased insulin requirements.[9]

2. Material and methods

Total 20 patients' undergoing Oral & Maxillofacial surgical procedure (eg.– mandibular fracture, ZMC fracture, mid-facial fracture, Oral Oncology etc.) with physical status ASA-I and ASA-II, under general anesthesia were included in the study. The study was conducted after obtaining the approval of the ethical committee of college and informed written consent from the participants. The patients were equally and randomly allocated to one of the below mentioned groups without any bias for the purpose of this study.

Group I (control group) – This group constituted patients who were kept fasting for 08 h before anesthesia.

Group II (placebo group) – patients in this were given 400 ml and 200 ml of water 08 h and 2 h respectively before anesthesia.

Group III (Glutamine group) – patients in this group were given 400 ml water with 50 gms of glucose and 40 gm of glutamine 08 h before and 200 ml water with 25 gms of glucose and 10 gm of glutamine 2 h before anesthesia.

[Glutamine ingestion: The Glutamine group received a total of 0.77g per kilogram of body weight (range, 0.61–0.97 g/kg).]

Group IV (carbohydrate group) – patients in this group were given 400 ml water with 50 gms of glucose 08 h before and 200 ml water with 25 gms of glucose 2 h before anesthesia.

2.1. *Exclusion criteria*

Patients with known cardiac disease, pulmonary disease, metabolic disease, disease affecting fluid and electrolyte balance of the body and patients who were not willing to be a part of study, were excluded from the study.

2.2. *Peri-operative protocol*

All surgeries were scheduled to begin at 9:00 am; the evening before the surgery, patients were allowed to eat solid foods until 12:00 am. Patients in group II, II, and IV were given beverages as described above before induction of anesthesia.

All patients underwent surgical procedures under general anesthesia. Peri-operative hydration was accomplished with appropriate intravenous fluid. Post-operative fasting was maintained for 12 h after second beverage. After that, all patients received liquid diet. Blood samples were collected both at induction of anesthesia and after surgery, before the first liquid meal. Blood sugar level below 50 mg/dl was the hypoglycemic limit for the purpose of our study. The focus of the study were insulin resistance assessed by HOMA-IR equation (homeostasis model assessment- Insulin resistance) proposed by Matthews et al, and haemodynamic response during peri-operative period. HOMA-IR was calculated as Insulin (ulU/ml by chemiluminescence micro-particle immunoassay) x blood glucose (mg/dl by enzymatic assay)/405.

3. Statistical analysis

Data was analyzed using Statistical Package for Social Sciences, Version 15.0. As the sample size was small, hence the data was assessed for normality. For many parameters, the distributions were not normal; hence a non-parametric evaluation plan was adopted. Chi-square test was used for categorical comparisons. Kruskal–Wallis test (non-parametric ANOVA) was used for intergroup comparisons. Mann–Whitney U test was used for between group comparisons. A "p" value less than 0.05 indicated a statistically significant association.

4. Results

All the patients had an un-eventful post-operative period and were discharged on the 2nd day after surgery with no difference seen between the groups. There were no cases of regurgitation during induction of anesthesia or post-operative complications. Table 1 showing baseline values for anthropometric, biochemical and hemodynamic parameters.

In this study we found that Post-operative insulin resistance was greater in control patients (2.0 [0.3]) compared with the other 3 groups (placebo = 1.8 [0.9]; glutamine = (1.8 [0.6]); carbohydrate = (1.9 [0.6]) (Table 3), Post surgery serum albumin levels were significantly higher in Group I (control group = 3.9 [0.4]) as compared to all the other groups (placebo = 3.3 [0.3]; glutamine = (2.9 [0.5]); carbohydrate = (3.1 [0.2]) (Table 3), Post-surgery Serum SGPT levels were significantly lower in Group I (27.1 [5.5]) as compared to Groups II (46.8 [18.4]) and III (44.6 [5.1]) (Table 3), Post Surgery, Serum creatinine levels were significantly lower in Group I as compared to Groups III and IV. Post-surgery serum CRP levels increased in all groups. Serum triglycerides and very low density lipoprotein cholesterol decreased in all groups from pre-operative to post-operative period.

4.1. *Hemodynamic changes*

For Diastolic blood pressure, statistically no significant intergroup difference was observed at any time interval ($p > 0.05$) (Table 2). For Systolic blood pressure too, except for end of surgery when intergroup difference was just significant (Table 5), at none of the other time intervals, the intergroup differences were significant statistically ($p > 0.05$). Statistically, a significant intergroup difference was observed for 20 min Glucose levels ($p = 0.041$). (Table 4)

5. Discussion

Many national clinics of anesthesia have changed their preoperative fasting guidelines and recommended oral intake of clear fluids until 2 h before induction of anesthesia, except surgery in emergency.

