PROSPECTIVE STUDY OF "EARLY VS LATE ENTERAL FEEDING IN EMERGENCY GASTRO INTESTINAL SURGERIES"

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CERTIFICATE BY THE DEAN

This is to certify that the dissertation entitled **"PROSPECTIVE STUDY OF "EARLY VS LATE ENTERAL FEEDING IN EMERGENCY GASTRO INTESTINAL SURGERIES"** is a bonafide and genuine research work carried out by **Dr.REMAN RAJENDRAN** under the guidance of **Dr.CHITRA M.S. DNB(OG),** Associate Professor, Department of General Surgery and HOD, Department of General Surgery, Madurai Medical College, Madurai.

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This is to certify that the dissertation entitled **"PROSPECTIVE STUDY OF "EARLY VS LATE ENTERAL FEEDING IN EMERGENCY GASTRO INTESTINAL SURGERIES"** is a bonafide research work done by **Dr. REMAN RAJENDRAN**, M.S. Postgraduate student in the Department of General Surgery, Madurai Medical College Madurai, under the guidance of **Dr.CHITRA M.S. DNB(OG),** Associate Professor, Department of General Surgery, Madurai Medical College, GRH, Madurai in partial fulfillment of the requirements for the degree of M.S. in GENERAL SURGERY.

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I hereby declare that the dissertation entitled **"PROSPECTIVE STUDY OF "EARLY VS LATE ENTERAL FEEDING IN EMERGENCY GASTRO INTESTINAL SURGERIES"** is a bonafide and genuine research work carried out by me under the guidance of **Dr.CHITRA, M.S DNB(OG).,** Associate Professor, Department of General Surgery, Madurai Medical College, Madurai.

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CONTENTS

INTRODUCTION

Nutritional support plays important roles in wound healing and postoperative recovery. A poor nutritional status is strongly associated with delayed wound healing and longer hospital stays after surgery. After emergency gastrointestinal (GI) surgery, nutritional status is impaired and basal energy expenditure is raised and thus, nutritional support is of considerable importance.

Several reports have emphasized that early enteral feeding should be started as soon as possible after resuscitation because the immunomodulatory effect of enteral feeding could assist recovery. Patients who undergo emergency GI surgery have an edematous or ischemic bowel, and are at high risk of postoperative complications, such as ileus, obstruction. For these reasons, the majority of surgeons are wary of early feeding after emergency GI surgery. Relatively few reports have been issued on the safety of early feeding after emergency GI surgery. Thus, this study is undertaken to assess the feasibility of early feeding in patients after emergency GI surgery.

AIMS AND OBJECTIVES

- To assess the feasibility of early enteral feeding in patients who have undergone emergency gastrointestinal surgeries and compare the complications and duration of hospital stay with that of late enteral feeding group in General Surgery department in GRH Madurai for 1 year from October 2016 to September 2017.

REVIEW OF LITERATURE

Barlow, et al.11 demonstrated that operative morbidity was less common after major upper GI surgery in patients that received early enteral nutrition. In particular, chest infections were significantly less common in these patients.

Moore, et al.,18 via meta-analysis of high-risk surgical patients, also found that early enteral feeding was associated with a lower incidence of pneumonia and other septic complications

Stephen, mathias demonstrated that there seems to be no clear advantage to keeping patients nil by mouth after elective gastrointestinal resection. Early feeding may be of benefit. An adequately powered trial is required to confirm or disprove the benefits seen in small trial. Early feeding reduced the risk of any type of infection, improve wound healing and decrease the mean length of stay in hospital.

Navaneeth, Maneesh, Vivek demonstrated that early enteral feeding through a nasoenteric tube is well tolerated by these patients and helps to improve energy and protein intake, reduces the amount of nasogastric aspirate, reduces the duration of postoperative ileus, and reduces the risk of serious complications.

In my study, I am going to include the patients undergoing emergency gastrointestinal surgeries in acute abdomen presenting within 24 hours and equal number ofcontrol groups, the case group being started enteral feeding within 48 hours and the control group started enteral feeding after the appearance of bowel sounds and, passing flatus.the variables being studied are postoperative pulmonary complications, wound infections, postoperative ileus and, length of hospital stay.

ENTERAL SUPPORT

Gut starvation can adversely affect surgical patients. Patients who have not started on early enteral nutrition postoperatively have a significantly higher mortality rate than those who receive nutrition support.

Preoperative malnutrition is also related to poor outcome. Worldwide studies show that 30% to 50% of hospitalized patients are malnourished, a condition associated with longer hospital stay, higher cost, and increased morbidity and mortality. Patients with malignancies, inflammatory bowel disease, or chronic heart failure are at particularly high risk. Suppressed immune function can increase risk for nosocomial infections and delayed wound healing. Decreased muscle function can lead to reduced cardiac function and greater difficulty in weaning patients from ventilators. It can also increase susceptibility to respiratory tract infection.

Appropriate use of nutritional support can benefit malnourished preoperative patients and certain groups of postoperative ones. Enteral nutrition (EN) involves the delivery of nutrients by tube into the gastrointestinal tract.

Parenteral nutrition entails the administration of nutrients intravenously. This chapter will review the rationale, administration, and prevention of complications associated with enteral nutrition.

Rationale Mucosal Atrophy

Guedon et al. found reduced enzyme activity but no gross morphologic changes in human intestinal mucosa after prolonged administration of total parenteral nutrition (TPN). Food in the intestinal lumen is critical to mucosal cell growth and function. Bowel rest and TPN in rats have been found to cause gut atrophy within days, an outcome thought to be the result of lack of functional stimulation as well as reduced pancreatic and biliary secretions.

Pironi et al. report significant changes in morphologic and cytoproliferative patterns of duodenal mucosa with the administration of long-term TPN. Similar data from Groos et al. show morphologic changes in human intestinal mucosa, epithelial cell turnover, and extracellular matrix.

The clinical repercussions of these changes are unknown and not all studies are consistent with these observations.

Bacterial Translocation

Animal studies suggest an association between bacteria translocation and postoperative sepsis. O'Boyle et al. report a relation between translocation and postoperative sepsis, but not mortality. Data from human studies show a relation between gut microflora and nosocomial infections, a link suggesting that the gut is a reservoir of bacteria and endotoxins. Other data report no relation between alterations in intestinal barrier function and a predisposition to translocation of enteric bacteria.

The prevalence of bacterial translocation is approximately 15% in elective surgical patients and higher in those patients with intestinal obstruction or a compromised immune system. Sedman et al. suggest that prevalence of bacterial translocation is the same in patients receiving either TPN or EN, i.e., that short-term use of TPN does not appear to produce changes in the morphology of intestinal villus or bacterial translocation in preoperative patients. However, there is insufficient evidence to determine if bacterial translocation causes septic complications in patients who receive TPN.

Infectious Complications

A recent meta-analysis examined the relation between nutritional interventions, complications, and mortality rates. Twenty-seven studies with 1,828 patients showed a 34% lower risk of infection with EN compared with TPN. EN was associated with a reduced risk of infection regardless of nutrition status, presence of cancer, year of study publication, or quality of study method.

These findings were also independent of catheter sepsis analysis. None of the studies in the meta-analysis examined the role of bacterial translocation as primary mechanism for infection in patients who receive TPN. Increased risk of infection may be related in part to a higher incidence of hyperglycemia in this population. Excess glucose load and stress response in TPN fed patients may lead to impaired immune responses that contribute to greater risk of infection Noninfectious Complications

A comparison of noninfectious complications showed a 36% greater risk for EN compared with TPN. Such complications included TPN-related and EN-related technical (caused by tube or catheter insertion) and mechanical problems (dislodged or occluded tube or catheter); aspiration; diarrhea; vomiting; fistula at the catheter or tube site; and hyperglycemia. Many of the complications associated with EN

(e.g., diarrhea or abdominal distention) occur frequently, but are considered less severe than catheter sepsis. Because EN and TPN are not without risks, their advantages and disadvantages must be carefully weighed before the initiation of either type of nutrition support.

Cost

Data show that EN is less expensive to administer than TPN. Costs include access devices, insertion, solutions, delivery hardware, laboratory monitoring, clinical monitoring, and complications.

Prolonged periods of inadequate nutrition increase risk of morbidity and mortality in hospitalized patients. When indicated, nutrition support should be considered the best practice care. If there are no contraindications, EN should be the treatment of first choice. Among other reasons, it is less expensive than TPN and is associated with fewer septic complications.

Indications and Contraindications: EN should be considered in patients who have a functional gut; who cannot, should not, or will not eat adequately; and for whom there is a safe method of access.

General indications for EN include:

a) protein-calorie malnutrition (>10% loss of usual weight or serum albumin levels <3.5 g/dL),

b) oral intake inadequate or likely to be inadequate for 7 to 14 days, and

c) a functional gastrointestinal tract (sufficient length and condition to allow adequate nutrient absorption).

Enteral Formulas

Large numbers of commercial enteral formulas are available for oral and tube feeding. All contain macronutrients and micronutrients of varying quantities and compositions.

These formulas have evolved from foods prepared in a blender to exact macronutrient and micronutrient compositions for specific disease states.

There are three major groups of enteral formulas: polymeric-balanced, monomeric (elemental), and disease-specific.

Indications and Contraindications for Enteral Nutrition

Indications for Enteral Nutrition

1. Neurologic

- Head injury
- Cerebrovascular diseases
- Demyelinating diseases
- Neoplasms
- Neuromuscular diseases

2. Oropharynx and esophageal

- Neoplasms
- Inflammation
- Trauma

3. Gastrointestinal

- Pancreatitis
- Inflammatory bowel disease
- Shortbowel syndrome
- Intestinal fistulas
- Malabsorption

4. Psychological

- Anorexia nervosa
- Severe depression

5. Miscellaneous

- Burns
- Chemotherapy
- Radiation therapy
- Kidney disease
- Liver disease
- Cystic fibrosis
- Organ transplantation

Contraindications for enteral nutrition

- Complete mechanical intestinal obstruction
- Diffuse peritonitis
- Intractable vomiting
- Paralytic ileus
- Intractable diarrhea
- Gastrointestinal ischemia
- Hemodynamic instability

Polymeric-Balanced Formulas

Polymeric formulas are widely used and generally well tolerated. When administered as prescribed, they provide nutritionally complete and balanced diets that include most required micronutrients and macronutrients. Formulas are generally 1 kcal/mL, with 50% to 55% carbohydrate, 15% to 20 % protein, and 30% fat. Calorie-dense formulas (1.5 to 2 kcal/mL) are also available, but should be reserved for patients who require high energy intake or fluid restriction. Carbohydrates in polymeric formulas range from starches to simple sugars. Oligosaccharides and polysaccharides are commonly used and well tolerated. Proteins are usually intact—i.e., whole protein from food or protein isolates. Normal levels of pancreatic enzymes are required to digest these proteins.

Vegetable oils, high in long-chain triglycerides (LCTs), are the major sources of fats.

Mixtures of LCTs and medium-chain triglycerides (MCTs) are also used in enteral formulas. MCTs, which are rapidly absorbed from the intestinal lumen and transported directly into the blood to the liver via the portal vein, are the preferred substrate. Polymeric-balanced formulas are less expensive than other options. For approximately 90% of surgical patients, they are the formula of choice.

Monomeric (Elemental) Formulas

Elemental formulas are more expensive than polymeric alternatives. They use free amino acids or small chain peptides as protein sources and are easy to digest.

