NEOSTIGMINE INFUSION VERSUS SYRUP LACTULOSE FOR THE TREATMENT OF CONSTIPATION IN INTENSIVE CARE UNIT (ICU): A RANDOMIZED, CONTROLLED STUDY

By

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“In the name of Allah, the most gracious and the most merciful”.

My praise to Allah, for providing me the willingness and the strength to accomplish this work.

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LIST OF ABBREVIATIONS

ACPO	Acute Colonic Pseudo-Obstruction
BO	Bowel Opening
BSC	Bristol stool chart
CIRCI	Critical Illness Related Colonic Ileus
DRG	Dorsal Root Ganglia
ENS	Enteric Nervous System
GI	Gastrointestinal
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
iv	Intravenous
MMC	Migrating Motor complex
MP	Myenteric Plexus
MVA	Motor Vehicle Accident
nACHRs	Nicotinic Cholinergic Receptors
NG	Nodose Ganglia
NH3	Ammonia
NH4+	Ammonium ions
PSE	Portal Systemic Encephalopathy
SMP	Submucosal plexus
SOFA	Sequential Organ Failure Assessment

ABSTRAK

Pengenalan

Masalah sembelit dan implikasinya telah menerima perhatian yang sedikit walaupun gangguan peristalsis usus ini sering berlaku di kalangan pesakit kritikal . Sembelit ditakrifkan sebagai kegagalan peristalsis usus untuk membuang air besar selama 3 hari berturut-turut. Keadaan ini boleh menimbulkan beberapa kesan buruk kepada pesakit kritikal seperti pesakit yang sembelit lebih sukar untuk diberhentikan daripada bantuan pernafasan mekanikal , jangkamasa median tinggal di unit rawatan rapi lebih lama dan ketidak toleransi kepada makanan enteral adalah lebih tinggi daripada pesakit bukan sembelit**.**

Objektif

Untuk membandingkan pembukaan usus di kalangan para pesakit yang menerima infusi neostigmine berbanding sirap lactulose untuk rawatan sembelit di ICU.

Kaedah

Ini adalah kajian prospektif. Pesakit yang menerima bantuan pernafasan yang memenuhi kriteria kajian dan dimasukkan ke ICU HUSM antara bulan Februari hingga Oktober 2015 dipilih secara rawak untuk menerima sama ada infusi neostigmine 0.4-0.8 mg / jam atau sirap lactulose 15 mls TDS . Insiden pembukaan usus, masa untuk pembukaan usus pertama dan apa-apa kesan sampingan direkodkan.

Keputusan

Seramai 40 pesakit secara rawak dibahagikan kepada 2 kumpulan, infusi neostigmine dan sirup lactulose dengan 20 pesakit dalam setiap kumpulan. Kumpulan infusi neostigmine mempunyai pembukaan usus dengan ketara (p-value = 0.027) dan jauh lebih cepat (p -value <0.001) berbanding kumpulan sirap lactulose . Tiada perbezaan purata yang ketara dari segi jangkamasa bantuan pernafasan mekanikal di antara dua kumpulan terapi (p-value = 0.542). Tiada komplikasi yang berlaku daripada infusi neostigmine.

Kesimpulan

Infusi neostigmine adalah berkesan untuk rawatan sembelit di ICU berbanding dengan rawatan sirup lactulose. Rawatan intravena infusi neostigmine sehingga 0.8 mg / jam untuk pesakit kritikal dilihat sebagai selamat.

ABSTRACT

Introduction

Constipation and its implications have received very little attention even though this gastrointestinal motility disorders are common in critically ill patients. Constipation is defined as failure of the bowel to open for 3 consecutive days. This condition can give rise few adverse implications in critically ill patients such as more constipated patient failed to wean from mechanical ventilation, the median length of stay in intensive care increase and the proportion of enteral feeding intolerance were greater than non-constipated patients.

Objectives

To compare bowel opening between groups of patients who receive neostigmine infusion versus syrup lactulose for treatment of constipation in ICU.

Methodology

This is a prospective study. The ventilated patients who fulfilled the inclusion criteria and were admitted to HUSM ICU between February till October 2015 were randomly received either neostigmine infusions 0.4 – 0.8 mg/hour or syrup lactulose 15 mls TDS. Incidence of bowel opening, time to first bowel opening and any adverse reactions were recorded.

