1. INTRODUCTION

1.1. PROBLEM DEFINITION

People are constantly exposed to numerous physical, psychological, chemical and social factors that jeopardize their physiological equilibrium. Every condition that threatens the state of homeostasis is considered a stress, and causes leading to it are termed stress factors. They have their effect through humoral and neural pathways, which together lead to many organ reactions. Stress response is the term used for the homeostatic changes which follow an injury or trauma. After early work on the stress response to accidental injury, attention was turned to surgical trauma, and responses to most types of surgery were reported (Desborough, 2000). A systemic stress response is the general reactivity of an organism and is unpredictable at the individual level. All components of the systemic stress response aim to protect the organism and avoid danger.

Objective signs of stress include, among many others, high serum levels of adrenocorticotrophic hormone, adrenaline and cortisol, depletion of serum eosinophils, elevation of insulin, somatotropin in serum, increase in heart rate & arterial blood pressure, and changes in electrical activity of the heart & brain.

Subjective signs of stress include excitement, palpitations, impulsive behaviour, fear, etc.

A sensitive method for stress evaluation implies measuring stress factors which are important in the acute-phase reaction (APR), i.e. cortisol, catecholamines, acute phase proteins, antioxidants etc. in states of oxidative stress. The APR is initiated and controlled by many cells and mediators; these mediators represent the elements of communication between vessels, immune system, bone marrow and CNS (Schlag & Redl, 1996; Gabay & Kushner, 1999). Serum levels of these mediators vary not only in diseased states including infection, infarction, burns, malignant diseases, etc but also in surgery of different types and nature.

1.1.1. Cortisol

It is considered to be a surgical stress indicator (Castejon-Casado, 2001). It is a glucocorticoid secreted from cortex of suprarenal gland. Its role in gluconeogenesis,
metabolism of fat, CNS, muscle and renal function, vascular reactivity and the immune response has been studied extensively and is well known. The serum level increases in operated patients and directly correlates with the extent of surgical trauma in general (Desborough, 2000). Measuring serum cortisol during surgery indicates the extent of immediate stress, while its concentration in 24-h urine samples shows overall stress during that day (Ruzic et al, 2005). The present study recorded and analyzed the cortisol response.

1.1.2. Catecholamines
Hypothalamic activation of the sympathetic autonomic nervous system results in increased secretion of catecholamines from the adrenal medulla and release of norepinephrine from pre-synaptic nerve terminals. Norepinephrine is primarily a neurotransmitter, but there is some spill-over of norepinephrine released from nerve terminals into the circulation which is accentuated under stress and strain.

The increased sympathetic activity results in the well recognized cardio-vascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs including the liver, pancreas and kidneys, is modified directly by efferent sympathetic stimulation and/ or circulating catecholamines (Desborough, 2000).

1.1.3. Acute-Phase Reactants
These are a heterogeneous group of proteins that mediate the acute-phase response (Gabay and Kushner, 1999). Their function is to induce a nonspecific host defence and limit the local immune response. In the present study, we analyzed C - Reactive Protein (CRP) and Tumour Necrosis Factor alpha (TNF-alpha).

1.1.4. Antioxidants
These are the compounds that prevent oxidative reactions; their presence is thought to underlie the cellular immune response. Disequilibrium between "free-radicals" production and scavenging leads to a state of oxidative stress (Halliwell, 1999), which represents excessive production of oxygen free-radicals that can harm cell structure and functions, changing DNA, proteins, carbohydrates and fats. These oxidative chain reactions may cause oxygen depletion as every O_2 molecule is a source of new free radicals and such reactions result in cell damage. Moreover, reactive oxygen species,
e.g. hydrogen peroxide etc. enhance oxidative stress. Antioxidants are classified into three groups, i.e. Antioxidative Enzymes, Antioxidative Scavengers and Preventive Antioxidants (Ruzic et al, 2005).

Controlled tissue damage during surgery causes release of various acute phase reactants, along with other circulating factors (Kehlet, 1998), with complex inter-play of various substances mainly under hypothalamic-pituitary-adrenal-axis which affect the peri-operative outcome (Roumen et al, 1992; Orloff, 1981; Kelbel, 2001). Grading of host systemic stress response has been tried according to the magnitude of the operative procedure (Udelsman et al, 1987; Kristiansson et al, 1999).

