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RESEARCH ARTICLE

A PROSPECTIVE CLINICAL STUDY OF GLYCEMIC CONTROL IN WELL CONTROLLED TYPE II DIABETES MELLITUS PATIENTS SUBJECTED TO OPERATIVE PROCEDURES UNDER REGIONAL VERSUS GENERAL ANAESTHESIA

[1]Dhulkhed, V. K., [2]Pavan Dhulkhed, [3,*]Bilal Mohammad, [4]Indrajit Gupta and [5]Gagandeep Singh

[1]Professor & HOD, Dept. of Anaesthesiology, Krishna Institute of Medical Sciences, Karad, Maharashtra
[3,4,5]Resident, Dept. of Anaesthesiology, Krishna Institute of Medical Sciences, Karad, Maharashtra
[2]Assistant Professor, Dept. of Anaesthesiology, J. N. Medical College, Belagavi, Karnataka

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ABSTRACT

Background: Surgery and anaesthesia by itself is a stress. Although a normal patient goes through it without adverse effects, in a patient with insulin dependent diabetes it can lead to significant hyperglycaemic reaction. It was observed that a skillfully conducted regional anaesthesia is better as far as glycemic control is concerned and overall outcome of the patient postoperatively, compared to general anaesthesia (GA) technique. Therefore, we though it prudent to test our hypothesis on patients with well controlled diabetes, on insulin therapy, to compare regional versus GA technique.

Method: We recruited 120 patients with well controlled DM on subcutaneousinsulin scheduled for surgery in this comparative clinical study into two groups, Group ITGA (Intratracheal General Anaesthesia) and Group NB (Neuraxial Block) of 60 each.The blood sugar levels were recorded before induction, intraoperatively every 20 minutes and post-operatively every hourly till 5 hours. The systolic and diastolic blood pressure, heart rate and SPO_2 were recorded every 20 minutes intraoperatively and post-operatively.

Result: BSL was significantly higher immediately after induction, intraoperatively and postoperatively at all levels in group ITGA compared to group NB. Insulin requirement was more in ITGA group as compared to NB group intraoperatively and postoperatively. Wound healing was better in group NB as compared to group ITGA.

Conclusion: In well controlled diabetic type 2 patients subjected to surgery, glycemic control under ITGA was poor compared to those under NB intra and post operatively and that the patients in former group needed early and more repeated insulin supplementation to control BSL to desired level.

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INTRODUCTION

The prevalence of Diabetes Mellitus (DM) is on constant rise with increasing number of patients being admitted to hospital and operative procedures, which poses a new challenge to anaesthesiologist (Stoelting's, 2012; McAnulty, 2003). The surgical procedures are incidental or more commonly they are related to the diabetic condition. (Subhankar Chowdray and Sujoy Ghosh, 2007) Today there is a consensus of opinion about a good metabolic control in these patients throughout, as well as perioperative period and has been shown to result into improved perioperative outcome. The good number of reviewers of this subject have emphasized regarding understanding of the pathophysiology. But till date there is no unequivocal acceptance regarding the technique of choice of anaesthesia in these types of patients.

****Corresponding author: Bilal Mohammad Indrajit Gupta,***
Resident, Dept. of Anaesthesiology, Krishna Institute of Medical Sciences, Karad, Maharashtra.

Only a few clinical research papers published have tried to explore the effects of the type or technique of anaesthesia to find out a better one in an effort to reach to a logical conclusion and improved perioperative outcome in these patients. It is also emphasized and recommended by many experts in this field to explore this area of managing patients with diabetes. Surgery and an anaesthesia by itself is a stress and although a normal patient goes through it without adverse effects (Dawn D. Smiley and Guillermo E. Umpiorrez, 2006), in a patient with insulin dependent diabetes it can lead to significant hyperglycaemic reaction as a result of uncontrolled increase in counter regulatory hormones with decrease in insulin secretion a varying degree of increased insulin resistance destabilizing patient's homeostasis. Like DM, there are increasing number of studies on surgical stress response (Henrik Kehlet, 1989), not necessarily two being linked together. During the management of such patients in day to day clinical practice, it was observed and realized that a skillfully conducted regional an anaesthesia as a technique shows more promising results so far as glycemic control is concerned and overall outcome of the patient postoperatively, compared to conventional general anaesthesia

(GA) technique. Therefore, we though it prudent to test our hypothesis by planning a prospective, controlled and standardized study on patients with well controlled diabetes, on insulin therapy, to compare regional versus GA technique.