Results

40 patients were randomized where 20 patients in each group either neostigmine infusion or syrup lactulose. Neostigmine infusion group significantly had bowel opening (p-value=0.027) and markedly had faster onset of bowel opening (p-value<0.001) compared to syrup lactulose group. There was no significant mean different in term of length of mechanical ventilation between two group of therapy (p-value=0.542). No complications occurred from the neostigmine infusion.

Conclusion

Neostigmine infusion was effective for treatment of constipation in ICU compared than standard therapy syrup lactulose. Continuous intravenous neostigmine infusion of up to 0.8 mg / hour to critically ill patients appears to be safe.

CHAPTER 1: INTRODUCTION

1.1: Background

Gastrointestinal motility disturbances are one of the common problems among patients in intensive care unit. Usually dysmotility abnormalities such as gastric emptying and diarrhoea get more attention during daily treatment. These two problems are well studied and have a considerable impact in critically ill patient's prognoses. However constipation problem tend to be ignored and has received much less attention in clinical studies. Constipation among patient in intensive care unit supposedly needs to be well treated because this condition also has its own implications toward the patients. Therefore effectiveness in treating constipation is also important to avoid or reduce adverse condition that can arise from constipation problem.

Patients in ICU are a special group of patients which are their condition, nature of illness and treatment that they received, make them prone to get hypomotility disorder of gastrointestinal tract include constipation. In ICU, gastrointestinal motility can be altered by sedation, analgesics, anticholinergics, immobility, surgery, enteral feeding, head and spinal injuries, inflammation and sepsis (Nguyen et al., 2013).

There are various medications that been used to treat constipation. Common medications are syrup lactulose and bisocodyl (Hsieh, 2005). Still not commonly use in Intensive Care Unit (ICU), neostigmine also is one of the medication that can be used to treat constipation

(Schiller, 2001). Therefore, this study wants to know the comparison in term of effectiveness between standard therapy syrup lactulose and neostigmine infusion for treatment of constipation among patients in ICU.

This study was conducted at ICU Hospital Universiti Sains Malaysia (HUSM). There are three categories of ICU at HUSM; General ICU, Surgical ICU and Neuro ICU which consisted of 10 beds, 4 beds and 12 beds respectively. However most of the subjects were Neuro ICU patients in view of they fulfill the study criteria most of the time. Progressiveness of the study is maintained by getting helping from the trained medical officer in anaesthesia and intensive care unit department as well as trained ICU staffs.

1.2: Problem statements.

Problem statement 1:

Constipation among ICU patients is a common hypomotility gastrointestinal disorder that can give rise to few implications toward critically ill patients.

Problem statement 2:

Medication that can effectively treat constipation are needed to avoid or reduce implications that can rise from this problem. Therefore it is important to know which medication that can effectively treat constipation, either standard therapy – syrup lactulose or neostigmine infusion.

1.3: Research justification

Previous studies reports suggested that neostigmine infusion was more effective in treating constipation among critically ill patient in ICU as compared to syrup lactulose. This study is crucial in providing more evidence of such finding in Malaysia hospital setting. The knowlegde gained from this study will provide information to support evidence-based practices on neostigmine infusion usage in ICU.

CHAPTER 2: LITERATURE REVIEW

2.1 Pharmacology of neostigmine

2.1.1 Classification

Neostigmine is an anticholinesterase drug. It is a quaternary ammonium compound that possesses a strongly basic carbamyl group. Chemically, neostigmine bromide is 3-[(Dimethylcarbamoyl)oxy]-N,N,N trimethylanilinium bromide (Reilly et al., 2005).

