Hormonal and metabolic responses of controlled hypotensive anaesthesia for functional endoscopic sinus surgery: A comparison between magnesium sulfate and nitroglycerin

Thesis

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بسم الله الرحمن الرحيم

" يَا أَيُّهَا الَّذِينَ آمَنُوا إِذَا قِيلَ لَكُمْ تَفَسَّحُوا فِي الْمَجَالِسِ فَافْسَحُوا يَفْسَحِ اللَّهُ لَكُمْ وَإِذَا قِيلَ انشُزُوا فَانشُزُوا يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ "

صدق الله العظيم

{سوره المجادلة,الأيه١١}

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Abbreviations	Antonyms
Ab	antibody
ACTH	adrenocorticotrophic hormone
ADRB1	β_1-adrenergic receptor
Ag	antigen
ARF	acute renal failure
ASA	American Society of Anesthesiologists
ATP	adenosine triphosphate
AV	atrioventricular
AVP	arginin-vasopressin
AZF	adrenal zona fasciculata
BBB	blood brain barrier
BIS	bispectral index
BP	blood pressure
bpm	beats per minute
C	clearance
cAMP	adenosine 3', 5'-cyclic monophosphate
CBF	cerebral blood flow
cGMP	cyclic guanosine monophosphate
CI	cardiac index
CMIA	Chemiluminescent Magnetic Immunoassay
CNS	central nervous system
CO	cardiac output
COX	cyclooxygenase enzymes
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
DHP	dihydropyridine
ECG	electrocardiograph
ED	effective dose
$ETCO_2$	end tidal carbon dioxide
FESS	functional endoscopic sinus surgery
FSH	follicle-stimulating hormone
GABA	gamma amino butyric acid
GC	guanylyl cyclase
GFR	glomerular filtration rate
GlyR	Glycine receptors

HPT	hypothalamic-pituitary-thyroid
HR	heart rate
ICP	intracranial pressure
IFN-α	interferon-alpha
IL-1	interleukin-1
IL-6	interleukin-6
LH	luteinizing hormone
LVEF	left ventricular ejection fraction
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MEIA	Microparticle Enzyme Immunoassay
NMBDs	Neuromuscular-blocking drugs
NMDA	N-Methyl-D-aspartate
NO	Nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OR	operating room
PACU	postanaesthesia care unit
PaO2	partial pressure for oxygen
PONV	postoperative nausea and vomiting
RSS	Ramsay Sedation Scale
rT_3	reverse T_3
SBP	systolic blood pressure
SNPs	Single nucleotide polymorphisms
SpO2	peripheral oxygen saturation
SVR	systemic vascular resistance
T3	triiodothyronine
T4	thyroxine
TBG	thyroid-binding globulin
TNF-α	tumor necrosis factor-alpha
TOF	train-of-four
TRH	thyrotropin-releasing hormone
TSH	thyroid-stimulating hormone
VAS	visual analog scale
V_D	volume of distribution
V_T	tidal volume

Abstract

Hypotensive anaesthesia is essential during functional endoscopic sinus surgery (FESS) for better visualization of the surgical field. In a prospective, randomized, double-blind study, we compared the hormonal and metabolic changes that evoked during FESS performed under general anaesthesia with deliberate hypotensive technique using either magnesium sulfate or nitroglycerin.

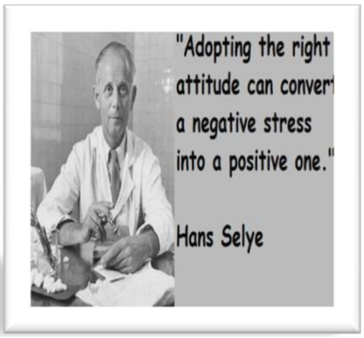
Sixty patients aged 18-50 years, scheduled for FESS under general anaesthesia were enrolled. After induction of anaesthesia, patients were randomized to receive a slow loading dose of either magnesium sulfate 30 mg/ kg, followed by continuous infusion of 10-30 mg /kg/h (Magnesium group; n= 30), or saline followed by infusion of nitroglycerin 1-3 µg/ kg/min (Nitroglycerin group; n= 30), to maintain mean arterial pressure between 60-65 mmHg throughout the surgery. Perioperative serum cortisol, blood glucose, triiodothyronine (T3), thyroxine (T4), serum uric acid and fibrinogen concentrations were measured. Postoperative pain and sedation scores were also measured.

Patients in nitroglycerin group had statistically higher cortisol level compared to magnesium group, and higher glucose level at the 2nd postoperative hour , with no significant difference in T3, T4, uric acid and fibrinogen levels .There was no difference in the levels of serum cortisol, blood glucose, T3, T4, serum uric acid and fibrinogen between pre- and 24 hour postoperative assessments in both groups .Pain scores were significantly lower in magnesium group till 90 min postoperatively with higher sedation scores.