Aims and objectives

To decide a better anaesthetic technique for precise maintenance of glycemic control between 100-180 mg dl-1 in a known type 2 diabetic patient on insulin, subjected to operative procedure under regional versus GA.

MATERIALS AND METHODS

After obtaining institutional ethical committee approval, we recruited 120 ASA physical status II patients with well controlled DM on subcutaneous insulin scheduled for elective or emergency lower limb, pelvic, perineal and lower abdominal surgery in this comparative clinical study into two groups of 60 each.

Group ITGA: Patients receiving Intratracheal general anaesthesia.

Group NB: Patients receiving Neuraxial block (NB), according to patients willingness or alternately.

All patients gave written, informed consent. Patients with uncontrolled diabetics with fasting BSL more than 180mg dl-1, gross cardiovascular disease, deranged RFT, acute chest infection, neuropathy, dehydration, metabolic derangements, ketoacidosis, spinal deformities, restricted neck movements, diabetic autonomic neuropathies, history of concomitant drugs like corticosteroids, diuretics, oral contraceptive pills were excluded. All the patients were evaluated prior to surgery and relevant investigations were done. All patients in our study were treated with S.C. insulin. All patients were fasted from the night before surgery (8-9hrs). Morning insulin dose is omitted on the day of surgery. All patients received tablet Diazepam 10mg HS orally day before surgery for anxiolysis.

Anesthetic technique used:

After receiving the patient inside the operation theatre, Intravenous (IV) line is secured with 20 gauge cannula and 0.9% Normal saline is started, standard monitoring, including noninvasive arterial blood pressure, electrocardiography, and pulse oximetry, was attached. Group NB patients received subarachnoid block. Under all aseptic precautions a midline lumbar puncture was performed at L3-L4 interspace with 25 gauge Quincke needle in lateral or sitting position. Following free flow of clear CSF, anaesthetic solution 0.5% bupivacaine was injected. Then patient was placed in supine position. The table tilt was managed to get a level of sensory block at T6 level. Group ITGA patients were given intratracheal general anaesthesia. All patients were preoxygeneated for 3 minutes. Premedication given as Inj. Fentanyl 2 mcg kg-1 and Inj. Diazepam 2mg I.V. Then patients are induced with Inj. Thiopentone 5mg kg-1andVecuronim 0.1mg kg-1 I.V and patients were intubated with proper sized cuffed end tracheal tube. An aesthesia is maintained on O2, N2O (50:50), sevoflurane in concentration 1.8% in closed circuit and Inj. Vecuronim 0.02mg kg-1.

At the end of surgery patient is reversed with Inj. Neostigmine 0.04 mg kg-1 with Inj. Glycopyrolate 0.005mg kg-1 I.V after return of spontaneous respiration. Patient were extubated when they become fully conscious and after return of good muscle power.

Vital signs and side effects

The blood sugar levels were recorded before induction, after induction and thereafter every 20 minutes throughout the surgery, post-operatively every hourly till 5 hours using Ascensia BREEZE blood glucose meter. The systolic and diastolic blood pressure (BP), heart rate (HR) and SPO2 were recorded every 20 minutes intraoperatively and post-operatively, from multipara monitors (SKANRAY Star 90). Nausea or vomiting was treated with intravenous metoclopramide 10 mg, and bradycardia, defined by an HR<50 bpm with intravenous atropine 0.6 mg. Oxygen saturation <95% treated by 100% oxygen supplementation through Magill's circuit. Pre-anaesthesia drill and emergency intubation kept ready. If blood sugar level (BSL) raised to more than 200mg dl -1 during any point of the study it was managed according to the requirement. During study the number of patients requiring insulin were recorded and the requirement doses of those atients were also recorded. Fallin BSLtoor below 60 mg dl-1 is treated with I.V. 5 % dextrose drip and these patients were excluded from the study. All 120 patients were monitored in post-operative recovery room for sedation, comfort, nausea and vomiting and analgesia.