Aggravation of resistance to insulin usually occurs during the peri-operative period and is related to undesirable complications.[10] Therefore, prevention of increase in insulin resistance can play an important role in improving the prognosis of patients undergoing surgery. Non-diabetic patients who had fasted before surgery had a 50% chance of increase in resistance to insulin from the standard preoperative fasting period.[11]

Mechanism by which carbohydrate ingestion itself improves insulin resistance is the fact that fasting for longer duration markedly increases the expression of pyruvate dehydrogenase kinase 4 (PDK4), which is linked to deterioration in insulin resistance.[12] So when carbohydrates are used in preoperative period they can suppress the expression of PDK4, which results in decreased incidence of insulin resistance. Another proposed mechanism which leads to decrease in insulin resistance is increase in phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB) signals (the intracellular signal that has the greatest influence on insulin activity) after carbohydrate ingestion before surgery.[13,14] The third possible mechanism is the down regulation of excessive β-oxidation in mitochondria. Lipolysis and non-esterified fatty acids are expected to be higher after overnight fasting in the absence of carbohydrate loading, which could lead to higher ketone body formation regardless of β-oxidation activity and improvement in insulin resistance. Since we did not assess PDK4 activity, the exact mechanism for insulin resistance could not be clarified in this study.

The findings of our present study showed that the addition of glutamine to a carbohydrate based beverage was safe and also associated with a mild inflammatory systemic response. On the other hand a 08 h fast was found to induce a greater organic response to trauma, mainly due to increased insulin resistance. Addition of glutamine pre-operatively may improve gastric emptying and because of this, safety during induction of anesthesia was also increased.[11] Taking this into consideration, the overall results suggest that shortening of the pre-operative fasting time for clear fluids upto 2-h before induction of anesthesia is safe.

Most of the studies on carbohydrate administration were performed in patients undergoing major surgeries.[11] This present study is related to the patients undergoing maxillofacial surgery. The results of this present study have shown that these beneficial effects may occur even in minimally invasive maxillofacial surgical procedure.

The adverse effect of fasting for longer duration on glucose metabolism has already been reported.[5,6,15,16] The results of this study showed that resistance to insulin was increased only in patients who underwent standard pre-operative fasting and similar findings were observed by Diana Borges Dock-Nascimento et al (2012) in their study.[11] In our study Glutamine group showed benefits in improving insulin resistance when compared to other groups. Reason for this is the surgical trauma in our present study influenced these differences in results as compared to surgical trauma of the previously mentioned study.

After an overnight fasting approximately 50% of glucose production in healthy individuals occurs because of gluconeogenesis and, if a healthy individual fasts for approximately 42 h almost all of glucose production occurs because of gluconeogenesis.[17] Surprisingly, the patients in placebo group in our study showed lower levels of HOMA-IR than patients in group I. This finding suggests that the ingestion of only water may trigger intrinsic responses in the regulation of carbohydrate metabolism that may mimic the incorporation of nutrients, at least for the first hours in the post-operative period.[9] This effect may be due to gastric distention followed by increased serum levels of ghrelin after meals. Low serum

Table 1 – Comparison of groups at baseline for anthropometric, biochemical and hemodynamic parameters.

SN	Parameter	Group I (n = 5)		Group II (n = 5)		Group III (n = 5)		Group IV (n = 5)		Statistical significance (Kruskal Wallis test)
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1.	Male:Female	5:0		4:1		5:0		4:1		$\chi^2 = 2.222$; p = 0.528[a]
2.	ASA I:II	3:2		5:0		4:1		4:1		$\chi^2 = 2.500$; p = 0.475[a]
3.	Age	33.6	14.5	24.8	6.4	23.2	9.7	29.0	12.9	z = 2.818; p = 0.420
4.	Wt	63.6	8.9	62.8	13.6	56.6	10.6	50.0	15.3	z = 4.237; p = 0.237
5.	Duration of operation (in minutes)	148.0	81.7	83.0	40.9	100.0	47.8	118.6	48.4	z = 2.772; p = 0.428
6.	BMI (kg/m^2)	23.6	3.1	21.9	4.2	18.5	2.4	20.0	2.6	z = 7.488; p = 0.058
7.	Glucose (mg/dl)	88.0	9.3	85.7	10.2	100.7	16.0	85.9	6.8	z = 4.761; p = 0.190
8.	SBP (mm Hg)	138.4	35.5	112.0	13.3	116.6	13.1	110.8	12.7	z = 4.115; p = 0.249
9.	DBP (mm Hg)	83.0	17.2	73.6	14.1	69.0	11.4	66.4	9.2	z = 2.998; p = 0.392
10.	HOMA-IR (units)	1.5	0.2	1.6	0.8	3.0	0.6	1.8	0.4	z = 10.453; p = 0.015
11.	Insulin (units)	7.1	0.6	7.6	3.8	12.1	2.2	8.3	1.8	z = 12.056; p = 0.007
12.	Albumin (units)	3.5	0.3	3.7	0.1	3.4	0.3	3.5	0.2	z = 4.608; p = 0.203
13.	CRP (units)	5.2	3.7	7.0	2.8	5.6	3.5	6.8	4.2	z = 1.145; p = 0.766
14.	TG (mg/dl)	118.6	30.0	101.8	11.8	133.6	44.3	113.4	19.3	z = 1.984; p = 0.576
15.	BUN (units)	12.5	2.2	12.2	4.4	17.3	5.5	10.8	0.5	z = 6.608; p = 0.085
16.	SCr (units)	1.2	0.2	0.9	0.1	1.0	0.1	0.9	0.1	z = 7.920; p = 0.048
17.	SGOT (units)	31.4	7.2	37.8	9.8	43.5	16.4	38.5	18.1	z = 1.910; p = 0.591
18.	SGPT (units)	33.9	8.0	50.6	20.5	55.7	7.6	44.7	15.2	z = 7.132; p = 0.068
19.	VLDL (mg/dl)	23.7	6.0	20.4	2.4	26.7	8.9	22.7	3.8	z = 1.984; p = 0.576