Elemental formulas are usually low in fat or high in MCTs. They are typically prescribed for patients with maldigestion and malabsorption; e.g., pancreatitis, critical illness, short-gut syndrome, enterocutaneous fistulas, and diarrhea. In patients undergoing routine gastrointestinal operations, elemental formulas offer no benefit over polymeric formulas. Similar data have been found in a study of patients who were critically ill with hypoalbuminemia.

Modular Supplements

In cases in which commercially available enteral formulas may not be optimal, patients may benefit from modular feeding systems. Modular supplements contain single or multiple nutrients (protein, carbohydrate, and/or fat) that can be added to liquid enteral formulas.

Disease-Specific Formulas

Disease-specific formulas modify nutrient profiles to achieve desired outcomes, such as immune enhancement, or address specific disease states, such as renal, hepatic, and pulmonary states.

Immune-Enhancing Formulas

Various enteral formulas contain substrates with immune-modulating properties, eg., glutamine, arginine, n-3 fatty acids, nucleotides, selenium, and vitamins A, C and E. Data suggest that these formulas reduce the incidence of infectious complications, decrease ventilator time, shorten hospital and intensive care stays and reduce patient hospital costs. At the same time, the use of immune-enhancing formulas in severely ill patients has been found to increase mortality, lengthen stays in hospital and intensive care units, extend ventilator time, and raise treatment costs. Data indicate that immune-enhancing diets benefit moderate-to-severely malnourished patients undergoing elective gastrointestinal surgery, those with severe blunt and penetrating torso trauma, and some critically ill patients.

Renal Diets

Patients with stable chronic renal failure typically need energy-dense, low-protein diets, and those undergoing hemodialysis require high-protein diets. Use of essential amino acids or branched chain amino acids (BCAAs) shows no clear benefit in efforts to meet caloric needs and avoid protein load. Studies have yet to show clinical efficacy of renal failure formulas; therefore, their use should be limited to efforts to avoid dialysis in cases of acute renal failure, or to reduce dialysis requirements.

With renal dysfunction, metabolism of certain vitamins and minerals (e.g., folic acid, pyridoxine, calcium, and vitamins A, C, and D) and excretion of electrolytes (e.g., potassium, magnesium, and phosphorus) may be impaired. It may be necessary to adjust the intake.

Hepatic Formulas

Hepatic enteral formulas contain large amounts of the BCAAs—valine, leucine, and isoleucine—and small amounts of the aromatic amino acids (AAAs)— phenylalanine, tyrosine, and tryptophan. The formulas are designed to reduce AAAs in the blood–brain barrier by normalizing AAA to BCAA ratios in the plasma of patients with hepatic encephalopathy.

Data suggest that BCAA supplements provide necessary nitrogen intake to some protein-intolerant patients with no adverse effect on mental state, and perhaps even improvement. Because the use of BCAA supplements remains controversial, administration of formulas for hepatic failure should be limited to patients with hepatic encephalopathy who do not respond to standard treatments.

Pulmonary Diets

Patients with pulmonary insufficiency exhibit carbon dioxide (CO2) retention and oxygen (O2) depletion. Pulmonary formulas are low

in carbohydrates and high in fats (approximately 50% of calories); they attempt to decrease respiratory quotient minimize CO2 production and retention. It is prudent to avoid carbohydrate overfeeding in patients with acute and chronic lung disease until data from clinical trials of adequate sample size become available. Critically ill patients who have difficulty weaning from ventilators may require a short-term decrease or discontinuation of feeding.

Patient Evaluation Nutritional Assessment

The main goals of nutritional assessment are (a) to identify patients who have, or are at risk for, protein-energy malnutrition or nutrient deficiency, and (b) to assess their risks for developing nutrition-related complications.

History and Physical Examination

The most important parts of nutritional assessment are the patient history and physical examination.

Measurement of body weight and height can be used to compare actual and ideal body weight. Body mass index (BMI = weight [kg]/ height [m2]) can be used to estimate body fat.

Unintentional weight loss greater than 10% within the previous 6 months indicates malnutrition and is associated with poor clinical outcome.

Biochemical Tests

Biochemical tests includethose for serum albumin, prealbumin, retinol-binding protein, transferrin, and creatinine.

Serum Albumin

Low serum levels of albumin have been shown to correlate with increased morbidity and mortality in hospitalized patients. However, the biomarker has relatively poor sensitivity and specificity for protein malnutrition, and low levels of serum albumin can be seen in several conditions (e.g., inflammatory, gastrointestinal, cardiac, kidney, and liver diseases). Plasma albumin is usually unaffected by nutrition intake and does not normalize in stressed patients until inflammatory stress is resolved.

Prealbumin and Retinal-Binding Protein

Prealbumin is a transport protein for thyroid hormones and a binding protein for retinol-binding protein.

Its half-life is 2 to 3 days. Energy and protein restrictions lower prealbumin levels, and refeeding restores them. Infection, liver, and kidney failure may affect plasma concentrations of prealbumin.

Transferrin

Transferrin has a shorter half-life than albumin, but the serum levels depend on a patient's iron store. Transferrin helps identify those who are most likely to develop malnutrition and require aggressive and closely monitored medical nutrition therapy.

Creatinine

Twenty-four hour urinary excretion of creatinine can provide an index of lean body mass. Accuracy of the index requires consumption of a meat-free diet and effective and complete urine collection.

Clinical Test

Subjective Global Assessment

Subjective global assessment is a clinical method for determining nutritional status Patients are categorized as well nourished, moderately malnourished, or severely malnourished based on evaluation of weight changes, dietary intake, gastrointestinal symptoms, functional capacity, and diagnosis. The technique is highly reproducible and is a good predictor of medical and surgical complications.

Energy Requirements

Individualized nutritional requirements should be based on current and past nutritional state and the nature and complexity of the patient's condition. Calories should be adequate to meet basal or resting energy expenditures plus energy required for physical activity. Resting energy expenditure can be measured using indirect calorimetry or the Harris-Benedict equation. Indirect calorimetry is considered the “gold standard” for estimating resting energy expenditure. However, it is technically demanding, time-consuming, involves the use of expensive, specialized equipment, and requires trained personnel.

The use of the Harris-Benedict equation tends to overestimate caloric needs. Another equation, the National Academy of Sciences equation, also can be employed for predicting the estimated total energy expenditure (TEE) of normal and overweight/obese adults (age,>19 years) and is shown here for men and women.

Another approach, a computer program, Electronic Parenteral and Enteral Nutrition, can provide a rapid definition of the TPN or EN prescription for adult and pediatric patients, with reduced likelihood of providing excessive glucose and energy. In general, 25 to 30 kcal/kg/d is sufficient to meet the energy requirements of most patients.

Proteins

In unstressed adult patients with adequate organ function, protein intake of 0.8 g/kg/d is enough to maintain nitrogen balance. However, in hypercatabolic patients with acute illness, protein requirements may increase to 1.5 to 2 g/kg/d. Protein and non protein energy can be added together to calculate caloric requirements

Carbohydrates

Carbohydrates are usually the main source of energy. However, they can put patients at risk if administered in excess of required needs. Excess glucose can promote net de novo lipogenesis, increase carbon dioxide production and thermogenesis, cause hepatic steatosis, and exacerbate hyperglycemia in glucoseintolerant patients. Patients are unable to oxidize more than 5 to 7 mg/kg of body weight per minute of intravenously administered glucose. The recommended rate of glucose infusion should not exceed 4 to 5 mg/kg/min or 7 g/kg/d.

Lipids

When administered with adequate protein, lipids and glucose are equally effective at protein sparing. Lipids usually supply 20% to 30% of energy requirements. In critically ill, fluid-restricted patients, they provide a concentrated source of calories and help avoid complications

from carbohydrate overfeeding. Infusion of LCTs at a rate greater than 0.11 g/kg/h is associated with numerous risks (e.g., impaired immune, liver, pulmonary, and platelet functions).

Lipid administration has been linked to abnormal liver tests, cholestasis, and fatty liver. These outcomes raise concerns about the use of omega-6–containing vegetable oils as the only source of lipids. Patients with gastrointestinal, biliary, or pancreatic disease can have low tolerance for enteral LCT. MCTs are more easily absorbed. Use of EN formulas with high concentrations of MCTs can help those patients.

Micronutrients

Most commercially available enteral formulas are supplemented with recommended daily allowances for vitamins (Table 3) and trace elements (Table 4). These formulas are usually sufficient for most patients fed at levels that meet their caloric needs.

Some patients, such as those with high losses and severe malnutrition, may require extra supplementation. Requirements for electrolytes (i.e., sodium, potassium, chloride, bicarbonate, calcium, magnesium, and phosphate) depend on baseline levels, calculated losses, and maintenance needs.

In general, 30 to 40 mL/kg of fluids per day meet the needs of most adults. Patients with excess loss from drains, fistulas, or diarrhea need extra fluids.

Monitoring

Patients receiving EN require careful monitoring. Standardized protocols for EN ordering, administration, and monitoring (Table 5) should be used. These allow for appropriate estimates of daily nutrient, fluid, and electrolyte requirements as well as early detection of toxicity and deficiency states, and complications. Daily clinical examinations are necessary to identify patients who are intolerant to enteral formulas.

Daily Trace Elements

Trace Element Daily Requirement		**Chromium**	**30 mcg**
Copper	0.9 mg	Fluoride	4 mg
Iodine	150 mcg	Iron mg	18
Manganese	2.3 mg	Molybdenum	45 mcg
Selenium	55 mcg	Zinc mg	11

Enteral Access and Insertion/Placement

Selection of proper enteral access is based on the patient's gastrointestinal tract anatomy and function, the anticipated duration of feeding, and the potential risk for aspiration. Gastric feeding is the preferred approach.

Gastric access is physiologically accessible, convenient, and makes feeding easy to begin. However, it requires intact gag and cough reflexes and adequate gastric emptying.

Types of Access Nasoenteric

Nasoenteric, the most commonly used enteral access, is indicated for short-term use(<4 weeks). Tubes can be inserted into the stomach, duodenum, or jejunum.

Complications

Complications associated with nasally inserted tubes include nasopharyngeal ulcers, nasal septum necrosis, sinusitis, otitis, hoarseness, and vocal cord paralysis. Smallbore feeding tubes made from silicone or polyurethane are soft, smooth, and more flexible than stiff, large-bore tubes used for decompression and drainage. Small-bore tubes are well tolerated for 3 to 4 weeks and they decrease the risk of nasal tissue necrosis.

Small Bowel

Small bowel access is indicated in patients with conditions associated with recurrent aspiration of gastric contents (e.g., severe gastroesophageal reflux disease, esophageal dysmotility, gastroparesis, and gastric outlet obstruction). It is also indicated when early postoperative feeding is planned after major abdominal surgery.

Advantages

In addition to lessening the aspiration risk, postpyloric feeding also minimizes the stimulation of pancreatic enzyme secretion. Therefore, it can be helpful in critically ill patients with acute pancreatitis and those at risk for gastric motility dysfunction.

Disadvantages

Major disadvantages of postpyloric feeding include difficult tube placement, maintenance of proper positioning, and clogging

STRESS RESPONSE IN SURGERY

Humans are highly mobile, active mammals, and as such possess metabolic systems that are amazingly adaptable and responsive to the demands of physical activity, stress, and injury. Our metabolic machinery and capacity have developed to make it possible to both combat infectious disease and recover from injury. However well adapted we are in dealing with infection and injury, these insults have the potential to demand an extreme workload from the body, and thus can push metabolic responses to a point of dysfunction or failure. Although one can conceptualize the processes of metabolism with relatively simple and familiar equations involving the "burning" of sugar or fat to produce adenosine triphosphate (ATP), the causes of metabolic dysfunction go

beyond biochemical reactions, and are complex at both the cellular and organ/system levels. In terms of management of patients with trauma and infection, the balance between homeostasis and crisis can shift rapidly, and thus it behooves the attending surgeon to closely monitor and preserve the patient's metabolic capacity to make possible recovery or even survival.