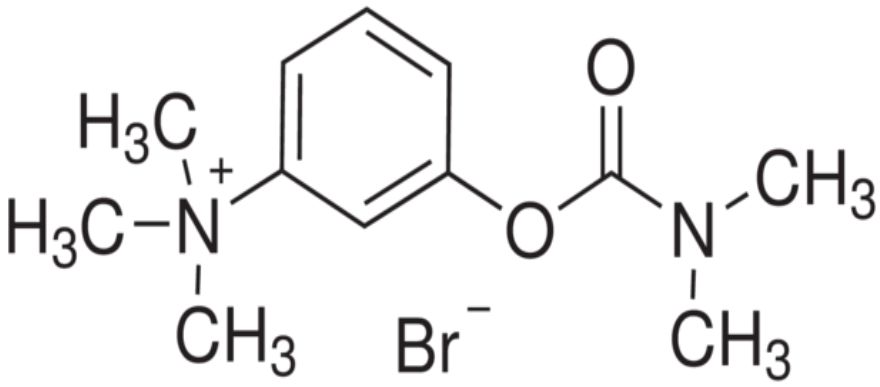

Figure 2.1 : Neostigmine structure (Reilly et al., 2005)

2.1.2 Mechanism of action.

Neostigmine inhibit the enzyme acetylcholinesterase (true cholinesterase), which usually responsible for the rapid hydrolysis of the neurotransmitter acetylcholine to choline and acetic acid (Reilly et al., 2005).

The acetylcholinesterase has two active sites, an anionic site and an esteratic site. Catalytic hydrolysis of acetylcholine occurs whereby the acetyl group is transferred to the esteratic site releasing a free choline molecule. Spontaneous hydrolysis of the enzyme follows and the acetylcholinesterase is reactivated (Nair et al., 2004).

Neostigmine creates reversible inhibition of acetylcholinesterase by formation of a carbamyl ester complex at the esteratic site of the enzyme. This inhibition leads to greater availability of acetylcholine at its sites of action, which include preganglionic sympathetic and parasympathetic nerve endings and the NMJ. Carbamate-enzyme bond must be dissociated for the carbamylated acetylcholinesterase hydrolyzes acetylcholine. Half-time for Carbamylated acetylcholinesterase is 15 to 30 minutes (Reilly et al., 2005).

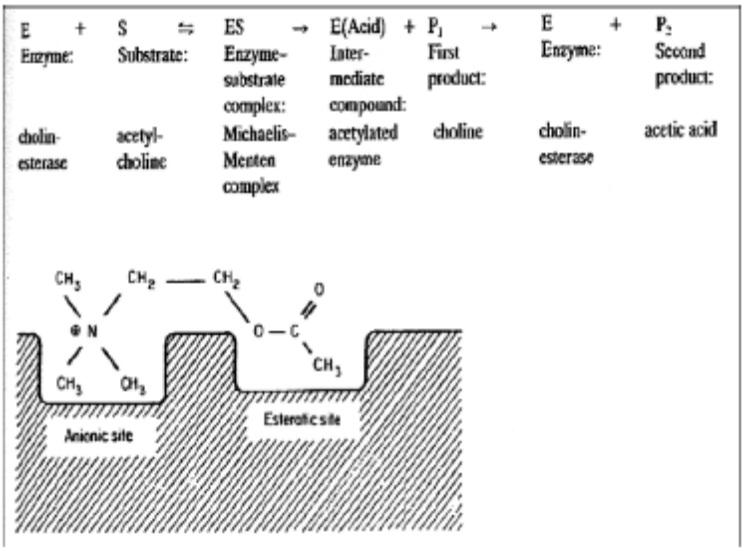

Figure. 2.2: Mechanism of acetylcholine hydrolysis by acetylcholinesterase. (Schematic diagram from Nair et al. 2004)

2.1.3 Uses

The standard clinical uses of neostigmine as an anticholinesterase drug are antagonist-assisted reversal of neuromuscular blockade produced by nondepolarizing neuromuscular-blocking drugs, treatment of the CNS effects produced by certain drugs, treatment of myasthenia gravis, treatment of glaucoma, treatment of paralytic ileus and treatment for atony of the urinary bladder. Intravenous dose is 0.05–0.07 mg kg^{-1}(Nair et al., 2004).

2.1.4 Pharmacokinetics

After a single bolus dose, the plasma concentrations of neostigmine reach a peak and decline rapidly during the first 5 to 10 minutes. The volume of distribution of neostigmine is in the range of 0.7 to 1.4 liters/kg, and the elimination half-times are 60 to 120 minutes.

The clearance of anticholinesterase drugs is in the range of 8 to 16 mL/kg per minute, which is much greater than glomerular filtration rate (Reilly et al., 2005).