Statistical Analysis

The categorical factors are represented by the number and frequency (%) of cases. The continuous variables are represented by measures of central frequency (like mean, median and mode) and deviation (SD and range). The statistical analysis was done using 2-independent sample student's t-test, and Fishers exact test. P-value<0.05 was considered statistically significant. The statistical software namely SYSTAT version 12 (made by Cranes Software's, Bangalore) was applied.

OBSERVATIONS AND RESULTS

Both the groups are statistically comparable with respect to age, weight, height and gender (Table 1). Before induction mean BSL for group ITGA and group NB was statistically insignificant (P=0.172 Graph 1, Table 2). So both groups are statistically comparable with respect to BSL before induction. BSL was significantly higher immediately after induction, intraoperatively at 20, 40, 60, 80 minutes and postoperatively for 1st, 2nd, 3rd, 4th, 5th hour in group ITGA compared to group NB (P<0.001 Graph 1, Table 2) 14 patients in ITGA group needed insulin supplementation intra operatively. Insulin supplementation is given as insulin 5 units added to 500 ml NS, to bring down the BSL level up to 160 – 170 mg/dl. Post operatively another 7 patients needed insulin supplementation. So in total perioperatively 21 patients in ITGA group needed insulin supplementation. In contrast to this none of the patients in NB group needed insulin supplementation perioperatively (Table 3). In group NB, 3 patients show poor wound healing with infection at operation site compared to 6 patients in group ITGA, (P 0.490, Graph 2, Table 4) which is not significant. Patients of ITGA group were sedated and incidence of post-operative nausea and vomiting were higher as compared to patients of NB group.

Table 1. Demographic parameters

Parameters	Group NB (n=60)		Group ITGA (n=60)		'p' value
	Mean ± SD		Mean ± SD		
Age in years	52.53±11.11		49.24±13.85		0.153
Weight in Kilograms	65.77±12.86		65.09±13.99		0.782
Height in Centimeters	157.97±32.43		155.33±29.31		0.640
Gender	Male	Female	Male	Female	1.000
	32	28	31	29	

Table 2. Comparison of BSL in two groups

BSL at	Number of cases	BSL (Mean ± SD)		p-value
		Group NB	Group ITGA	
Before induction	60	136.80 ± 12.42	139.16 ± 4.80	0.172
After induction	60	126.36 ± 24.08	166.62 ± 14.26	< 0.001
At 20th min	60	123.78 ± 24.13	170.36 ± 13.51	< 0.001
At 40th min	60	126.06 ± 20.14	178.06 ± 18.47	< 0.001
At 60th min	60	125.36 ± 18.17	187.48 ± 20.64	< 0.001
At 80th min	60	126.32 ± 20.71	201.86 ± 27.39	< 0.001
Post-operative 1st hour	60	129.36 ± 25.46	214.11 ± 30.18	< 0.001
2nd hour	60	129.09 ± 18.79	221.29 ± 31.41	< 0.001
3rd hour	60	128.79 ± 16.74	228.42 ± 32.32	< 0.001
4th hour	60	131.89 ± 16.29	237.50 ± 31.98	< 0.001
5th hour	60	134.52 ± 16.28	245.86 ± 32.98	< 0.001

Table 3. Comparison between insulin supplementation in two groups

Group	Insulin supplementation		Total No.
	Intra operative	Post-operative	
NB	0	0	0
ITGA	14(23 %)	7 (12 %)	21 (35 %)