Mitochondria: The Center of Metabolism

Although metabolic dysfunction from trauma and infection affects critical organ systems in a variety of ways, its genesis generally is linked to a single organelle, the mitochondrion. Mitochondria are commonly referred to as the “powerhouse of the cell.” The power is distributed via the high-energy phosphate bonds of ATP. This energy resides in the terminal phosphate of ATP. When this bond (i.e., that between the second and third phosphates) is cleaved, it releases a substantial amount of energy (~7 kcal/mol ATP). ATP is thus a safe and stable fuel, which contains a large amount of energy that may be used to facilitate a wide variety of biologic processes. Among these are the powering of enzymes that make or break chemical bonds, muscle contractions, phosphorylation of signaling proteins, ion pumps, and active transport activities. The conversion of substrates (glucose, ketones, fatty acids, lactate, etc.) to ATP is accomplished via a highly efficient process that uses oxygen. For

example, oxidation in the Krebs citric acid cycle of one molecule of glucose has the potential to yield >30 molecules of ATP. This remarkable efficiency derives from the close physical and biochemical coupling of a series of enzymes situated along the inner membrane of the mitochondrion. This chain of enzymes is more complex than the nomenclature suggests, being comprised of >80 peptides. They and their substrates are shown in a schematic form in Figure 1. Complexes I, III, and IV are proton (H+) pumps, which are engaged in creating an electrochemical gradient, whereas complex V utilizes the H+ to add the terminal high-energy phosphate to the adenosine diphosphate (ADP) donor. Complex VI likewise consumes H+, functioning to uncouple electron transport for thermogenesis, and can also protect the mitochondrion by diverting electrons to the inner membrane. Although it is extremely efficient, the process is not absolutely perfect, and the features shown in gray have the capacity to “leak” electrons. As a consequence, these free electrons can generate reactive oxygen, which has great importance in the pathophysiology of infection and trauma .Mitochondria can increase the output of ATP in response to a variety of triggering events.These include accumulation of ADP or the greater availability of “fuel” and oxygen. Cellstimulatory signals, such as the presence of increased Ca2+ in the cytoplasm, also stimulate the mitochondria to generate more ATP. These stimuli are tied to an

increased demand for work from the body, be it muscular (heart or skeletal muscle contraction), biosynthesis (production of proteins by the liver), cell division (immune responses or tissue repair), or the generation of heat (response to hypothermia). Clearly, all of these functions can be tied to the demands of dealing with infection and injury.

Mitochondrial Dysfunction

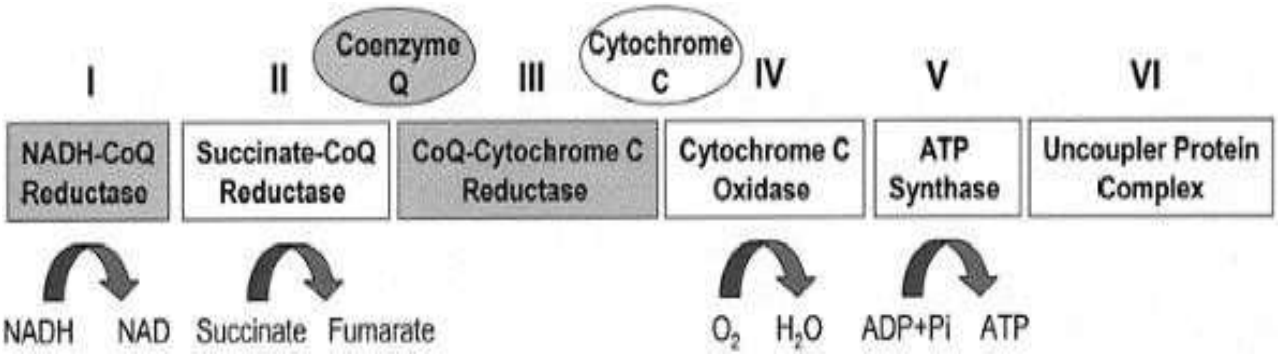
The failure of mitochondrial energy production lies not with the organelle itself, but with its various "supplies." The situation is analogous to that seen in a manufacturing plant that uses the Japanese-style just-in-time inventory strategy. In this example, under ordinary manufacturing conditions, the various components come together from outside shippers in a timely fashion, and the products roll off the assembly line, with a minimum drain on operating capital. However, the vulnerability of this strategy becomes apparent when any critical components come into short supply; production abruptly ceases, and the entire plant must shut down. This analogy holds with the mitochondrion, owing to a curious fact in the nature of ATP production.

Unlike sugars or fats, which are stored as glycogen or adipose tissue, respectively, there are no depot stores of ATP. Thus, with a failure to deliver any of the essential components (cardiac output and/or blood flow, lung oxygenation, glucose transport, etc.), there is a rapid onset of

metabolic dysfunction. At the level of the mitochondrion, this dysfunction has many forms.

One failure of the mitochondrion with immediate biochemical consequences is the production of reactive oxygen species (ROS). These products take numerous forms, such as superoxide, peroxides, nitric oxide, and peroxynitrite. Because ROS are constitutively produced by mitochondria, there are neutralizing compounds (antioxidants) such as glutathione that buffer against the damage of ROS. An additional consequence of mitochondrial dysfunction is spillage of the contents of the mitochondrion into the cell's cytoplasm. This occurs through “permeability transition pores,” which open in a fission response to stress, and provide a channel for substances such as cytochrome c to enter the cytoplasm and trigger programmed cell death (apoptosis). These events are depicted schematically

ELECTRON TRANSPORT CHAIN



Mitochondrial Metabolism in Infection and Injury

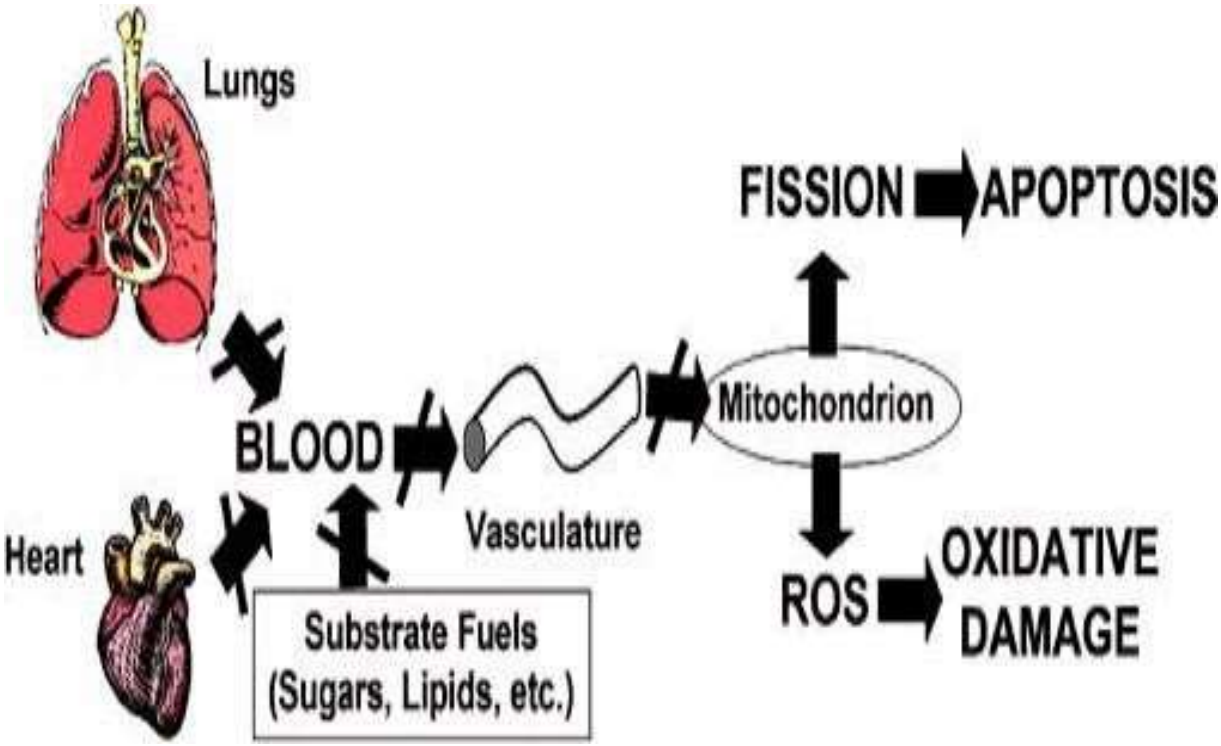
The effects of infection on metabolism have been extensively studied, and will be covered in detail later in this chapter. However, there are some generalities that are specific to mitochondria with reference to sepsis and injury, and how they are studied. At the outset it should be stated that the experimental literature is somewhat confusing, largely because of the varied animal models and experimental designs that have been brought to bear on the problem.

Thus, although a model may focus on a single variable to dissect one component of infection away from “noise,” this compromise itself may fail to replicate what a physician sees at the bedside. A good example of this is found in experimental sepsis, which can range from injection of a single pure strain of microbe, to polymicrobial sepsis using the animal's own gut flora, to those involving no living organisms but instead their metabolites or cellular components. A common example of the latter is the infusion of lipopolysaccharide (LPS, also known as endotoxin).

Although it may seem meaningless to employ a model devoid of living organisms, it has been observed that LPS alone can trigger severe metabolic dysfunction at higher doses. This is because the effects of LPS are amplified through interaction with specific receptors that trigger a

cascade of responses (cytokine secretion, gene transcription, apoptosis, etc.). Thus, in light of the variety of laboratory conditions used to model sepsis, it is not surprising that experimental sepsis has shown a range of mitochondrial damage, from none to mild to severe.

MITOCHONDRIAL METABOLISM



There are some common features of sepsis vis-à-vis mitochondria, however. Under conditions of sepsis, and especially septic shock, there will very likely be severe morphologic damage to the mitochondria. Also, ATP levels will decline, as observed clinically and with experimental sepsis. ROS will also increase to harmful levels, exhausting the reserve of antioxidants.

ROS can damage not only the mitochondrion itself, but other organelles and molecules within the cell, including DNA. These events all become more likely to occur with a longer duration of infection, which allows for microbial growth and expansion, toxin accumulation, and increased workload energy demands. Not unexpectedly, the likelihood of multiple organ systems being affected by sepsis also increases with time. There may be serious impairment of vital (renal, hepatic, lung, cardiac) and nonvital (skeletal muscle) organ function.

These failures are exacerbated by persistent hypotension, even in the face of more than adequate volume resuscitation. In most cases these tissues exhibit a loss of mitochondrial function. There will also be a fall in cellular/tissue ATP levels, matched by a rise in ADP and adenosine monophosphate (AMP). A final apparent self-preservation response is often seen in advanced sepsis (marked by widespread organ failure and systemic inflammation)—namely, a broad shutdown of energy

consumption, not unlike a hibernation response. Taking these facts together, it is not hard to understand why the syndrome of multiorgan dysfunction or failure is a common cause of death among critically ill patients.

Although injuries vary greatly, serious injuries have common features that can unfavorably affect mitochondrial metabolism. Hemorrhage effectively produces hypoxia, which initiates a cascade of responses that are directed toward adaptation to lowered oxygen, which can at the same time be damaging to an already injured body. Hypoxia and ischemia-reperfusion, with their lowered oxygen availability to the tissues, will drive the cells to depend on anaerobic glycolysis for their high-energy phosphate production. This can initiate a feedback situation, wherein lactic acid increases, effectively shutting down anaerobic glycolysis as an energy source. In this setting, free fatty acids can also increase systemically, probably from peripheral adrenergic stimulation of lipolysis. Limited oxygen also compromises β-oxidation, the principal means of converting fats to energy.