Neostigmine comprising a quaternary ammonium group is poorly lipid soluble and thus do not easily penetrate lipid cell membrane barriers such as the gastrointestinal tract or blood brain barrier. This explained neostigmine is poorly absorbed orally and oral bioavailability 1-2% (Reilly et al., 2005).

This anticholinesterase drug is actively secreted into the lumens of the renal tubules. Approximately 50 % of the elimination of neostigmine is by renal clearance. As a result, the elimination half-time of neostigmine is greatly prolonged by renal failure. In the failure of renal function, hepatic metabolism accounts for 50 % of a dose of neostigmine. 3-hydroxyphenyltrimethylammonium is the principal metabolite for neostigmine. This metabolite has approximately one-tenth the antagonist activity of the parent compound (Reilly, 2015).

2.1.5 Pharmacodynamics

The pharmacologic effect of neostigmine as an anticholinesterase drug is expectable and reflects the accumulation of acetylcholine at muscarinic and nicotinic cholinergic receptors (nAChRs). Depending on the purpose for administration of anticholinesterase drugs, these effects may be considered therapeutic or undesirable (Reilly et al., 2005).

The cardiovascular effects of neostigmine reflect effects of accumulated acetylcholine at the heart (vagal effects), blood vessels, autonomic ganglia and postganglionic cholinergic nerve endings (Reilly et al., 2005).

Bradycardia and/or bradydysrhythmia for example nodal and ventricular escape beats may occur. Bradycardia most likely reflects slowing of the conduction of cardiac impulses through the atrioventricular node. These cardiac effects of anticholinesterase drugs can be

reduced by the administration of an anticholinergic drug that blocks muscarinic receptors but not nAChRs. Reductions in systemic blood pressure that may accompany accumulation of acetylcholine presumably reflect reductions in systemic vascular resistance, although the coronary and pulmonary circulations may manifest an opposite response (Reilly et al., 2005).

Neostigmine enhances gastric fluid secretion by parietal cells and increases the motility of the entire gastrointestinal tract, particularly the large intestine. The action of anticholinesterase drug on gastrointestinal motility is due to the effects of accumulated acetylcholine on the ganglion cells of Auerbach's plexus and on smooth muscle fibers. Neostigmine 0.5 to 1 mg given subcutaneously may be effective in the treatment of paralytic ileus or atony of the urinary bladder. This treatment, however should not be used when there is present of mechanical obstruction of the gastrointestinal tract. The lower portion of the esophagus is stimulated by anticholinesterase drug, resulting in beneficial increase in tone and peristalsis in patients with achalasia (Reilly et al., 2005).

As an anticholinesterase drug, neostigmine increases production of secretions of glands that are innervated by postganglionic cholinergic fibers. Such glands include the bronchial, lacrimal, sweat, salivary, gastric, intestine and acini pancreatic glands (Reilly et al., 2005)

Smooth muscle fibers of bronchioles and ureters also been contracted by anticholinesterase drug. Cholinergic stimulation of the bronchi resulting bronchoconstriction and anticholinesterase drug has the potential to increase airway resistance (Reilly et al., 2005).

Neostigmine if applied topically to the cornea can cause constriction of the sphincter of the iris (miosis) and ciliary muscle. Constriction of the ciliary muscle leads to inability to focus

for near vision. Interference with accommodation is normally shorter in duration than is miosis. Intraocular pressure decreases because the outflow of aqueous humor is facilitated (Reilly et al., 2005).

2.2 Pharmacology of syrup lactulose

2.2.1 Description

Syrup lactulose is a synthetic disaccharide which is in solution form for oral administration. 4-O-β-D galactopyranosyl-D- fructofuranose is a chemical name for lactulose.

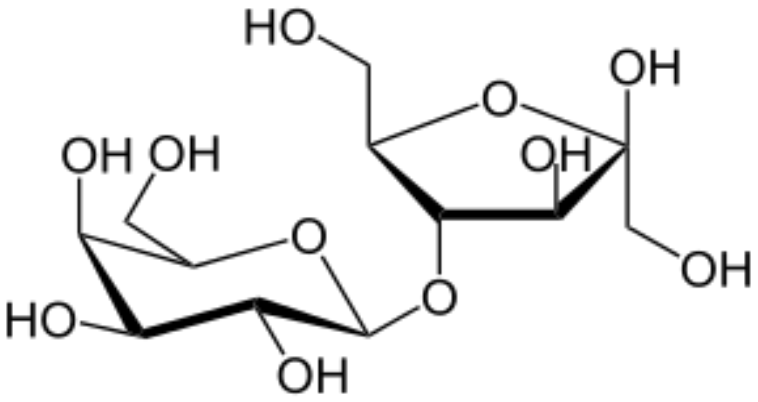

Figure 2.3: Syrup lactulose structure (Reilly et al., 2005).