Table 4. Comparison of patients with respect to wound healing

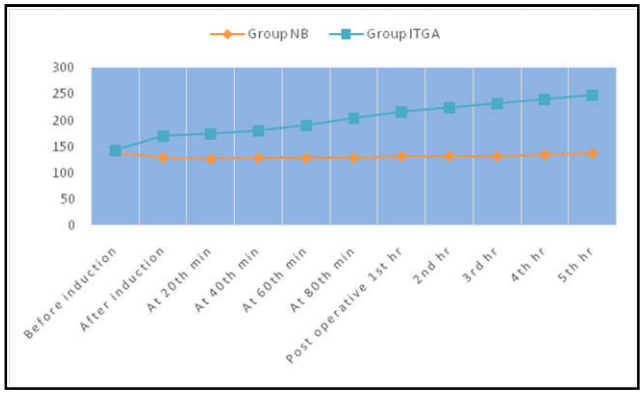
Group	Wound healing		Total	p-value
	Good	Poor		
NB	57	3	60	0.490
ITGA	54	6	60	

NB group patients were completely awake and comfortable due to post-operative analgesia of neuraxial blockade. ITGA group patients required more I.V analgesic.

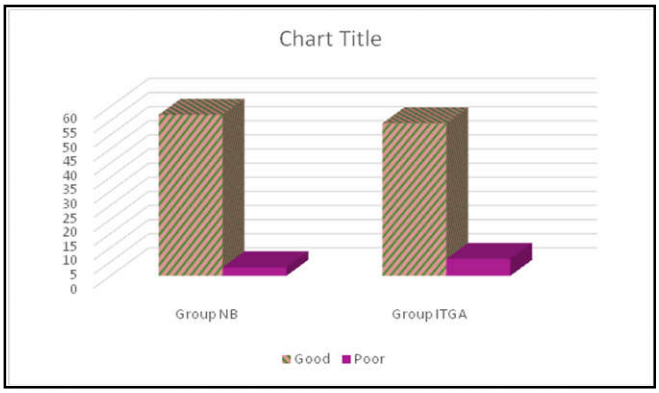
DISCUSSION

In the initial few decades since 1950s, operation on a diabetic patients who was on insulin therapy was fraught more with possible accidental hypoglycaemia under an unconscious state of G.A. which invariably can result into a permanent brain damage and, therefore it was an unwritten dictum to avoid the use of intraoperative insulin and to keep the patient always on a hyperglycaemic side perioperatively. For almost 25 years the situation remained the same, however sometimes severe hyperglycaemic episodes were observed in diabetic patients resulting in significant fluid and electrolyte imbalances, ketoacidotic episodes and even pre coma. It was then realized that such type of patients should be managed with glucose + insulin + potassium premixed preparation. The justification for this regimen (Alberti regimen) (Alberti and Thomas, 1979) was quiet convincing and ensured three things, one that insulin has to be administered only I.V. in a continuous drip form with glucose and potassium, secondly to maintain blood glucose level between 5 to 10 mmol Lit-1, and third the regimen must be followed with users with common sense with regards to particular patient's status, co-morbid conditions, surgical procedure and with repeated measurements of BSL. The Alberti regimen became so popular because of its inherent safety factor incorporated within it, that it was followed meticulously for next 30 years, till it was reassessed by experienced anaesthetists again in 2009. The multicentric retrospective studies and large number of patients with meta-analysis made it evident that a loose control in blood glucose, with slight hyperglycaemic levels was one of the important culprit which led to increased incidence of post-operative wound infection, delayed wound healing, increasing morbidity with prolonged hospital stay and even greater morbidity and mortality which also led to tremendous escalation of cost treatment because of this there was reconsideration about loose control regimen and experts advocated tight control of blood glucose not only intra operatively but throughout the perioperative period. What level of glycemic control is

associated with the best risk benefit ratio for diabetic patients is obvious from various following studies. A study of 1548 critical care patients by Van Den Berghe demonstrated an improved outcome in patients who had their blood glucose maintained between 80-110 mg dl-1 compared with those in