This in turn causes a similar “stacking up” of free fatty acids, acyl coenzyme A (acyl CoA), acylcarnitines, and so on, which compromises the heart. Under these conditions the heart and other tissues are already at a disadvantage because, despite the high energy stored in fat, β-oxidation

cannot match the efficiency of carbohydrate metabolism. Thus, reoxygenation, if it occurs, may take place in a setting in which aerobic metabolism is not possible, because of large-scale diversion of metabolism into the less efficient "backup" modes of β-oxidation and anaerobic glycolysis.

There is one additional consequence of elevated lactic acid worth noting. As mentioned previously, an intracellular flux of calcium will cause a demand for increased ATP synthesis.

The presence of increased lactic acid in the cell will cause calcium to enter the cytoplasm from the exterior, providing a spurious signal for increased workload at a time when the metabolic machinery is incapable of reacting appropriately.

This has the untoward effect of further depleting already low supplies of ATP. Finally, regarding the lowered ATP supplies, an obvious solution for treatment would be to administer agents/drugs that increase ATP production under low-flow conditions. However, such agents will not be effective if the microcirculation is markedly impaired prior to their administration.

Trauma, Infection, and Metabolism as Related to Medicine

Trauma and infection initiate changes in metabolism that can affect virtually all organs and tissues, by altering carbohydrate, lipid, and protein metabolism. The metabolic response to injury and sepsis has traditionally been divided into an ebb phase and a flow phase followed by a convalescence phase.

This metabolic pattern is better defined after injury than during sepsis. The metabolic course during sepsis is more convoluted because the septic insult is usually more insidious in its onset and can vary in its duration and intensity. Individuals with severe sepsis or septic shock display many of the characteristics of the ebb phase, whereas patients with a more chronic, less severe sepsis display the hypermetabolism and catabolism of the flow phase ("hypermetabolic sepsis"). The ebb phase is dominated by glycogenolysis and lipolysis, which provides the organism with energy substrates for "fight or flight" responses.

This is followed by the flow phase, a state of catabolism manifested by elevated metabolic rate and increases in body temperature, pulse rate, urinary nitrogen excretion, and muscle catabolism. The subsequent anabolic "recovery" phase can last from weeks to months.

This section describes, at the tissue and cellular levels, the characteristic changes in carbohydrate, lipid, and protein metabolism that occur in trauma and sepsis, and discusses mediators, including hormones and cytokines, that regulate the metabolic changes. In addition, intracellular mechanisms and molecular regulation of metabolic consequences of injury and severe infection are discussed.

Understanding the metabolic response to injury and sepsis is important from a clinical perspective for several reasons. Some of the metabolic alterations that occur after injury and severe infection are essential for survival.

For example, several studies have found a correlation between survival and maintenance of the acute-phase response in the liver. In contrast, the excessive muscle catabolism that occurs during sepsis may be detrimental to patients, delaying recovery, slowing ambulation, and increasing the risk of pulmonary complications if the respiratory muscles undergo proteolysis.

Identifying methods to limit excessive catabolism may therefore be advantageous. By understanding the mediators and mechanisms of the physiologic and metabolic response to trauma and infection, one may develop novel therapeutic strategies to target specific metabolic alterations, which may possibly lead to improved survival.

Metabolic Mediators

Many of the metabolic alterations that occur in response to trauma and infection are regulated by hormones and cytokines. Frequently, these substances interact with each other to induce a complete metabolic response. Before the role of these mediators in the regulation of metabolism is discussed, the influence of injury and sepsis on their release is reviewed. Although a number of other biologically active substances are released after injury and sepsis, such as nitric oxide (NO), oxygen radicals, prostaglandins, leukotrienes, and complement components, this section focuses on hormones and cytokines because they have been studied extensively as regulators of metabolism. Whereas classically the counterregulatory hypothalmic-sympathoadrenal pathway has been regarded as separate from the cytokine cascade, in fact they are related and interact (Fig. 3).

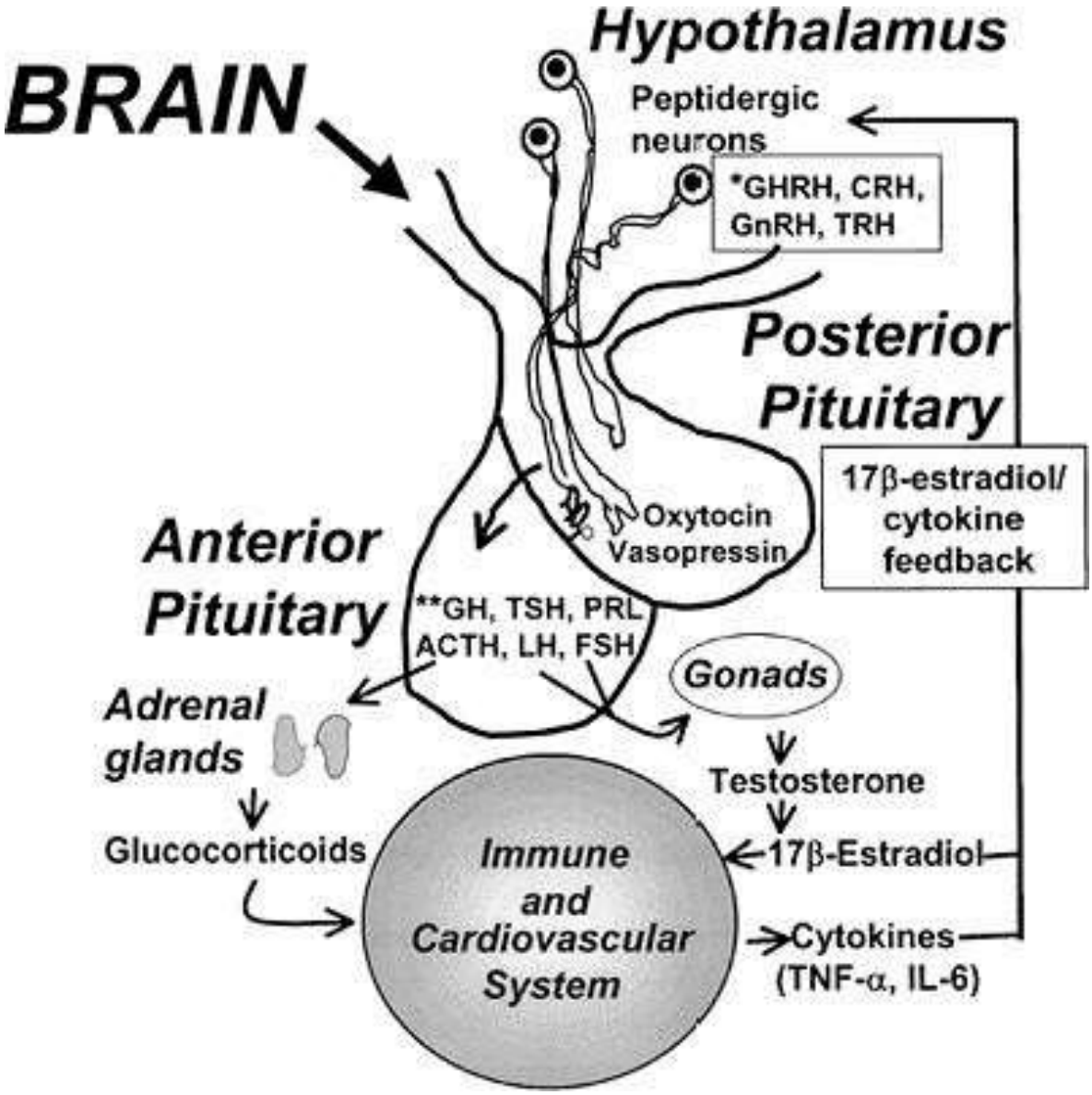
Hormones the classification of hormones can be based on different properties. For example, hormones can be classified as being regulated at the level of the hypothalamus (e.g., corticotropin releasing hormone, thyrotropin-releasing hormone), pituitary gland (adrenocorticotropic hormone, thyroid-stimulating hormone), or autonomic nervous system (epinephrine, norepinephrine).

Another classification is based on the chemical properties and divides hormones into polypeptides (e.g., insulin, glucagon), amino acid derivatives (e.g., thyroxine, epinephrine, norepinephrine), and fatty acid derivatives, originating either from cholesterol (e.g., glucocorticoids) or arachidonic acid (prostaglandins, leukotrienes).

Hormones can also be classified based on binding to intracellular receptors (e.g., glucocorticoids, thyroid hormones) or cell membrane receptors. Binding of hormones to cell membrane receptors, in turn, can influence cell metabolism through activation of different second messengers, including cAMP (e.g., catecholamines, glucagons), cGMP (e.g.,atrial natriuretic peptide), calcium and phosphatidylinositides (e.g., epidermal growth factor), and kinase/phosphatase cascades (e.g., insulin, IGF-I).

Cell membrane receptors can be divided into receptor kinases, G-protein-coupled receptors, and ligand-gated ion channels. From a metabolic standpoint, hormones can also be divided into anabolic and catabolic (counter regulatory) hormones. Injury and sepsis are associated with a pronounced neuroendocrine response with an initial sympathoadrenal discharge, which stimulates the release of the counter regulatory hormones glucagon, epinephrine, norepinephrine, growth hormone (GH), and cortisol. The stimuli that activate the neuroendocrine

response during trauma and infection include hemodynamic changes (caused by hemorrhage, dehydration, third space losses, etc.), changes in pH, pO2, pCO2, ambient or body temperature, substrate availability (e.g., plasma glucose and amino acids), pain, and anxiety.


BRAIN
Hypothalamus
Peptidergic neurons
*GHRH, CRH, GnRH, TRH
Posterior Pituitary
Oxytocin
Vasopressin
17β-estradiol/ cytokine feedback
Anterior Pituitary
**GH, TSH, PRL ACTH, LH, FSH
Gonads
Adrenal glands
Testosterone
Glucocorticoids
17β-Estradiol
Immune and Cardiovascular System
Cytokines (TNF-α, IL-6)

The counterregulatory hormones respond to hypoglycemia and play a role in glucose "counterregulation." Several of the counterregulatory hormones have a catabolic effect and are called catabolic hormones.

The counterregulatory hormones are usually elevated during the ebb phase after injury but can remain increased into the flow phase during sustained injury, such as burn injury, and during sepsis. Numerous reports are found in the literature of increased levels of cortisol, glucagon, catecholamines, and GH after trauma, burn injury, infection, and sepsis. From a metabolic standpoint, cortisol is probably the most important among the counterregulatory hormones, with widespread effects on glucose, amino acid, and fatty acid metabolism. The release of glucocorticoids in trauma and sepsis is centrally regulated. Thus, stress results in hypothalamic release of corticotropin-releasing factor, which in turn stimulates pituitary release of adrenocorticotropic hormone (ACTH). ACTH regulates cortisol synthesis and release from the adrenal cortex.

The importance of the role of the central nervous system during trauma and infection is illustrated by the fact that the glucocorticoid response can be abolished by blocking afferent nervous stimuli. Studies suggest a role for endogenous opiates and opioids as contributing mediators in the neuroendocrine response. Central nervous system

hypoglycemia during the early part of the ebb phase likely causes increased release of central nervous system morphine. The elevated morphine levels may play a role in mediating metabolic alterations, including intestinal proteolysis.

