ORIGINAL RESEARCH PAPER

Anaesthesiology

KEY WORDS: Obese, nondiabetic, insulin sensitivity, anaesthesia.

ASSESSMENT OF INSULIN SENSITIVITY IN OBESE, NONDIABETIC SUBJECTS UNDERGOING INFRAUMBILICAL SURGERY AND ITS VARIATION WITH GENERAL AND REGIONAL ANAESTHESIA - A PROSPECTIVE RANDOMIZED STUDY.

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ABSTRACT

The greatest degree of insulin resistance occur on the second post-operative day after major surgery and persist upto three weeks.

Aim: To compare changes in insulin sensitivity of nondiabetic obese patients undergoing general and regional anaesthesia.

Methods: 100 non diabetic obese posted for infra-umbilical abdominal surgeries under general and epidural anaesthesia. Serum insulin, glucose, cortisol, TNFα, IL6 and HOMA estimated before operation , immediately after operation and 48 hrs after operation.

Result: There is significant increase of mean HOMA within Group G from preoperative to 48 hrs postoperative period, no changes seen within Group R at three point of time. Borderline difference (p-0.059) in immediate postoperative period , and significant difference(p 0.000) at 48 hrs postoperative period seen between two groups. Changes in IL6, TNF-α between two groups at three different point of times shows no significant changes , but mean increase of IL6 and TNFα from preoperative to immediately and 48hrs postoperative period. Significant changes revealed in cortisol level between two groups from preoperative period to immediately and 48hrs postoperative periodwithin and between the groups..

Conclusion: Suitable anaesthetic and analgesic prevent deterioration of insulin sensitivity status in obese non diabetic patients undergoing surgery under anaesthesia.

INTRODUCTION:

Development of awareness for a major surgery under anaesthesia to quantify insulin sensitivity or resistance, should have been an important objective when dealing a obese nondiabetic patient. Both surgery and anaesthesia may induce an increase in levels of stress hormones (epinephrine, cortisol, growth hormone) and inflammatory cytokines (interleukin-6 and tumor necrosis factor–alpha), resulting in insulin resistance and impaired insulin secretion (even among patients who present with adequate insulin secretion). These in turn contribute to lipolysis and protein catabolism, leading to hyperglycemia and, if a patient is severely insulin deficient, ketoacidosis.

Optimal or the best approach to peri-operative glycemic control, their relative need for insulin, and control over any factors that may be likely to increase insulin requirements are essential goal for anaesthetic management, as surgery and anaesthesia can induce hormonal and inflammatory stress that increase the risk of complications in obese patients. The present and future challenge is to find out suitable anaesthetic procedure for major surgeries in context of improving or worsening the insulin-sensitivity state and their connection with the anaesthesia. Compared with epidural anesthesia, general anaesthesia is associated with greater stimulation of the sympathetic nervous system and increased catecholamine levels, resulting in more pronounced hyperglycemia.

Insulin sensitivity can be estimated by "Homeostatic Model Assessment" score (HOMA)[1,2], which is considered having similar efficacy with hyperinsulinaemic - euglycaemic clamp test. Questions raised that, is there any link between obesity and inflammation to play a pathogenic role in the development and progression of these insulin resistant state?.[3,4] Interleukin-6 (IL-6) is a cytokine closely associated with obesity and insulin resistance.[5] Role of TNF-α in systemic insulin resistance in obese non diabetic patients need further investigation.[6] Cortisol is another endocrine factor produced by adipose tissue.

Blood glucose levels are not routinely monitored for nondiabetic patients during the perioperative period. Glycemic control before, during, and after surgery reduces the risk of infectious complications; in critically ill surgical patients, intensive glycemic control may reduce mortality as well.

Therefore aim is to compare the changes in insulin sensitivity state of nondiabetic obese patients under general and regional anaesthesia posted for infraumbilical surgeries.