Evaluation of the mechanism of the systemic stress response and its modulation if possible, is of paramount importance to both surgeon and anaesthesiologists as knowledge of the haemodynamic and hormonal disturbances during anaesthesia and surgery is essential to deliver adequate and proper care to a patient during peri-operative period for a successful outcome. Furthermore, this assumes more importance in patients in whom cardiovascular system is the seat of proclaimed or latent disorders.

The stress response has more detrimental effects in upper abdominal surgery as compared to other surgeries and this may prove more catastrophic due to relative or absolute increase in sympathetic tone secondary to tractions and manipulations during biliary tract surgery (Katz et al, 1970; Giesecke et al, 1988; Desborough, 1989; Haleem et al, 1991), especially in patients with diseased heart as the resultant tachycardia, hypertension, arrhythmias, ventricular ectopics, pulmonary oedema, angina or even myocardial infarction during intra-operative period are the important causes of postoperative morbidity & mortality. The pathway of above-mentioned phenomenon may possibly be mediated: (a) either through fifth thoracic segment of spinal cord, a common source of sympathetic supply to heart and gallbladder via cardiac plexus & celiac plexus respectively, (b) or, through reflex stimulation of adrenal gland via celiac plexus, being stimulated by surgical manipulation with adrenal burst of catecholamine secretions (McGregor 1969; Mendelssohn and Monheit, 1956; Orloff, 1981; Warwick and Williams, 1973). These responses may possibly be attenuated during peri-operative period by modifying the surgical and anaesthetic technique whenever conditions permit.
1.2. HISTORICAL BACKGROUND

Gallstones are one of the most important causes of morbidity in the world. The estimated incidence of symptomatic cholecystolithiasis is up to 2.17 per 1000 populations (Legorreta, 1993; Steiner et al, 1994). More than 500,000 cholecystectomies are annually performed in the USA itself (Olsen, 1991; NIH Consensus, 1993; Roslyn, 1993).

Open cholecystectomy was considered as the gold standard for treatment of the gallbladder stones till late 1980s. Laparoscopic cholecystectomy was performed first time by Mühe in 1986 and rapidly became the method of choice for surgical removal of the gallbladder (NIH Consensus, 1993), although the evidence of superiority of this newer ‘minimally invasive’ technique of the cholecystectomy over the classical open cholecystectomy was not clearly evident at that time.

Following publications of some large series on marked clinical benefits of laparoscopic cholecystectomy in the last decade of the previous century (Reddick and Olsen, 1990; Scott et al, 1992; Southern Surgeons Club, 1991; Cuschieri et al, 1991; Steiner et al, 1994; Escarce et al, 1995), monumental interest generated in the medical community to objectively evaluate these benefits and to find the physiologic alterations & modulations for the favourable clinical outcome.

In the recent past, most of the studies investigated the degree of surgical stress by comparing laparoscopic and classical open surgical procedures (Holub et al, 2002; Marana et al, 2003; Polat et al, 2003; Luo et al, 2003) and majority of the investigators studied cortisol, catecholamines, CRP, and some cytokines (TNF-alpha, interleukin- 2 and -6) in order to assess the systemic response to surgery and some included haemodynamic parameters also. Studies to compare stress between upper and lower abdominal surgery are scarce, and consensus for reproducible systemic stress response in open and laparoscopic surgery has not been achieved as yet to confidently predict the surgical outcome in an individual patient.

Critical analysis of available randomized, controlled studies comprising laparoscopic and open surgery has not convincingly shown that laparoscopic surgery invariably improves the outcome except in a few operations. Reports available in literature still reveal variable or even conflicting results of the comparative evaluation of laparoscopic versus open cholecystectomy. Till date, no study has been done to
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compare the extent of stress involved to the patients by both ways of cholecystectomy in comparison to open abdominal hysterectomy in a subset of Indian population during perioperative periods.

1.3. NEED OF THE PRESENT STUDY

The very few early prospective trials conducted in last decade of the previous century were burdened with problems of recruitment (Barkun et al, 1992; Attwood et al, 1992). Later on, marketing forces for short length of hospital stay, public demand and acceptance by surgeons under the media hype prevented prospective controlled randomized trials between laparoscopic cholecystectomy and conventional open cholecystectomy (Glaser et al, 1995; Sawyers, 1996) because of ethical constraints on the planning of a controlled randomized trial, especially due to the fast receding control group of the classical open cholecystectomy.