In addition to the catabolic hormones, trauma and infection influence other hormones as well most notably insulin, insulin-like growth factor I (IGF-I), and thyroid hormone. Plasma insulin levels decrease during the ebb phase and rise during the catabolic flow phase. Although levels of plasma insulin are high during the flow phase, plasma glucose levels remain elevated, a finding that supports the concept of "insulin resistance" in peripheral tissues, in particular in skeletal muscle, during sepsis and after trauma. Evidence suggests that the insulin resistance in these conditions is at the postreceptor level and may be mediated by β-adrenergic receptor activity and tumor necrosis factor-alpha (TNF-α).

Circulating IGF-I levels decrease in critically ill patients and in patients with sepsis. IGF-I and insulin are anabolic hormones that promote protein and glycogen synthesis and block protein breakdown. Reduced levels of the anabolic hormones, in addition to increased levels of the catabolic hormones, may represent an important mechanism by which metabolic alterations occur during trauma and infection. Not only

is there a reduction in IGF-I levels, peripheral tissues become resistant to IGF-I in various catabolic conditions, including sepsis. Both IGF-I and insulin have been used as therapeutic agents in an effort to reduce post injury catabolism. One reason this treatment has not always been successful is probably the development of hormone resistance.

Gender Differences in Injury Response

Hormones, especially sex steroids, have been found to play a highly significant role in the response to injury, in addition to their role in modulating metabolism. Principal among these observations is that high estrogen levels have a protective effect against injuries, such as shock, trauma hemorrhage, and sepsis, insofar as protecting from immune and cardiovascular depression.

This finding stemmed from the observation that proestrus females, but not postestrus females or male mice, were resistant to sepsis induced by cecal ligation and puncture. Moreover, proestrus females also showed maintained or enhanced immune as well as cardiovascular responses as opposed to decreased responses in postestrus females and males following trauma hemorrhage. Further investigation confirmed these observations, and led to the finding that administration of exogenous estrogen (i.e., to males, or females with low/no estrogen) following trauma hemorrhage was capable of replicating the protective

effect of high levels of endogenous hormone. For androgens, the converse appears to be true, in that blockade of androgen receptors with antagonists such as flutamide improves performance and outcomes for males.

These findings with estrogen (E2) have been extended to other steroid intermediates of estrogen biosynthesis (DHEA, adiol) and nonsteroid peptide hormones (prolactin). Blockade of the estrogen receptor with estrogen mimetic antagonists (ICI 182,780) results in a loss of estrogen protection, demonstrating that the effects are receptor mediated. Thus, the systemic and functional level of hormones may have implications for injury outcomes from either an epidemiologic or therapeutic standpoint. Although these gender effects are secondary to the direct ability of hormones to alter metabolism, it is clear that they have significant influence on injury and infection, and thus will likewise affect the metabolic status of the host.

Metabolic Responses to Injury and Infection

Trauma and sepsis induce substantial changes in carbohydrate, lipid, and protein metabolism in most organs and tissues. In addition, important changes in fluid balance, electrolytes, acid–base balance, and tissue oxygenation occurCarbohydrate Metabolism Early in the course of sepsis and endotoxemia, serum glucose levels rise, mainly reflecting

increased hepatic glucose production caused by stimulated glycogenolysis and gluconeogenesis. Concomitant with the increased hepatic glucose production is increased glucose utilization in multiple tissues, including liver, spleen, small intestine, skin, and some (but not all) muscles. A common feature of some of these tissues is a high content of macrophages.

Studies have shown that, in the liver, the high glucose uptake reflects increased utilization of glucose by Kupffer cells. In addition, endotoxemia is associated with a substantial inflow of neutrophils into the liver, and these cells also contribute to the increase in glucose uptake. Interestingly, the hepatocyte uptake of glucose does not change, which suggests a dichotomy in glucose kinetics between hepatocytes and Kupffer cells during sepsis and endotoxemia. Because the rate of glucose production exceeds the rate of glucose disposal during this phase of sepsis and endotoxemia, serum glucose levels are elevated.

Another factor contributing to increased serum glucose is the insulin resistance in muscle and fat, which results in a relative inhibition of glucose uptake by these tissues. If sepsis is prolonged, hypoglycemia usually develops as hepatic glucose production fails. Hepatic glycogen is depleted during protracted sepsis, and the liver has to rely on gluconeogenesis for glucose production. In late sepsis, gluconeogenesis

may be inhibited secondary to decreased supply of gluconeogenic substrates and altered enzyme function.

Some studies suggest that decreased phosphoenol pyruvate carboxykinase activity is a mechanism of reduced hepatic gluconeogenesis, whereas other reports have implicated stimulated phosphofructokinase 1 activity.

Despite decreased glucose production and hypoglycemia in prolonged and severe sepsis, uptake remains high in macrophage-rich tissues, which further exacerbates hypoglycemia. This in turn may contribute to mortality during septic shock.

Regulation of Carbohydrate Metabolism during Trauma and Infection

This section focuses on the role of hormones and cytokines and their interaction in the regulation of metabolism after trauma and infection. Other factors also participate in the regulation of metabolism during infection and injury, including NO and prostaglandins. The hormones involved in the regulation of carbohydrate metabolism during trauma and infection include the counterregulatory hormones and insulin.

In this respect, catecholamines and glucagon are the major counterregulatory hormones in humans. Evidence in support of the role of the counterregulatory hormones was found in experiments in which intravenous infusion of a combination of glucagon, epinephrine, and cortisol ("triple hormone infusion") resulted in alterations in whole-body carbohydrate metabolism similar to those seen in sepsis and other critical illness. Regulation of carbohydrate metabolism by catecholamines is well recognized.

Epinephrine influences carbohydrate metabolism by increasing hepatic glycogenolysis, followed by stimulated gluconeogenesis, and by inhibiting the metabolic clearance rate of glucose, which further increases serum glucose levels. In addition, epinephrine stimulates release of glucagon and inhibits release of insulin, further contributing to hyperglycemia. In burned patients, treatment with phentolamine and propranolol reduced whole-body metabolic rate, the role of catecholamines in the regulation of metabolism after injury.

Glucagon plays a more important role in the control of carbohydrate metabolism during sepsis, at least in the regulation of hepatic glucose production.

The important role of hyperglucagonemia seen during sepsis was demonstrated in experiments in which the hormone was blocked by infusion of somatostatin in septic rats and the elevated rate of glucose production was reduced to control levels. In contrast, treatment with somatostatin did not decrease sepsis-induced increase in glucose disposal, which suggests that the two aspects of carbohydrate metabolism (hepatic glucose production and glucose clearance) are controlled by different mechanisms during sepsis. Glucagon probably does not act alone during sepsis but instead acts synergistically with other mediators, such as glucocorticoids and catecholamines.

Insulin also plays a key role in the regulation of carbohydrate metabolism in injury and sepsis. Insulin levels vary depending on the phase of injury. During the ebb phase, insulin levels are reduced despite hyperglycemia. The combined effects of catecholamines, somatostatin, glucocorticoids, and reduced pancreatic blood flow may reduce pancreatic β- cell sensitivity to glucose. During the flow phase, β cells regain their sensitivity and insulin concentrations rise. Despite increased insulin concentrations, however, hyperglycemia may persist, consistent with peripheral insulin resistance. Clinically, the presence of insulin resistance is evident from reduced hormone response when exogenous insulin is administered to septic or injured patients. The insulin resistance

is secondary to a postreceptor alteration resulting in decreased cellular responsiveness to insulin, possibly mediated by TNF and catecholamines. In addition to hormones, cytokines also regulate carbohydrate metabolism. The most extensively studied cytokine in terms of regulation of carbohydrate metabolism is TNF. Changes in glucose metabolism during endotoxemia and sepsis can be reproduced by the in vivo administration of TNF with increased hepatic production of glucose, hyperglycemia, and stimulated glucose utilization by macrophage-rich tissues and diaphragm. The effect of TNF on glucose kinetics is dose dependent, with relatively modest doses causing hyperglycemia and larger doses inducing hypoglycemia.

The hypoglycemia seen after high doses of TNF can be explained at least in part by increased peripheral glucose utilization, although impaired hepatic gluconeogenesis may contribute. The data from in vivo studies do not define whether TNF has a direct or indirect effect on hepatic glucose metabolism. Administration of TNF induces a stress response, and the effects of TNF may be secondary to release of counterregulatory hormones. Indeed, infusion of phentolamine and propranolol prevented the increase in glucose appearance noted in rats treated with TNF, a finding which suggests that the TNF-induced increase in hepatic glucose production may be indirect and at least in part

mediated by catecholamines. This observation provides an additional example of interaction between cytokines and hormones. Because pretreatment of septic or endotoxemic rats with anti-TNF antibodies did not modify the changes in whole-body carbohydrate metabolism as assessed from measurements of plasma glucose and lactate levels and rates of glucose appearance and clearance, endogenous production of TNF probably is not a requirement for the increase in hepatic glucose production and whole-body glucose disposal seen in endotoxemia and hypermetabolic sepsis. Unlike in the liver, TNF may have a direct effect on cellular glucose kinetics in muscle and adipose tissue.

Exposure of cultured adipocytes to TNF resulted in a dose- and time dependent increase in glucose transport, measured as uptake of 2-deoxyglucose. The molecular regulation of the TNF-induced glucose transport was multifaceted; TNF caused an initial translocation of the glucose transporter to the cell surface, followed by an increased transcription rate of the glucose transporter gene , stabilization of glucose transporter mRNA, and increased production of the glucose transporter protein. In addition to TNF, IL-1 also can influence carbohydrate metabolism. For example, previous experimental work demonstrated that plasma glucose levels decreased after administration of IL-1 to rats. When equal doses of IL-1 were injected intracerebroventricularly and

intraperitoneally, only animals receiving the IL-1 intracerebroventricularly demonstrated hypoglycemia, suggesting that IL-1 exerts its effect on carbohydrate metabolism through the central nervous system.

Decreased hepatic glucose production and increased peripheral glucose transport and utilization are mechanisms by which IL-1 may induce hypoglycemia. Lipid Metabolism Circulating levels of free fatty acids, triglycerides, and cholesterol are increased during injury and sepsis.

The mechanism of these changes is multifactorial, with stimulated synthesis in the liver of apolipoproteins and triglycerides being the major mechanism of hypertriglyceridemia. Contributing factors include reduced activity of the enzyme lipoprotein lipase in muscle and adipose tissue, which decreases the clearance of triglyceride-rich lipoproteins, and increased lipolysis in adipose tissue. Although the fact that hepatic synthesis of triglycerides increases during sepsis is fairly well accepted, the influence of sepsis and endotoxemia on the secretion of triglycerides is more controversial, with studies showing both unchanged and reduced secretion. Although plasma levels of free fatty acids and triglycerides are usually elevated during sepsis and endotoxemia, this is not always the case. One reason for this may be decreased perfusion of adipose tissue

during severe sepsis or endotoxic shock, which results in reduced lipolysis and decreased plasma levels of free fatty acids. Fatty acids are also used as an alternative energy source by peripheral tissues after injury and sepsis, and if the rate of fatty acid clearance (peripheral oxidation) is higher than the rate of appearance (lipolysis) or production (hepatic lipogenesis), plasma fatty acid concentrations do not increase. Alterations in lipid metabolism as manifested by increased lipolysis and stimulated hepatic production of triglycerides and fatty acids are beneficial to the injured and septic organism for several reasons.

Because lipid substrates are provided as an alternative energy source for peripheral tissues, including muscle and the immune system, glucose is spared for the nervous system. In addition, lipoproteins can bind endotoxin and a number of different viruses. Increase in plasma lipoproteins may therefore help protect the organism from the toxic and lethal effects of endotoxin and infectious agents.