In this study, Induced hypotension and proper quality of the operative field had been achieved effectively by both magnesium sulfate and nitroglycerin administration during FESS performed under general anaesthesia represented by remarkable decrease in MAP during the surgery. However, the patients treated with magnesium had a more favorable postoperative course regarding attenuation of the surgical stress response estimated by observed lower levels of cortisol and glucose postoperatively and improvement of postoperative analgesia detected by lower pain scores recorded postoperatively, observed lower analgesics consumption and remarkable reduction of the time needed for the first analgesic demand.

Introduction

1. An overview of the surgical stress response



Hans Selye (1907- 1982)

The human body's response to stress has been of interest to basic scientists and clinicians. Since the contributions of Hans Selye, psychiatrists have investigated the response to acute and chronic mental stresses **(Frankenhaesur et al., 1978)**;

Physiologists have investigated the responses to environmental stresses;

Sir David P. Cuthbertson(1900-1989)

and surgeons have investigated the responses to injury and sepsis **(Wilmore 1983).** In 1932, Cuthbertson described in detail the metabolic responses of four patients with lower limb injuries (**Cuthbertson1932**).

He documented and quantified the time course of the changes.The terms ‘ebb’ and ‘flow’ were introduced to describe an initial decrease and subsequent increase in metabolic activity. The description of the ‘ebb’ phase was based partly on work in experimental animals and the estimations of increases in metabolic rate in the ‘flow’ phase were exaggerated. These descriptions have been perpetuated and are still quoted, but have been redefined **(Little and Girolami 1999)** and are perhaps not critical to an understanding of the actual changes which occur. There has been increasing interest among anaesthesiologists in the responses to surgical stress occasioned by the realization that anaesthetic techniques can modulate this response (**Weissman C and Hollinger 1988**). The metabolic, hormonal and immunologic responses that occur during surgical injury are especially timely in light of the recent explosion of knowledge in the areas of immunology and endocrinology. The importance of the components of the immunologic system in controlling many nonimmune functions, coupled with the discovery of many potent endocrine, apocrine and eccrine substances has allowed for a better understanding of the response to stress. It is now recognized that there are many links between the endocrine and immunologic systems.

Major body injury (surgical or accidental) evokes reproducible metabolic, hormonal and hemodynamic responses (**Buckingham1985**). These responses are characterized by altered protein homeostasis **(Bergström M et al., 2014),** hypermetabolism (**Kinney 1980**)**,** altered carbohydrate metabolism (**Imamura et al., 1975**), sodium and water retention **(Le Quesne et al., 1985)** and increased lipolysis **(Meguid et al., 1974)**.The abnormal carbohydrate metab-olism includes increased endogenous hepatic glucose production (gluconeogenesis) and reduced glucose clearance (insulin resistance) which results in hyperglycemia. The major body fuel becomes fat; therefore, lipolysis is increased and lipogenesis is retarded(**Frayn 1985**).Protein abnormalities are manifested by negative nitrogen balance reflecting accelerated net protein breakdown i.e catabolism **(Oppenheim et al., 1980)**.The magnitude of these changes is essentially proportional to the extent of the injury **(Chernow B et al., 1987)** .

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system**.** The changes in pituitary secretion have secondary effects on hormone secretion from target organs (Table A). For example, release of corticotrophin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin (AVP) is secreted from the posterior pituitary and has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilizes substrates to provide energy sources and a mechanism to retain salt and water and maintain fluid volume and cardiovascular homeostasis **(Desborough 2000)**.

Surgical stress response is triggered by the surgical incision and its magnitude is related to the site, extent and duration of the surgical trauma. Less invasive and more peripheral surgical procedures are associated with a mild to moderate stress response. Surgical responses to the more invasive upper abdominal and thoracic surgery may continue up to three weeks. Although stress response to surgery represents a defensive mechanism, it might be related if amplified and prolonged to the development of physiological changes in the function of organs that results in a poor surgical outcome, longer hospital stay, higher costs of medical care and prolonged convalescence **(Deborah et al., 2004).**

Table A: **Principal hormonal responses to surgery**

Endocrine gland	Hormones	Change in secretion
Anterior pituitary	ACTH	Increases
	Growth hormone	Increases
	TSH	May increase or decrease
	FSH and LH	May increase or decrease
Posterior pituitary	AVP	Increases
Adrenal cortex	Cortisol	Increases
	Aldosterone	Increases
Pancreas	Insulin	Often decreases
	Glucagon	Usually small increases
Thyroid	Thyroxine, tri-iodothyronine	Decrease

ACTH, adreno-corticotrophic hormone (corticotrophin); AVP, arginine vasopressin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

Desborough JP. Physiological responses to surgery and trauma. *Br J Anaesth*. 2000; **85(**1): 109–17

Clinical consequences of the stress response include hypertension, tachycardia, arrhythmia, myocardic ischemia, protein catabolism, suppression of the immune response and loss of renal excretory function with water and salt retention. The greatest increase of the stress response in the post-operative period correlates with frequent episodes of post-operative complications. The stress response is a significant marker for an increased risk of unsatisfactory outcomes including cardiovascular morbidity, immunosuppression and infection, increased coagulability, inhibition of fibrinolytic activity and thrombosis formation. Thus, reduction and modulation of the stress response during surgery can significantly reduce post-operative complications and frequency of morbidity **(Malenković et al., 2008).**