Glaser and associates (1995) supported the opinion of Neugebauer and colleagues (1991) that it is not adequate to describe the clinical significance of technologies solely in terms of case studies or empirical judgments. This was further supported by variable and often conflicting results of a huge list of such observational case studies and nonrandomized trials in recent past, thereby always maintaining the dire need of prospective controlled randomized study especially in relation to a local subset of human population for improvement of quality of their care and the desired favourable outcome of surgery.

In 1999, Henrik Kehlet emphasized that the data are not consistent in spite of the common observation that Laparoscopic surgery as compared with similar open operation has no markedly different effects on the classic endocrine metabolic responses but may slightly reduce the inflammatory responses and immune functions.

Therefore, the current prospective controlled randomized study was undertaken in a subset of Indian patients belonging mainly to the poor socio-economic class who are hard pressed to meet the expenses of current surgical treatment and who in general present themselves to government-funded secondary care institution such as our own institution, for treatment of the symptomatic gallstone disease and benign uterine disorders.
1.4. OBJECTIVE ISSUE INVOLVED

In view of the on-going scenario of variable reports from different places, I designed a prospective, controlled, randomized study under a Doctoral research programme first time in my Department of Anaesthesiology to determine the degree of systemic stress response to upper abdominal surgery (laparoscopic and open cholecystectomy) as well as lower abdominal surgery (open abdominal hysterectomy), by recording the clinical parameters as well as by measuring the serum levels of six known biomarkers under the following major aspects:

1. Serum Glucose Estimation for Metabolic Response Assessment
2. Serum Cortisol and Catecholamines (Epinephrine and Norepinephrine) estimations for Hormonal Response Assessment
3. Serum Plasma C-Reactive Protein (CRP) estimation for Acute-Phase Reactant Response Assessment
4. Serum Tumour Necrosis Factor-alpha (TNF-alpha) estimation for Immune Function Assessment
5. Heart Rate and Arterial Blood Pressures (systolic and diastolic) recording coupled with calculation of Mean Arterial Pressure (MAP) and Rate-Pressure Product (RPP) for Hemodynamic Response Assessment.
6. Determination of Correlations among the simultaneously measured serum biomarkers as well as between the haemodynamic changes and the hormonal responses.

1.5. RESEARCH METHODOLOGY ADOPTED

1.5.1. Approval by Ethical and Scientific Committee of the University
The present study commenced in a prospective manner after it was approved in 2004 by the Committee of Advance Scientific Research (CASR) of Faculty of Medicine, Aligarh Muslim University, Aligarh, India. (Copy of approval attached).

1.5.2. Informed Consent from the Patients
All patients were fully informed about indication of surgery, technique of surgery-open or laparoscopic, technique of anaesthesia, risks of surgery & anaesthesia and
prospects of successful outcome in the Surgical/ Gynaecological OPD (Out-patient department) and PAC (Pre-Anaesthetic Check-up) OPD. Patients were further explained in the wards about any query when required. Patients’ informed consent for the operation was obtained in the wards in the evening before the day of operation.

1.5.3. Admission to the Hospital
All patients were admitted to the hospital 1-2 days before operation as a part of the general routine policy of our hospital for all the elective operations.

1.5.4. Criteria for Randomization of the Study
The study was randomized on the basis of following selection criteria of recruitment into either laparoscopic cholecystectomy (LC) group or open cholecystectomy (OC) group for uncomplicated symptomatic cholelithiasis:
1. Patient’s choice under informed consent
2. Patient’s financial status (our institution charges double for the laparoscopic cholecystectomy as compared to the open cholecystectomy)
3. Availability of functioning equipment
4. Availability of expertise (laparoscopic surgeon)
5. Pre-operative feasibility of laparoscopic cholecystectomy (lap Chole) based on clinico-radiological signs

1.5.5. Inclusion Criteria for the Study
The present study was designed to include the following patients who underwent Cholecystectomy (Open/ laparoscopic) or Open Abdominal Hysterectomy:
Normal healthy adult patients belonging to 18-60 years of age (ASA grade I) and Treated hypertensive healthy adult patients belonging to 18-60 years of age without any other co-morbidity (ASA grade II).