Regulation of Lipid Metabolism

Hormones regulate lipid metabolism in both adipose and other tissues. The role of hormonal control of lipid metabolism in injury and infection, however, is probably less prominent than that of other mediators, such as cytokines. An exception to this may be the catecholamines. For example, the sepsis-induced increase in palmitate

appearance can be inhibited by combined α- and β-adrenergic blockade. This is consistent with other reports that catecholamines stimulate lipolysis in adipose tissue, producing, in part, the "posttraumatic lipemia."

There is evidence that cytokines may participate in the regulation of lipid metabolism after injury and infection. TNF has received most attention in this respect, in part because of work done in the characterization of the cause of cancer cachexia. In early studies, a factor, then called cachectin, was identified from the serum of patients with cancer and shown to be an inducer of both the cachexia and hyperlipidemia that accompany some tumors. Subsequent studies showed that cachectin and TNF are the same substance. TNF infusion in vivo causes several changes in lipid metabolism that are similar to those that occur during sepsis and injury.

One mechanism by which TNF may alter lipid metabolism is reduction of lipoprotein lipase activity, so that degradation of lipoproteins is decreased. This regulation probably occurs at the molecular level by downregulated lipoprotein lipase gene expression in adipose tissue. Downregulation of lipoprotein lipase, however, may not be the only mechanism by which TNF induces hypertriglyceridemia, because in some studies, serum levels of triglycerides were increased before a

decreased lipoprotein lipase activity could be detected in adipose tissue after administration of TNF.

The liver is probably the major site at which TNF influences lipid metabolism. Evidence exists that TNF stimulates both synthesis and secretion of triglycerides in the liver. Fatty acids are the rate-limiting substrates in triglyceride synthesis. TNF treatment does not change activities of the enzymes involved in the esterification of fatty acids to glycerol, which suggests that the stimulated triglyceride production in the liver is due primarily to availability of fatty acids.

In addition to stimulated liver synthesis of fatty acids, increased lipolysis in adipose tissue can also increase fatty acid availability. TNF stimulates both these processes. Interestingly, the effect of TNF on fatty acid synthesis is site specific. Thus, whereas TNF increases fatty acid synthesis in the liver, it does not influence this process in muscle, fat tissue, or small intestine.

The mechanism for this differential effect is not clear but may reflect differences between tissues in the activity of enzymes responsible for fatty acid synthesis. Other factors may contribute to the ability of TNF to alter lipid metabolism. For example, catecholamines and TNF act synergistically to increase lipolysis. Nutritional status may also be important in TNF-induced hypertriglyceridemia. In chow-fed rats,

lipolysis in adipose tissue was stimulated after TNF administration, increasing the availability of fatty acids. In contrast, in sucrose-fed rats, TNF markedly stimulated hepatic de novo synthesis of fatty acids. Both conditions resulted in increased triglyceride production by the liver. The observation that TNF can stimulate hepatic triglyceride synthesis and increase plasma triglyceride levels through multiple mechanisms supports the concept that changes in lipid metabolism play an important role in the overall response to infection and inflammation.

Although the role of TNF has been studied most extensively in the regulation of lipid metabolism, other cytokines as well may influence lipid metabolism, including IL-1, interferon-α (IFN-α), interferon-β (IFN-β), and IFN–γ.

The mechanism by which different cytokines alter fatty acid synthesis may vary. For example, citrate levels increase after TNF, IL-1, and IL- 6 treatment of adipocytes in culture. Citrate is an activator of acetyl coenzyme-A carboxylase, the rate-limiting enzyme in fatty acid synthesis. IFN-α treatment does not increase citrate levels, which suggests an alternative mechanism. These different mechanisms may explain the results of simultaneous cytokine treatment. Thus, administration of IFN-α and either TNF or IL- 1 resulted in an additive effect on fatty acid synthesis. In contrast, maximal doses of TNF and IL-

1 given together (presumably working through the same mechanism) did not further increase fatty acid synthesis. Not all cytokines stimulate fatty acid synthesis.

Studies suggest that IL-4 inhibits hepatic fatty acid synthesis induced by TNF, IL-1, or IL-6. IL-4 alone had no effect and did not influence the stimulated hepatic fatty acid synthesis stimulated by IFN-α. These results are further support of the concept that different cytokines induce hepatic lipogenesis through distinct mechanisms.

Protein Metabolism

Among the metabolic alterations that occur after injury and infection, those affecting protein metabolism have been studied extensively.

This section of the chapter focuses on changes in protein metabolism in skeletal muscle, liver, and intestine and argues for the concept that these changes are part of an integrated metabolic response to injury and sepsis.

Muscle

Interest in protein metabolism after trauma began when studies by Sir David Cuthbertson more than 70 years ago demonstrated increased urinary excretion of nitrogen, phosphate, and sulfate in patients with

long-bone fractures. A number of subsequent studies provided evidence that skeletal muscle is the major source of increased urinary nitrogen secretion after injury and sepsis. Negative nitrogen balance and muscle catabolism are well-recognized metabolic responses to these conditions. The catabolic condition in muscle that develops during critical illness is multifactorial and is caused by a combination of reduced protein syntheses, increased protein breakdown, and inhibited amino acid uptake. From a quantitative standpoint, the increase in protein breakdown, in particular the breakdown of the myofibrillar proteins actin and myosin, is the most prominent component of muscle catabolism after injury and sepsis.

Increased myofibrillar protein breakdown results in increased urinary excretion of 3- methylhistidine in injured and septic patients and increased release of 3-methylhistidine by incubated muscles from septic animals.

The breakdown of myofibrillar proteins may in part explain the muscle weakness typically seen in patients with severe trauma and sepsis and may severely impair recovery in these patients.

The net result of decreased protein synthesis and increased protein breakdown is the release of amino acids from muscle, in particular glutamine. Inhibited cellular uptake of amino acids contributes to the peripheral release of amino acids in injury and sepsis. As no storage protein per se exists, skeletal muscle may be viewed as an endogenous source of amino acids for the rest of the body during infection and injury, which is of particular importance for protein synthesis and function in liver, intestine, and cells of the immune system.

METHODOLOGY

- **DESIGN OF STUDY :** Prospective Study
- **PERIOD OF STUDY :** 1 Year (October 2016 - September 2017)
- **COLLABORATING DEPARTMENT :** None
- **SELECTION OF STUDY SUBJECTS :**all patient satisfying inclusion criteriaadmitted in govt rajaji hospital for a period of 1 year

INCLUSION CRITERIA

All Patients undergoing emergency gastrointestinal surgeries in acute abdomen within 24 hours.

EXCLUSION CRITERIA

- Patients with severe shock.
- Patients managed in ICU for more than 2 days postoperatively
- Patients requiring bowel resection and anastomosis .

METHOD OF COLLECTING DATA

All patients in general surgical ward undergoing emergency gastrointestinal surgeries in acute abdomen within 24 hours under critertia will be subjected to 2 groups. Group 1 getting early enteral feeding(E group) by oral or nasogastric 24 to 48 hrs after surgery(POD - 2) and group 2 getting late enteral feeding(L group)(more than 48 hrs). After that patients are followed up closely for various complication namely wound infections, pulmonary complications and post op ileus along with duration of hospital stay.

FEEDING MATERIALS GIVEN

Tender coconut water/fruit juices(carbohydrate drinks)+protein powder solution in 2:1 ratio. Patients were started on 500mL of above mentioned feed within the first 48 hours and the feeds increased by 500mL incrementally on each consecutive post operative day.

CONSENT **:** Individual written and Informed consent

ANALYSIS **:** Statistical Analysis using SPSS software

CONFLICT OF INTEREST **:** None

FINANCIAL SUPPORT **:** Nil From The Institution

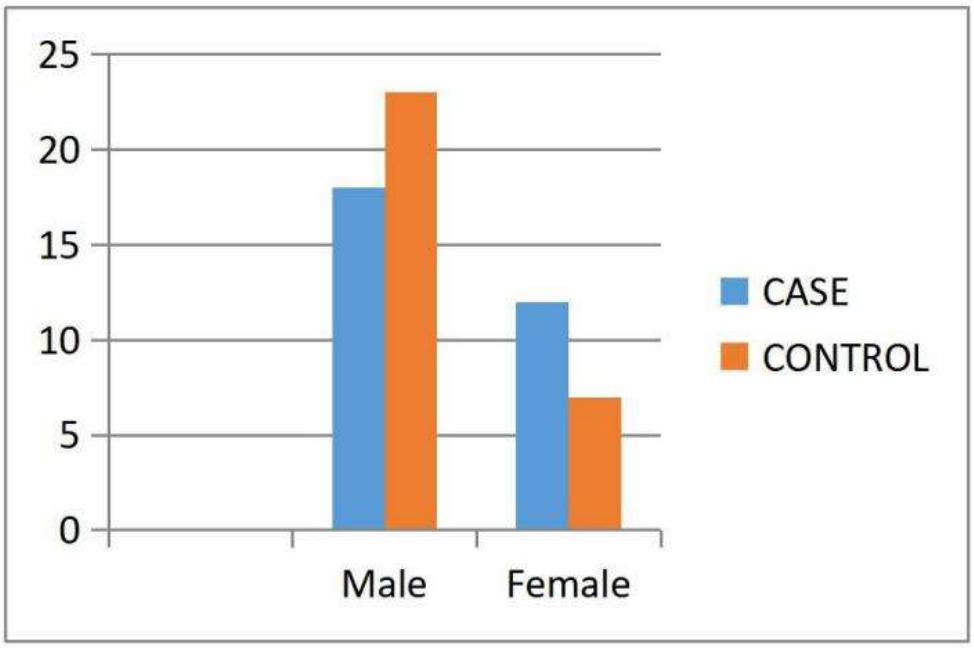
OBSERVATIONS AND RESULTS

The cases were studied from a period of October 2016 to September 2017. Total of 60 cases were studied and analysed.

GENDER DISTRIBUTION

A total pf 30 cases and 30 controls were studied. The gender distribution among cases and controls were demonstrated to be according to the table below.

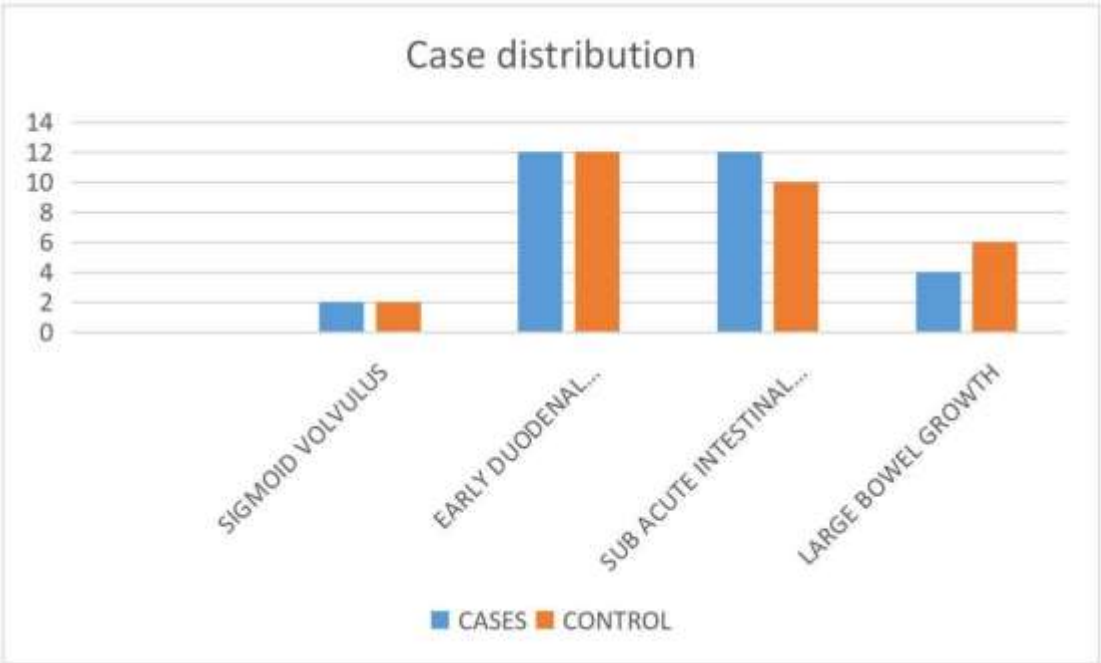
SEX	CASE	CONTROL
Male	18	23
Female	12	7
Total	30	30



CASE DISTRIBUTION

Among the cases admitted and underwent emergency laparotomy, most common case operated was early duodenal perforation.