Graph 1. Comparison of BSL intra operatively and post operatively



Graph 2. Comparison of patients with respect to wound healing

whom insulin therapy was only instituted if blood glucose rose above 215 mg dl-1. This beneficial effect was seen in diabetics and non-diabetics alike (Van Den Berghe *et al*., 2001). More recent observational study of 523 patients (16.4 % diabetics) by Finney SJ and Zekved C in 2003 in predominantly post operative cardiothoracic surgical critical care unit, suggest a more liberal blood glucose target of < 145 mg dl-1 and again a beneficial effect was equally in diabetic and non-diabetic patients (Finney *et al*., 2003). NICE SUGAR is a large multicenter study published in April 2009, which included 6104 intensive care unit patient in three different countries. 90 day mortality was a main outcome measure in which significantly more patients in intensive insulin therapy(IIT) group died than conventional control group (21.5% versus24.9%).The IIT group had tight glycemic control with blood glucose maintained between 80-110 mg dl-1 compared to 140 and 180 mg dl-1 in conventional group (Tejal *et al*., 2009). According to all above mentioned studies tight glycemic control between 80 to 110 mg dl-1 is associated with higher rate of hypoglycemic events and higher mortality. So BSL between 140-180 mg dl-1 is now considered best glycemic control associated with best risk benefit ratio. Dawn D.*et al* studied that, single blood glucose level >220 mg dl-1 on 1st postoperative day is associated with infection rate 2.7 times higher (Dawn *et al*., 2006). In last few decades with the presumed safety about balanced GA over a conventional regional technique, we used it for managing the operations on diabetic patients; and this practice was also supported by few clinicians concerned about introducing infection, autonomic neuropathy and hypotension; however today the time has come to reassess the ability of GA in control of melieuinterior of the anaesthetized patient subjected for surgery.

The GA creates a state of unconsciousness and amnesia fairly well and today even the depth of anaesthesia is also judged by cortical suppression, modifying EMG signals and by bispectral index; however the afferent impulses of pain from peripheral tissue injury may or may not reach central cortex but they do reach limbic system, thalamus and hypothalamus. Which have a servo control with pituitary and sympathetic efferent control. Hence in such situations afferent impulses from site of injury do reach subconscious levels of brain to create a state of surgical stress response; although without patient feeling, realizing or recalling it. The routine use of muscle relaxants for GA makes the situation worst because even the protective withdrawal reflex functional at the subconscious level is also totally blocked. This may lead to the body systems pain sensitized to tissue injury intraoperatively due to various hormones and a state of hyperalgesia may be created in immediate post-operative period which may lead to exaggerated post-operative stress response. We are guided intraoperatively only by changes in heart rate, rhythm and rise in blood pressure as an indirect evidence of inadequate pain relief but by that time the stress response has already been triggered. Most of us treat these signs by increasing depth of anaesthesia, adding narcotics analgesics, increasing inhalational anaesthetics or worst by using cardio selective drugs to dampen the changes if and when they are too high. This management now appears to be deceptive as evidenced from our study. Although indirectly we showed that metabolic changes are significantly greater than anticipated in patients given GA in diabetic patients.

In the other group of patients regional anaesthesia (NB) was used, the pain relief was total in a patient who was fully conscious and can communicate. The fact that there was no significant metabolic change in the form of rise in BSL throughout the operative procedure, nor any tachycardia or pressor response, indicates that the technique is far superior in achieving the block of surgical stress response leading to metabolic derangements intraoperatively compared to GA, and is likely to be due to effective neuronal blockade both afferent as well as efferent paths. For the practicing anaesthetist the time has come to rethink about their management in the perspective of surgical stress response. Just presence of pain is the nature's provision and the overt response indicating tissue injury or trauma and basically response is the protective reaction. Pain perceived by patient can be described aptly as just the tip of an iceberg floating in the sea water, and there are a lot more events that are occurring within the body which are important but remain concealed and therefore very difficult to appreciate clinically. Therefore, achieving pain relief alone by any means by either intra or post operatively may not solve all the problems associated with surgical stress response but our target of managing these patients should be to control the later, more effectively. Ever since 1950s Inj. Morphine has been shown and used to suppress the hypothalamic and pituitary adrenal hormone secretions. This led to use of morphine and other opioids, to suppress stress response of surgery, however the dose required to achieve this is too large (around 10 to 20 times normal) to be used in routine surgery (McDonald *et al*.,