CRP, C-reactive protein; BUN, blood urea nitrogen; TG, triglycerides; S.Cr, Serum creatinine; DBP, diastolic blood pressure, SCr, Serum Creatinine; VLDL, very low density lipoprotein.
[a] Chi-square test.

levels of ghrelin are associated with increased fasting insulin levels and resistance to insulin.[18] Ghrelin is involved in the regulation of hormones such as insulin and glucagon and may inhibit insulin resistance.[19]

The response after surgery depends on the extent of surgery and is mediated through a variety of mechanisms that include insulin resistance. Our finding showed that standard 08 h pre-operative fast enhanced insulin resistance even in least traumatic surgeries.

In our study we found no regurgitation of gastric contents during induction of anesthesia and similar findings were observed in the study conducted by Aguilar-Nascimento JE et al (2007), in which patients were given a solution of 400 ml of 12.5% dextrinomaltose 6 h before, and 200 ml 2 h before surgery.[20]

Manchikanti L et al in their nonrandomized prospective study allowed patients to take solid foods till 2 h before and liquids till 15 min before procedure and among those patients, only 1.6% complained of nausea and 0.02% complained of vomiting, and no aspiration was registered,[21] but in our study we used only clear liquid fluids 2 h before induction of anesthesia and did not observed any aspiration, nausea or vomiting.

In our study none of the blood glucose determinations was found to be in the hypoglycemic range. Our observations are in accordance with the study conducted by Bevan et al[22] in

Table 2 – Intergroup Comparison of SBP and DBP at different time intervals.

SN	Time interval	Group I (n = 5)		Group II (n = 5)		Group III (n = 5)		Group IV (n = 5)		Statistical significance (Kruskal Wallis test)
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Systolic blood pressure										
1.	Baseline	138.4	35.5	112.0	13.3	116.6	13.1	110.8	12.7	$\chi^2 = 4.115$; p = 0.249
2.	5 min	127.6	15.8	117.2	19.7	118.4	24.6	109.4	17.6	$\chi^2 = 2.236$; p = 0.525
3.	10 min	130.6	20.5	109.2	12.3	126.2	8.4	116.0	7.2	$\chi^2 = 7.274$; p = 0.064
4.	15 min	124.8	16.3	111.4	15.2	114.0	9.3	117.0	1.9	$\chi^2 = 1.926$; p = 0.588
5.	20 min	131.0	34.6	118.0	12.0	112.0	4.5	111.0	2.2	$\chi^2 = 4.838$; p = 0.184
6.	End of surgery	124.8	12.1	108.8	4.6	115.0	7.0	113.6	5.0	$\chi^2 = 7.827$; p = 0.050
Diastolic blood pressure										
1.	Baseline	83.0	17.2	73.6	14.1	69.0	11.4	66.4	9.2	$\chi^2 = 2.998$; p = 0.392
2.	5 min	82.4	11.3	76.4	12.5	70.0	18.5	72.2	12.6	$\chi^2 = 2.594$; p = 0.459
3.	10 min	75.8	11.8	69.4	7.6	78.0	9.9	66.8	13.6	$\chi^2 = 3.896$; p = 0.273
4.	15 min	77.6	5.0	75.0	8.4	78.0	7.1	69.2	11.3	$\chi^2 = 2.024$; p = 0.567
5.	20 min	79.4	16.0	77.0	9.7	69.8	6.4	69.4	4.0	$\chi^2 = 3.862$; p = 0.277
6.	End of surgery	82.4	10.4	71.2	5.0	73.0	5.3	72.4	4.3	$\chi^2 = 4.854$; p = 0.183

Table 3 – Post-surgery comparison of Groups at for biochemical and hemodynamic parameters.