DIAGNOSIS	CASES	CONTROL
SIGMOID VOLVULUS	2	2
EARLY DUODENAL PERFORATION	12	12
SUB ACUTE INTESTINAL OBSTRUCTION	12	10
LARGE BOWEL GROWTH	4	6
TOTAL	30	30



COMPLICATIONS

The case were followed up and the complications were recorded in both groups.

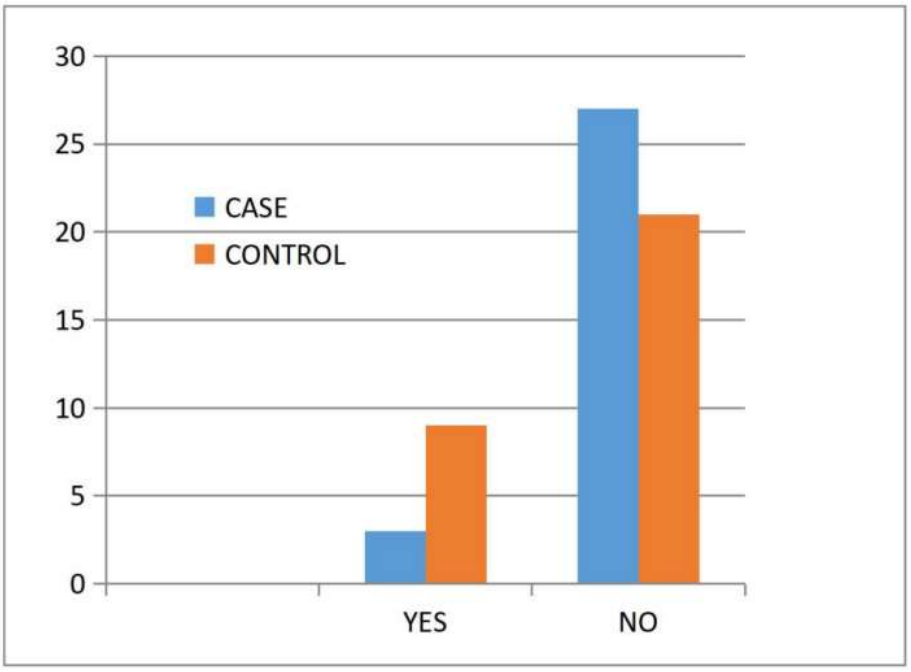
A. WOUND INFECTIONS

In case group 3 patients developed wound infection with discharge (2 case on POD 3 and one case on POD 5) of which 2 case developed wound gaping and needed secondary suturing

In control group 9 patients developed wound infection with discharge (3 case on POD 2 and 3 case on POD 3) Another 3 cases developed wound gaping and needed secondary suturing.

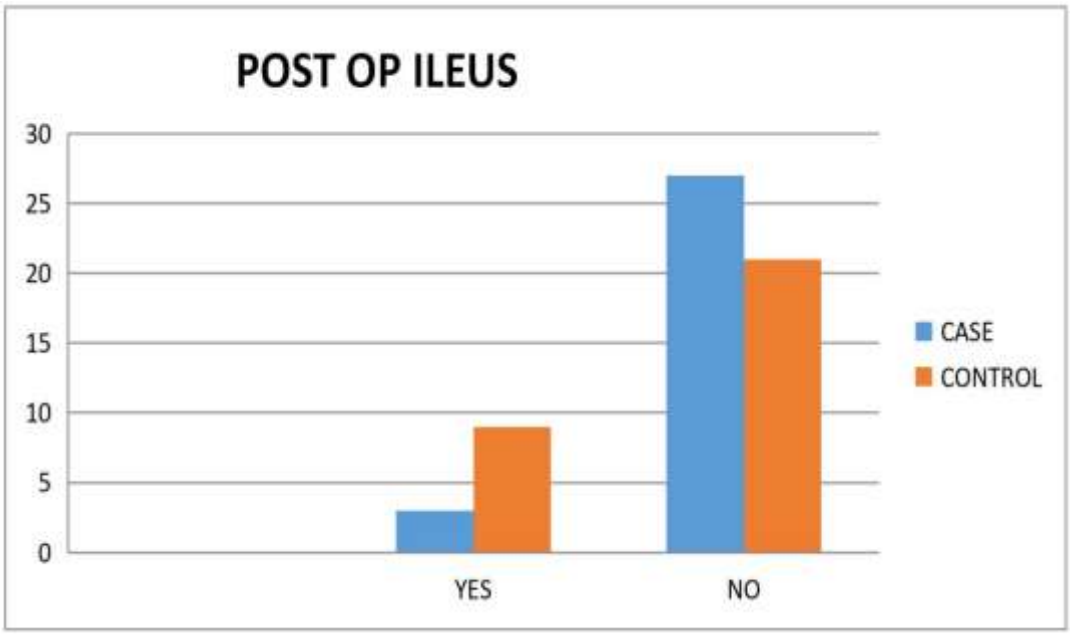
The rates of wound infections were significantly lower in the case group when compared to the control group ($p=0.0213$)

WOUND INFECTION	CASE	CONTROL
YES	3	9
NO	27	21
Total	30	30



B. POST OPERATIVE ILEUS

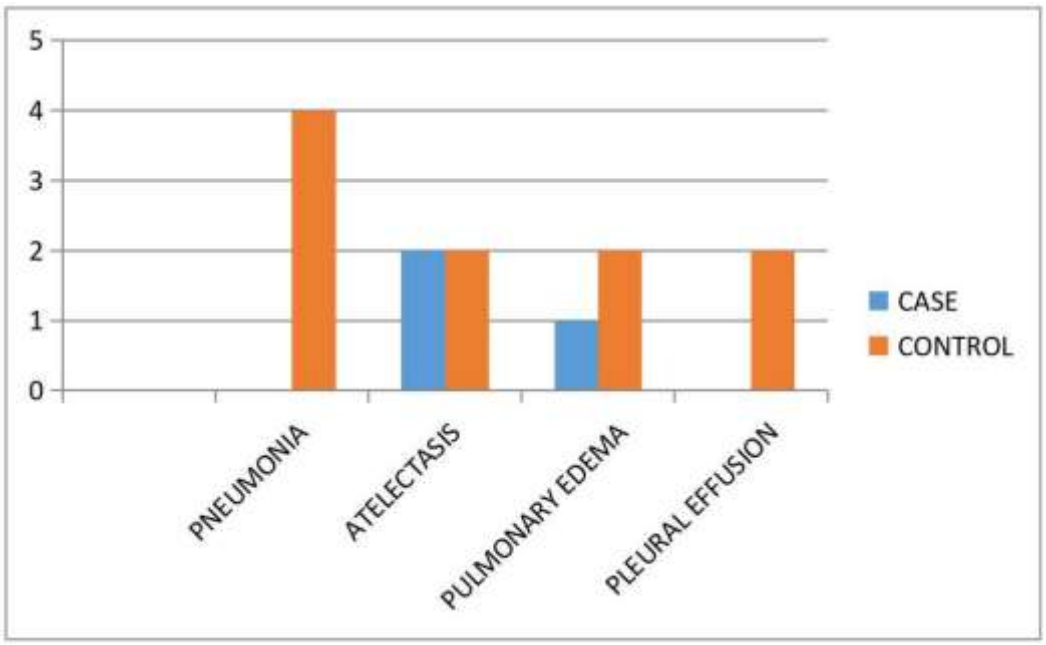
POST OP ILEUS	CASE	CONTROL
YES	3	9
NO	27	21
Total	30	30



The incidence of post operative ileus was significantly lower in the case group when compared to the control group (p=0.049)

C. PULMONARY COMPLICATIONS

PULMONARY COMPLICATION	CASE	CONTROL
PNEUMONIA	0	4
ATELECTASIS	2	2
PULMONARY EDEMA	1	2
PLEURAL EFFUSION	0	2
TOTAL	3	10

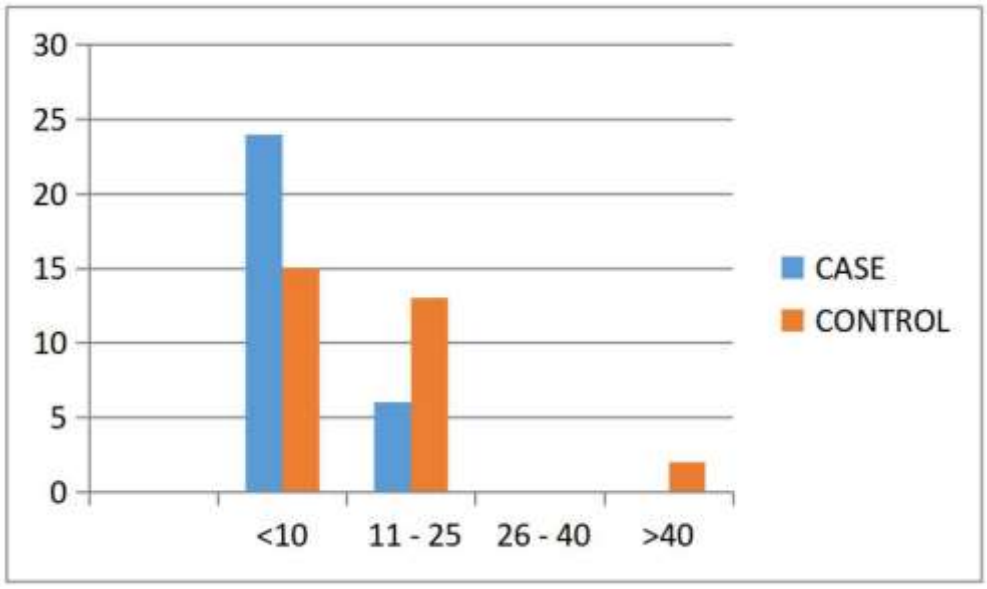


The pulmonary complications were **significantly lower** in the case group when compared to the control group (P= 0.028).

D. LENGTH OF HOSPITAL STAY (LOS)

The length of hospital stay is significantly lower in the case group as a result of significant reduction in the rate of complications like pulmonary complications, wound infections and post operative ileus. (p=0.014)

LOS	CASE	CONTROL
<10	24	15
11 - 25	6	13
26 - 40	0	0
>40	0	2
Total	30	30



Statistical analysis

Analysis was done using SOFTWARE- SPSS version 17. TEST applied : Chi square test

Control	case	P value	S/NS
Wound infection			
9/30	3/30	P=0.0213	S
Pulmonary complication			
10/30	3/30	P=0.028	S
Length of stay			
(<10 days) 15/30	24/30	P=0.047	S
(11-25days) 13/30	6/30	P=0.047	S
(26-40days) 0/30	0/30		
(>40days) 2/30	0/30	P=0.553	NS
Post op ileus			
(9/30 days)	3/30	P=0.04	S

DISCUSSION

In this study 60 patients (30 cases and 30 controls) who underwent emergency gastrointestinal surgeries in acute abdomen presenting within 24 hours were studied post operatively. In control group oral feeding was started according to the standard practice of

1. Appearance of bowel sounds

2. Ryles tube aspirate less than 150ml

In study group early entereal feeding was started within 48hours by oral or via ryles tube.