1959). In open heart surgery, once the patient is taken on CPB, even these higher doses of opioids fail to suppress stress response and all these patients have severe respiratory depression post operatively leading ventilator support. IV Etomidate as anaesthetic has a role in decreasing steroid level by interfering their synthesis with little control of glycemic response (Fragen *et al*., 1984; Lacoumenta *et al*., 1986). However because of its cost it is not widely in practice today. Benzodiazepines, midazolam attenuates cortisol response to surgery but is if little value (Desborough *et al*., 1991). Clonidine and alpha adrenergic agonists has sympatholytic activity and is used to obtund cardiovascular responses secondary to surgical stimuli. Thus all these drugs although help to curtail many CVS responses, they do not have effective control on metabolic state of body and overall homeostasis intraoperatively. During surgery not only a large number of counter regulatory hormones (ADH, Cortisol, Epinephrine, Norepinephrine, Aldosterone, Renin) (Engquist *et al*., 1980; Brandt *et al*., 1979; Engquist *et al*., 1977; George *et al*., 1974) are released but there is evidence to suggest suppression of endogenous insulin and development of insulin resistance. Therefore, probably, the routinely administered GA is ineffective in controlling hyperglycemic response in a diabetic patient as being observed and proved in our study. Compared to GA a well-managed RA technique, preferably neuraxial blockade with sufficient segmental height of block, showed a significantly well maintained blood sugar, intra as well as post operatively in our study. With this technique, it is said to result from effective blockade of neurohumerol axis i.e. afferent fibers from site of operation to thalamic level similarly efferent from CNS to various organ functions dealing with metabolic state of body.

Besides consideration of controlling effects of surgical stress response specifically the metabolic alterations seen in a diabetic patients there are quite a large number of technical reasons that regional technique has many advantages compared to GA. Today, some of surgical techniques in lower part of the body in clinical practice are specifically done under neuraxial blockade as a technique of choice over ITGA. E.g. LSCS, TKR, Plastic surgeries, vascular surgeries, TURP etc. From finding of our present study we would like to add to this list the patients with diabetes mellitus type II. In our present study, we have only included surgical procedures on limited part of the body i.e. lower limb, perineum and lower abdomen. We have not included upper abdominal and thoracic surgeries. Further studies can be done including surgeries on upper part of the body by using techniques such as thoracic and cervical epidural alone or in combination with ITGA. To evaluate stress response in totality hormonal study i.e. cortisol, epinephrine, nor epinephrine growth hormones should be done along with BSL, which is the end point of all the hormonal changes. But we could not study these hormonal levels as facilities were not available in our institutes at the time of conducting the present study. In NB group, we have used SAB as an aesthetic technique because it is technically easy to perform, the success rate of this techniques is high.

Conclusion

From present control study it is concluded that in well controlled diabetic type 2 patients subjected to surgery showed that glycemic controlled under ITGA was poor compared to those under regional block intra and post operatively and that the patients in former group needed early and more repeated insulin supplementation intra venous to control BSL to desired level. This may indicate increase insulin resistance in ITGA group of patient. In present day clinical practice there are specific condition or operations were neuraxial block is recommended as technique of choice; likewise we recommend that in above diabetic patients operated for lower abdomen, pelvis, perineal and lower limb surgery the regional anaesthesia should be considered as a technique of choice over ITGA.

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