Objective is to assess the insulin sensitivity in terms of HOMA score varies with the BMI status of subjects undergoing surgeries, comparison of insulin sensitivity state before and after surgery under general and regional anaesthesia, and to detect the batter anaesthetic option in obese nondiabetic subjects.

Material and Methods:

After obtaining the IEC and informed consent from 100 nondiabetic, obese patients with body mass index (BMI) more than 30kg/mt^2 aged between 25 and 60 years posted for infra-umbilical abdominal surgery with no contraindication to epidural and or general anaesthesia were included in this prospective, randomized, open label, parallel group study conducted between 2014 and 2016 in IPGME&R .Kolkata .

Patients with anticipated difficult airway, received any medication known to affect glucose metabolism, having autonomic neuropathy, allergy to the study drugs, haemoglobin <10 gm / dl., receiving anti-platelets or anti-coagulants, having sepsis, HbA_{1c} > 7% and those refuses to receive epidural anaesthesia were excluded from the study.

Sample size calculation was done on basis of the HOMA score 48 hours after completion of surgery as the primary outcome measure for the study. A minimum of 33 subjects were required per group in order to detect a difference of 0.7 in 48 hours post-operative HOMA score with 80% power and 5% probability of Type-1 error. This calculation assumed a standard deviation of 1 for 48 hours post-operative HOMA score on the basis of an earlier study [7]. A total of 100 patients were included for this research work. All the patients were allocated between two groups through a computer generated random number to receive general anaesthesia (n=50), and epidural anaesthesia (n=50).

Routine preoperative investigations were carried out in all patients including total hemogram, urine blood glucose, urea and creatinine estimation.Chest X-ray , ECG, and coagulation profile. specific laboratory investigations included estimation of blood glucose and blood insulin, serum cortisol, TNFα and Il6 at- day before surgery, immediately after extubation, 48 hrs after surgery. Parameters analyzed also for this study included HOMA score,Visual analogue scale (VAS) – *for pain assessment.* Calculation of HOMA-IR was done by fasting insulin (μIU/ml) × fasting glucose (mmol/ml)/22.5. Insulin resistant (IR) was considered, when HOMA 2.1.

On the day before surgery blood samples collected for fasting glucose and insulin (F_G & F_I) ,IL6.TNFα for all patients. Patients of Group G were induced with inj. thiopentone sodium 5mg/kg and

inj. fentanyl 2 µg/kg; patients were intubated with : inj vecuronium 0.1 mg/kg. artificial ventilation to maintain normocapnia (35-40 mm hg) with halothane (0.25 % to 0.75 %) in 33% O2 along with N2O , supplemental doses of fentanyl and vecuronium as top up dose. Reversal of neuro muscular blockade done at the end of surgery by inj neostigmine 0.05mg/kg i.v. and inj glycopyrrolate 0.01 mg/kg i.v. Vas recorded immediately after extubation. and maintained between 3 and 4 upto 48 hrs post operative period.

For patients of Group R , epidural blocked were established between L_3- L_4 interspaces with 0.25% bupivacaine & 100g fentanyl to achieve bilateral sensory block for T_5-S_2 and maintained with intermittent boluses of 0.25% bupivacaine. Heart rate within 20% of pre-operative value were kept throughout the procedure. Blood glucose, serum insulin, serum cortisol , IL6, TNFα were measured on the day before the operation, Immediately after extubation and at 48 hr. after extubation intraoperative analgesia for Group G were done with infusion of inj. fentanyl iv, & inj.midazolam (0.03mg/kg/hr) for prevention of awareness maintaining BIS between 45 to 55. And for Group R Inj. fentanyl and local anaesthetic infusion through epidural route. In addition iv infusion of inj. midazolam (0.03mg/kg/hr) for intra-operative period sedation.