The stress response to surgery and the resultant hyperglycemia, osmotic diuresis, and hypoinsulinemia can lead to perioperative ketoacidosis or hyperosmolar syndrome. Hyperglycemia impairs leukocyte function and wound healing. The management goal is to optimize metabolic control through close monitoring, adequate fluid and caloric repletion, and judicious use of insulin. Patients with diabetes undergo surgical procedures at a higher rate than do nondiabetic people. Major surgical operations require a period of fasting during which oral antidiabetic medications cannot be used. The stress of surgery itself results in metabolic perturbations that alter glucose homeostasis, and persistent hyperglycemia is a risk factor for endothelial dysfunction, postoperative sepsis, impaired wound healing, and cerebral ischemia. The stress response itself may precipitate diabetic crises (diabetic ketoacidosis [DKA], hyperglycemic hyperosmolar syndrome [HHS]) during surgery or postoperatively, with negative prognostic consequences. HHS is a well known postoperative complication following certain procedures, including cardiac bypass surgery, where it is associated with 42% mortality (**Dagogo-Jack and Alberti 2002).** Choice of the anaesthetic technique can reduce or even eliminate stress responses to surgery and decrease the incidence of complications **(Hadimioglu et al.,2012).**

2-Surgical stress response biomarkers

- **Cortisol**

Cortisol secretion from the adrenal cortex increases rapidly following the start of surgery, as a result of stimulation by adrenocorticotrophic hormone (ACTH). From baseline values of around 400 nmol /litre, cortisol concentrations increase to a maximum at about 4–6 h and may reach >1500 nmol/ L depending on the severity of the surgical trauma (**Nicholson et al., 1998**) .The cortisol response can be modified by anaesthetic intervention . Usually, a feedback mechanism operates so that increased concentrations of circulating cortisol inhibit further secretion of ACTH. This control mechanism appears to be ineffective after surgery so that concentrations of both hormones remain high.Cortisol has complex metabolic effects on carbohydrate, fat and protein. It promotes protein breakdown and gluconeogenesis in the liver. Glucose used by cells is inhibited, so that blood glucose concentrations are increased. Cortisol promotes lipolysis which increases the production of gluconeogenic precursors from the breakdown of triglyceride into glycerol and fatty acids. Cortisol has other glucocorticoid effects, notably those associated with anti-inflammatory activity. Corticosteroids inhibit the accumulation of macrophages and neutrophils into areas of inflammation and can interfere with the synthesis of inflammatory mediators, particularly prostaglandins **(Hardie 2012).** Anti-inflammatory corticosteroids significantly impair wound healing. They have antagonistic effects on growth factors and collagen deposition in wound healing (Wicke et al.2000).

- **Glucose**

Blood glucose concentrations increase after surgery begins. Cortisol and catecholamines facilitate glucose production as a result of increased hepatic glycogenolysis and gluconeogenesis. In addition, peripheral use of glucose decreased. Blood glucose concentrations are related to the intensity of the surgical injury; the changes follow closely the increases in catecholamines.

In cardiac surgery, blood glucose can increase up to 10–12 mmol/ L and remain elevated for >24 h after surgery. The changes are less marked with minor surgery. Insulin is synthesized and secreted by the β cells of the pancreas. It is released after food intake, when blood glucose and amino acid concentrations increase. Insulin promotes the uptake of glucose into muscle and adipose tissue and the conversion of glucose into glycogen and triglycerides. It also stimulates the formation of glycogen from glucose in the liver. Protein catabolism and lipolysis are inhibited by insulin **(Desborough 2000)**. Insulin concentrations may decrease after the induction of anaesthesia and during surgery. There is a failure of insulin secretion to match the catabolic, hyperglycaemic response. This may be caused partly by α-adrenergic inhibition of β cell secretion. In addition, there is a failure of the usual cellular response to insulin, the so-called 'insulin resistance' which occurs in the perioperative period. Glucagon is produced in the cells of the pancreas. This hormone promotes hepatic glycogenolysis. It also increases gluconeogenesis from amino acids in the liver and has lipolytic activity. Although plasma glucagon concentrations increase transiently after major surgery, this does not make a major contribution to the hyperglycaemic response **(Wallace et al., 1996)**. The usual mechanisms that maintain glucose homeostasis are ineffective in the perioperative period. Hyperglycaemia persists because catabolic hormones promote glucose production and there is a relative lack of insulin together with peripheral insulin resistance **(Deborah et al., 2004)**.

It is now established that poor glycaemic control in diabetic subjects is associated with an increase in diabetic complications which can be avoided with tight control of blood glucose **(King et al., 1999)**. The risks of prolonged perioperative hyperglycaemia are less well established, although potential risks