1.5.6. Exclusion Criteria for the Study
Patients were excluded from the study when one of the following criteria was detected at any point of time during the study:
1. Patient’s age less than 18 years or more than 60 years
2. Pregnant and lactating females
3. ASA grade II with untreated hypertension.
4. ASA grade more than II with co-morbidity other than treated hypertension.
5. ASA grade more than II
6. Patients who suffered from intra-operative injury to adjacent organ/structure including bile duct injury were also excluded from the study.

1.5.7. **Inclusion Criteria for Cholecystectomy**

Following patients with uncomplicated cholecystolithiasis were considered for recruitment in the present study:

1. Patients with simple biliary colic(s)
2. Patients with history of acute cholecystitis before more than 4-6 weeks
3. Patients with chronic cholecystitis but without signs of acute inflammations at the time of admission and operation.

1.5.8. **Inclusion Criteria for Laparoscopic Cholecystectomy**

All patients with uncomplicated symptomatic cholecystolithiasis were offered Laparoscopic Cholecystectomy as a first choice in terms of the current ‘Gold Standard’.

1.5.9. **Inclusion Criteria for Open Cholecystectomy**

Only those patients who were otherwise fit for laparoscopic cholecystectomy were recruited for open cholecystectomy on the basis of non-medical reasons as mentioned below:

1. Patient’s refusal for laparoscopic cholecystectomy due to anxiety and apprehension in relation to the newer technique and technology
2. Patient’s inability to pay extra charges for laparoscopic procedure
3. Non-availability/ Malfunctioning of laparoscopic equipment on the day of scheduled operation
4. Non-availability of the laparoscopic expertise on the day of scheduled operation

1.5.10. **Exclusion Criteria for Cholecystectomy (Open/ Laparoscopic)**

Patients were excluded from the study when one of the following criteria was detected at any point of time during the study:

1. Patients with acute cholecystitis
2. Patients with jaundice
3. Pre-operative clinico-radiological signs suggestive of difficult cholecystectomy.

4. Lap cholecystectomy converted to open cholecystectomy because of any reason.

1.5.11. Inclusion Criteria for Open Abdominal Hysterectomy
Patients with benign uterine diseases who were posted for open abdominal hysterectomy were incorporated in the present study as a sort of non-biliary control group because this is the common non-biliary operation being performed at our institution almost as frequently as the cholecystectomy.

1.5.12. Exclusion Criteria for Open Abdominal Hysterectomy
Patients found to have malignant uterine disease at any point of time during the management were excluded from the study.

1.6. SCOPE OF THE RESEARCH
As gallbladder stone disease has currently assumed a sort of epidemic proportion in a developing country like India, development of reproducible predictive criteria of systemic stress response will go a long way for peri-operative deliberate modulation by surgico-anaesthetic team to safely conduct anaesthesia and to improve the quality of patient care to the masses at an affordable price.

This study assumes more importance in current trend of fast urbanization in India with its attendant diseases especially of the cardiovascular system because surgery-induced systemic stress responses may be exaggerated to the point of danger mark when the cardiovascular system is the seat of proclaimed or latent disorders as said earlier.

Similarly, benign uterine diseases are quite commonly seen at least at our institution and are operated upon almost as frequently as gallstone disease. The study will rather be more fruitful in this subset of population as majority of these patients are beyond the reproductive age group where hormonal imbalances are known to occur and body’s defensive mechanisms are supposed to be at low ebb.

Attempts to probe the extent of adrenal burst during initial and later part of excision of diseased gall bladder by both techniques of cholecystectomy and comparison with a non-biliary surgery (open abdominal hysterectomy) in normotensive and treated
hypertensive patients will definitely help to detect and quantify the risk to an individual patient for possible planning of a rational surgico-anaesthetic approach in a particular patient to obtund the adverse metabolic and hormonal changes to achieve the desired favourable outcome.

1.7. COMPLETION OF THE RESEARCH

The present study was completed in about four years' time and recruited a total of sixty three female patients who underwent, after informed consent, laparoscopic cholecystectomy (n=21) and open cholecystectomy (n=21) for uncomplicated symptomatic cholecystolithiasis as well as open abdominal hysterectomy for non-malignant uterine diseases (n=21) at our institution- Jawaharlal Nehru Medical College Hospital, A.M.U., Aligarh, India.