For post-operative analgesia: in Group G, Inj. tramadol 2 mg/kg iv administered at every 8 hrs. and for Group R with intermittent boluses of 0.0625% preservative free bupivacaine at every 8 hrs. as a top up dose through epidural route. Goal to maintain blood glucose<180mg/dl.Inj. paracetamol (1 gm) iv infusion 8 hourly for 48 to both the groups. Inj. tramadol 2 mg/kg iv as top up dose when VAS > 3in both the group .

All the data were analyzed and compared between the two groups by a person who were blind to the technique of anaesthesia. Data were summarized as mean ± SD for numerical variables and counts & percentages for categorical variables. Median and inter-quartile range were presented for numerical variables that were not normally distributed. Numerical variables were compared between groups by student's unpaired't' test for normally distributed data, or by Mann-Whitney U test if otherwise. The Fisher's exact test was employed for inter-group comparison of categorical variables. All analysis were two-tailed and P<0.05 was considered statistically significant.

Table:1.

Parameters	Group G. Mean ± SD	Group R Mean ± SD	p-value
AGE (YRS)	43.28 ± 10.094	47.66 ±10.737	0.038 *
WEIGHT (KG)	70.55 ± 4.883	70.19±4.749	0.71
HEIGHT (CM)	148.90 ± 5.027	148.39±3.545	0.559
Total dose of Insulin received(IU)	53.54 ± 21.248	3.94 ± 3.569	0.000 *
Duration of surgery(hrs)	49.00 ± 7.242	52.80±5.425	0.004*
Estimated blood loss(mL)	74.28 ± 22.116	72.50±19.750	0.672
Crystalloid in mL	3289.56 ± 557.761	3869.90±439.067	0.000*
Blood (mL)	34.00 ± 73.151	18.00±55.107	0.672
Serum Hb%	12.60 ± 1.055	12.74±1.184	0.668

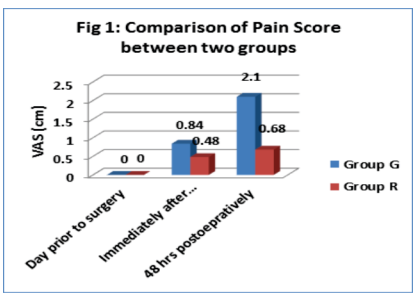

Table .2.

Parameter	Group n = 50	Immediately after surgery Mean ± SD	Day prior to surgery Mean ± SD	48hrs post operative. Mean ± SD
Blood Glucose mmol/lt	G	5.10 ±0.735	5.61 ±0.628	5.83 ±0.774
	R	5.00 ±0.841	5.15 ± 0.527	5.00 ± 0.867
	p-value	0.540	0,000	0.000
Blood Insulin level (pmol/L)	G	8.76± 11.658	4.96±5.285	25.35±30.122
	R	11.48±10.636	3.91±1.801	3.33±1.041
	p-value	0.226	0.185	0.000
HOMA Score	G	1.98± 2.189	1.29±1.425	6.71±8.303
	R	2.68±2.852	0.89±0.446	0.80 ± 0.423
	p-value	0.171	0.059	0.000
IL6 level in (pg/ml)	G	14.99 ± 36.396	58.24± 201±354	30.78± 79.728
	R	23.43±63.810	117.39±372.440	18.53 ±46.523
	p-value	0.464	0.374	0.383
TNF –α (pg/ml)	G	612±1221.345	1034.57±1560±995	1808.50±2122.104
	R	885.25±1894.247	949.04±1785.546	1013.87±2799.168
	p-value	0.415	0.808	0.130
Cortisol level in (pg/ml)	G	12.82±14.153	15.20±17.212	24.24± 29.110
	R	-2.84±31.309	-5.20±30.374	-3.36± 32.574
	p-value	0.002 *	0.000*	0.000*

Results:

Table 1 shows comparable demographic profile between the two groups except, total dose of insulin needed significantly higher in general anaesthesia group, duration of surgery, crystalloid needed significantly higher in epidural receiving group, to maintain hemodynamic stability following neuraxial block.(P=Significant difference). Figure 1 shows, significant difference (P<0.05) in VAS between two groups at three different point of time analysed by Student's unpaired t-test .