SN	Parameter	Group I (n = 5)		Group II (n = 5)		Group III (n = 5)		Group IV (n = 5)		Statistical significance (Kruskal Wallis test)
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
1.	Glucose (20 min after ind.)	126.6	5.3	133.2	26.4	136.4	6.7	120.4	6.2	$\chi^2 = 8.246$; p = 0.041
2.	Glucose (mg/dl)	127.6	22.2	121.0	35.0	115.4	11.7	111.9	33.5	$\chi^2 = 1.680$; p = 0.641
3.	HOMA-IR (units)	2.0	0.3	1.8	0.9	1.8	0.6	1.9	0.6	$\chi^2 = 0.209$; p = 0.974
4.	Insulin (units)	6.4	0.2	6.2	3.1	6.3	1.6	7.0	1.3	$\chi^2 = 1.061$; p = 0.786
5.	Albumin (units)	3.9	0.4	3.3	0.3	2.9	0.5	3.1	0.2	$\chi^2 = 10.769$; p = 0.013
6.	CRP (units)	6.6	4.5	8.8	3.3	7.1	3.6	7.6	4.7	$\chi^2 = 0.931$; p = 0.818
7.	TG (mg/dl)	107.3	27.2	87.4	14.8	116.0	47.7	101.3	19.4	$\chi^2 = 1.924$; p = 0.588
8.	BUN (units)	14.3	2.4	14.4	4.6	17.2	4.3	12.4	0.5	$\chi^2 = 4.178$; p = 0.243
9.	SCr (units)	1.0	0.1	1.1	0.1	1.2	0.1	1.2	0.1	$\chi^2 = 9.033$; p = 0.029
10.	Gastric Fluid Vol (units)	3.0	0.4	2.9	0.2	3.3	0.3	3.3	0.5	$\chi^2 = 5.224$; p = 0.156
11.	SGOT (units)	33.9	8.0	50.6	20.5	55.7	7.6	44.7	15.2	$\chi^2 = 7.132$; p = 0.068
12.	SGPT (units)	27.1	5.5	46.8	18.4	44.6	5.1	42.1	13.5	$\chi^2 = 8.173$; p = 0.043
13.	VLDL (mg/dl)	21.5	5.4	17.5	3.0	23.2	9.5	20.3	3.9	$\chi^2 = 1.924$; p = 0.588

Table 4 – Between Group comparison of 20-min post-induction glucose (Mann–Whitney U test).

Parameter	I vs II		I vs III		I vs IV		II vs III		II vs IV		III vs IV	
	z	p	z	p	z	p	z	p	z	p	z	p
20-min post-induction glucose levels	0.731	0.548	2.102	0.032	1.261	0.222	1.571	0.151	1.051	0.310	2.530	0.008

Table 5 – Between Group Comparison of SBP at end of surgery interval.

I vs II		I vs III		I vs IV		II vs III		II vs IV		III vs IV	
z	p	z	p	z	p	z	p	z	p	z	p
2.305	0.016	1.467	0.151	1.622	0.151	1.476	0.151	1.724	0.095	0.324	0.841

which the mean values of blood glucose in each age group tended to be higher in the "fed" and in the "starved" group.

In our study the patients in Group I were exposed to standard fasting of 08 h. None of the patients in this group had blood sugar levels below 50 mg/dl, which was the hypoglycemic limit for the purpose of our study. The observation was in accordance to the studies conducted by J.H. Vanderwalt et al,[23] and Graham et al[24]

In our study the comparison of blood glucose levels prior to induction of anesthesia and 20 min after induction of anesthesia was statistically significant and similar findings were observed by Vikas Sharma et al, in 2011.[25]

A possible criticism of this study may be the inclusion of small number of surgical cases. Some other clinical studies having insulin resistance as the end-point has also randomized fewer than 10 patients in the study.[14]

In conclusion, reducing the time of preoperative fasting with glutamine or a carbohydrate solution until 2 h before the surgery, bring numerous benefits to the patient and prevent decrease in insulin resistance and did not increase the risk of aspiration during induction of anesthesia.

Conflicts of interest

All authors have none to declare.

Ethical approval

Ethical approval was taken by Ethical committee of "Kothiwal Dental College & Research Centre, Moradabad, Uttar Pradesh, India". Reference No. – KDCRC/ETH/RES/2013/12/09.

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