In our study, as we have seen the most common case operated was Early duodenal perforation. (40 %) in case and control group.

In case group wound infection was also significantly lesser (p=0.0213) which gives a results as same as that of study by *Moore et al Annals of surgery 1992;216:172-83*

Post operative ileus was significantly lesser (p=0.049) in patients who were given early enteral feeding which was consistent with the study by *N Kaur, MK Gupta, VR Minocha, World Journal of Surgery 2005:29:1023-7*

The follow up of the patients revealed that the rates of pulmonary compliations like pneumonia, atelectasis, pleural effusions was found to be significantly more in control group who were kept in starvation for around 6 days with parentral fluids only and with no immunomodulatory effects of nutrition.(p=0.028).

This finding was consistent with the study by *HS Lee, H Shim, JY Jhang, H Lee, JG Lee in the Yonsei Medical Journal July 11, 2013*

Compiling the results of the above complications the length of hospital stay among the case group was also significantly low. (p=0.014)

SUMMARY

- This is a prospective study conducted on cases who under went emergency gastro intestinal surgeries in Department of General Surgery, Madurai Medical College, Madurai.
- The most common case operated was early duodenal perforation
- A total of 60 cases were studied and the post operative outcome was documented and analysed
- The rates of complications (pulmonary complications(p=), wound infections(p=) and ileus(p=) () and length of hospital stay was found to be significantly lower in the Early enteral feeding group (p)

CONCLUSION

In this study we have documented and analysed cases patients undergoing emergency gastrointestinal surgeries and studied the outcome of early enteral feeding versus late enteral feeeding in such patients. The post-operative follow up and documentation of various complications in the post-operative period were noted and statistically analysed comparing the case and control group. In conclusion we infer that.

- Early enteral feeding is feasible in patients undergoing emergency gastrointestinal surgeries post operatively.
- The rates of complications like pulmonary complications, wound infections and ileus in post-operative patients is found to be significantly lower in the Early enteral feeding group
- The length of hospital stay in patients started on early enteral feeds were significantly lower.

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PROFORMA

Name : I.P. No : Age : Unit :

Sex : D.O.A :

Occupation : D.O.D :

Address :

Phone No : D.O. Surgery

CHIEF COMPLAINTS

1) Abdominal Pain :

2) Bleeding PR :

3) Constipation :

4) Tenesmus :

5) altered bowel habits :

6) Loss of Appetite :

7) Weight Loss :

8) Abdominal distension :

PAST HISTORY:

1) History of similar complaints

2) Treatment taken

3) History of Drug intake

4) History suggestive of Hypertension / Diabetes / Tuberculosis / heart disease / jaundice / thyroid disorder.

PERSONAL HISTORY

Diet : Vegetarian / Mixed

Habits : Smoking / Alcohol / Tobacco Bowel habits

Bladder Sleep

FAMILY HISTORY

Relevant / Not MENSTRUAL HISTORY

Amenorrhoea / menorrhagia

Regular / Not Duration

Associated / Not with pain L.M.P.

GENERAL PHYSICAL EXAMINATION

1. General survey
2. Body build and nourishment
3. Appearance
4. Attitude : Restless / Quiet
5. Dehydration : Mild/ Moderate / Severe / Nil
6. Anaemia / Jaundice / Clubbing Cyanosis / Lymphadenopathy / Pedal oedema.
7. Eye signs
8. Skin Changes
9. Pulse
10. Temperature
11. Respiratory rate
12. Blood pressure SYSTEMIC EXAMINATION

- Cardiovascular system
- Respiratory System
- Central nervous system
- Genito - urinary system
- Abdomen INVESTIGATIONS:-

1. Blood : Hb%
2. TLC
3. DLC
4. BT
5. CT
6. ESR
7. Blood group and rh type.
8. Urine : Albumin / Sugar / Microscopy
9. Blood : sugar / Urea / creatinine
10. ECG
11. USG abdomen and pelvis
12. CECT Abdomen/pelvis
13. Colonoscopy
14. HPE
15. HIV
16. HbsAg
17. Others DIAGNOSIS MANAGEMENT SURGICAL

Pre-operative instructions Type of Anaesthesia

Post - operative instructions

Post - operative period/Post - operative complication management

MASTER CHART

CASE										
SL.NO	**NAME**	**AGE**	**SEX**	**IP NO**	**DIAGNOSIS**	**PROCEDURE**	**PULMONARY COMPLICATION**	**LOS**	**WOUND INFECTION**	**POST OP ILEUS**
1	AZHAGUVALLI	59	FEMALE	5057	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	7	YES	-
2	KRISHNAN	47	MALE	98442	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	8	YES	-
3	KARUPAYEE	65	FEMALE	65352	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	8	YES	-
4	ALAGAMMAL	55	FEMALE	64116	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	12	YES	YES
5	ANDISAMY	47	MALE	17031	SUB ACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	-	7	-	-
6	ADAIKKALAM	65	MALE	159826	SIGMOID GROWTH	COLOSTOMY	-	15	YES	-

7	PERIYAVEETHI	59	FEMALE	60555	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	5	YES	-
8	PONNALAGU	80	FEMALE	1146084	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	9	-	-
9	NAGAMANI	53	FEMALE	1145965	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	8	-	-
10	SHANMUGAM	55	MALE	14998	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	9	YES	-
11	SASIREKHA	60	FEMALE	1142404	SUB ACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	-	5	YES	-
12	CHANDRASEKAR	68	MALE	55482	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	12	YES	-
13	KANNAN	61	MALE	12410	SIGMOID VOLVULUS	HARTMANNS PROCEDURE	-	14	YES	-
14	VALLIRAJA	62	MALE	1136881	SIGMOID GROWTH	COLOSTOMY	-	7	-	YES
15	MURUGAN	50	MALE	57533	SUB ACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	-	14	YES	-
16	SHANTHI	52	FEMALE	57298	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	5	-	-

17	VIJAYENDRAN	49	MALE	9915	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	8	YES	-
18	RAJU	62	MALE	123651	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	10	YES	-
19	PERIYAPANDI	52	MALE	112682	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	7	-	-
20	AMMALU	63	FEMALE	112682	SUB ACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	-	9	-	-
21	KANDASAMY	60	MALE	1127357	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	5	YES	-
22	KASIRAJAN	71	MALE	1127361	DESCENDING COLON GROWTH	COLOSTOMY	-	8	YES	YES
23	AMMALU	65	FEMALE	1120759	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	12	YES	-
24	RAMALAKSHMI	45	FEMALE	1124625	DESCENDING COLON GROWTH	COLOSTOMY	-	11	-	-
25	KANNAN	45	MALE	6328	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	7	-	-

26	AANDISAMY	78	MALE	56432	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	8	-	-
27	MUTHUIRULAN	57	MALE	1105627	SUB ACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	8	YES	-
28	MUTHUSAMY	76	MALE	1104723	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	10	YES	-
29	DOMINIC	64	MALE	1104284	SIGMOID VOLVULUS	HARTMANNS PROCEDURE	-	5	-	-
30	RAJAVALLI	52	FEMALE	109812	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	7	-	-

CONTROL										
SL. NO	**NAME**	**AGE**	**SEX**	**IP NO**	**DIAGNOSIS**	**PROCEDURE**	**PULMONARY COMPLICATION**	**LOS**	**WOUND COMPLICATION**	**POST OP ILEUS**
1	BALAJI	40	MALE	110098	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	8	YES	-
2	MARY	57	FEMALE	1093786	SIGMOID COLON GROWTH	COLOSTOMY	YES	6	YES	-
3	MAHARAJA	49	MALE	109510 8	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	12	YES	-
4	AMARAVATHY	78	FEMALE	1094769	SUBACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	YES	11	YES	-
5	SARASWATHI	70	FEMALE	1094763	DESCNDING COLON GROWTH	COLOSTOMY	YES	7	-	-
6	MALAISAMY	62	MALE	566	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	17	YES	-
7	KANNAN	50	MALE	1094	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	11	YES	YES
8	AYYAPPAN	49	MALE	2467	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	22	YES	-
9	CHINNARASSU	48	MALE	1291	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	13	YES	-
10	SELVAM	43	MALE	2681	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	7	-	-

11	THANGARAJ	42	MALE	1093167	SUBACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	YES	9	YES	-
12	MARIMUTHU	48	MALE	107684	SUBACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	YES	13	YES	-
13	THANGAVEL	53	MALE	1038412	SIGMOID COLON GROWTH	COLOSTOMY	-	6	-	-
14	SELVARAJ	60	MALE	1094	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	8	YES	YES
15	AYYAVOO	60	MALE	821	SIGMOID COLON GROWTH	COLOSTOMY	YES	44	YES	-
16	RASU	50	MALE	682	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	12	-	-
17	THANGAPANDI	35	MALE	1094572	SUBACUTE INTESTINAL OBSTRUCTION	ADHESIOLYSIS	YES	7	YES	-
18	PANDIAMMAL	60	FEMALE	29956	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	8	-	-
19	PONGODHAI	40	FEMALE	1286514	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	-	11	YES	-
20	SILAMBATHURAI	61	MALE	10099	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	19	YES	-
21	SATHAIYYAL	61	MALE	1093629	SIGMOID COLON GROWTH	COLOSTOMY	YES	11	YES	-

22	GANAPATHIRAJA	41	MALE	4821	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	12	YES	-
23	SUNDARAPANDI	54	MALE	685	SUBACUTE INTESTINAL OBSTRUCTION	PRIMARY CLOSURE	YES	7	YES	YES
24	GANESAN	48	MALE	271	DESCNDING COLON GROWTH	COLOSTOMY	YES	13	-	-
25	SUSHEELA	48	FEMALE	1093	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	11	YES	-
26	MANIKANDAN	49	MALE	402	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	-	9	YES	-
27	AANDISAMY	52	MALE	820	SUBACUTE INTESTINAL OBSTRUCTION	BAND RELEASE	YES	7	-	-
28	MARIYYAMMAL	41	FEMALE	1093112	SIGMOID VOLVULUS	HARTMANNS PROCEDURE	YES	6	YES	-
29	PALANIVELU	50	MALE	1093972	EARLY DUODENAL PERFORATION	PRIMARY CLOSURE	YES	7	YES	-
30	SHARATH KUMAR	42	MALE	1094259	SIGMOID VOLVULUS	HARTMANNS PROCEDURE	YES	7	-	-

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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Reman Rajendran
Course	:	PG in MS., General Surgery
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	"Early VS late enteral feeding in emergency gastrointestinal surgeries"
Ethical Committee as on	:	21.04.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary

Chairman

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
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CERTIFICATE – II

This is to certify that this dissertation work titled **PROSPECTIVE STUDY OF EARLY VS LATE ENTERAL FEEDING IN EMERGENCY GASTRO INTESTINAL SURGERIES** of the candidate **Dr REMAN RAJENDRAN** with registration Number **22151115** for the award of **MASTER DEGREE** in the branch of **GENERAL SURGERY.** I have personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **THREE** percentage of plagiarism in the dissertation.

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