Changes in CBG (Table 2) between two groups at three different point of time analysed by Student's unpaired t-test shows significant difference (P<0.05). Changes of insulin level at three point of times of analysis between two groups. There is no difference between pre-operative and immediately after operation but after 48 hrs a significant difference observed between two groups. Changes in HOMA score from preoperative value to immediately after and 48 hrs postoperative periods. There is significant increase of mean HOMA score within general anaesthesia group from preoperative to 48 hrs postoperative period within the group, whereas no changes revealed within the epidural group at three point of time. Difference in changes between the two groups shows borderline difference (p-0.059) in immediate postoperative period ,and significant difference(p 0.000) at 48 hrs postoperative period. Changes in IL6 level between two groups at three different point of times shows no significant changes between two groups at three different point of times, whereas there is mean increase of IL6 level(pg/ml) from preoperative period to immediately and 48hrs postoperative period. Changes in TNF-α level between two groups at three different point of times also shows no significant changes between two groups at three different point of times, whereas there is mean increase of TNF-α level (pg/ml) from preoperative period to immediately and 48hrs postoperative period. There are significant changes revealed in cortisol level in pg/ml at three different point of time between two groups from preoperative period to immediately and 48hrs postoperative period.

Discussion: Suitable anaesthetic and analgesic must be combined with the precise, careful and sympathetic approach to prevent deterioration of insulin sensitivity status in obese non diabetic patients undergoing surgery under anaesthesia. This research work was aided by the Department of science and technology (Govt of West Bengal.)(vide sponsor sanction letter No: 1069(Sanc) / ST/P/S&T/9G-19/2014 dated 20.02.2015) to procure reagents and ELISA machines along with accessories for the laboratory analysis of the blood samples were collected and kept stored at -20 degree centigrade in refrigerator of the departmental laboratory of department of plastic surgery .IPGME&R, Kolkata. Demographic profile between the two groups were comparable. Total dose of insulin needed significantly higher in general anaesthesia group, duration of surgery was more in epidural group , crystalloid needed significantly higher in epidural group as needed more to maintain hemodynamic stability following neuraxial block. Spearman's rank correlation coefficient showed poor and insignificant correlation between BMI and HOMA within general anaesthesia group of patients at different time point ,and only two correlations revealed moderate and significant in epidural group at the level of $p<0.05$. Significant changes in blood glucose from base line to immediately after operation and at 48 hrs of operation between the groups detected. Within both the groups significant difference from base line to immediately after operation and base line to 48 hrs after operation detected, whereas no difference detected from immediately after operation to 48 hrs postoperative period. Changes of insulin level at three point of times of analysis between two groups revealed no significant difference between pre-operative and immediately after operation, but after 48 hrs a significant difference observed between two groups. Analysis within the groups showed significant difference between any two time points throughout the study period.

Conclusion: Determination of the insulin sensitivity status in obese nondiabetic subjects has paramount importance before major surgery. Body weight, BMI is not found a determinant factor in obese, nondiabetic patients, as they are already at the threshold of insulin resistance. There was no significant correlation of HOMA with BMI in study patients detected. Circulating insulin level detected as a determinant factor ,which may be considered as a hidden truth. Insulin level and HOMA changed significantly in generel anaesthesia group at different point of analysis.. Moreover significant dose of insulin required for General anaesthesia group to maintain normoglycemia during study period. Epidural anesthesia found safer in this point of view. as no changes in HOMA revealed within the epidural group at three point of time. Rise of insulin level from base line to different point of time in general anaesthesia group was significant. Hence changes in HOMA was also very much significant within the group at three different point of time. Anaesthesia cannot change cytokine level. In this study circulating cytokines could not establish any positive impact.

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