Each 15 ml of lactulose solution contains 10 g lactulose (and less than 1.6g galactose, less than 1.2g lactose and 1.2g or less of other sugars). Recommended doses range from 10 – 20g per day (Reilly et al., 2005).

2.2.2 Uses

Lactulose is use for treatment of constipation. Number of bowel movements per day and the number of days on which bowel movements occurs increases with syrup lactulose therapy. Syrup lactulose also been use for ammonia detoxicant. It is used as an adjunct to protein restriction and supportive therapy for prevention and treatment of portal systemic encephalopathy (PSE) including hepatic pre-coma and coma (Reilly et al., 2005).

2.2.3 Pharmacodynamics and pharmacokinetics

No enzyme in human gastrointestinal tissue capable to hydrolyze disaccharide make the syrup lactulose is poorly absorbed from the gastrointestinal tract. Following oral administration, less than 3% absorbed from small bowel and negligible absorption from colon. Therefore, oral doses of syrup lactulose that reach the colon virtually unchanged. In the colon, colonic bacteria break down syrup lactulose primarily to lactic acid and also to small amount of formic and acetic acids. This result increase in osmotic pressure and slight acidification of the colonic content, subsequently increase in stool water content and softens the stool (Reilly et al., 2005).

Acidification of colon contents inhibits the nonionic diffusion of ammonia from the colon into the blood. Since colon contents are more acidic than is blood, ammonia can diffuse from the blood into the colon. In the acidic environment, ammonia (NH3) is converted to ammonium ions (NH4+) thereby preventing its absorption. Finally lactulose expels the

trapped ammonium ions and possibly other nitrogenous substances from the colon (Reilly et al., 2005).

Meanwhile, 24 to 48 hours may be required to produce the desired bowel movement. This is because syrup lactulose does not exert its effect until it reach the colon and transit time through colon maybe slow. The absorbed drug will be excreted in urine unchanged within 24 hours (Reilly et al., 2005).

2.2.4 Contraindications and precautions

Syrup lactulose is contraindicated in patients who require a low galactose diet since syrup lactulose contains galactose (less than 1.6g / 15 ml). For the same reason, diabetes mellitus patient also should use syrup lactulose with caution in view of has risk of hyperglycaemia (Reilly et al., 2005).

2.3 An overview of patients in Intensive Care Unit (ICU)

An Intensive Care Unit is a specific area in the hospital, specially staffed and equipped unit, where patients with life-threatening illnesses or disorders are monitored and treated. It is dedicated to the observation, care and treatment of patients with life threatening illnesses, injuries or complications from which recovery is generally possible. The patients in Intensive Care Unit can be classified either surgical or medical patients. The common causes of ICU admission from surgical discipline are perioperative stabilization, postoperative

weaning, hypovolemic shock, septic shock and trauma – head injury, chest and cervical spine injury (Geok et al., 2012).

The common causes of medical admission are septicaemic shock and acute respiratory failure requiring ventilator support. The patients with acute respiratory failure who were admitted to ICU require noninvasive or invasive mechanical ventilation.

The first ICU in Malaysia was established in 1968. Since then, intensive care has developed rapidly and ICUs are now available in all tertiary care hospitals and selected secondary care hospitals in the Ministry of Health. There are wide varieties of critically ill patients managed in ICU which can be categorized as operative and non-operative patients. SOFA score is a scoring system which provides an estimation of ICU mortality. The other scores used for prediction of in hospital mortality were APACHE score and SAPS II score.

2.4 Sequential Organ Failure Assessment (SOFA)

The Sequential Organ Failure Assessment (SOFA) score was introduced in 1994 is one of the model that been developed to quantify the severity of patients' illness based on the degree of organ dysfunction; serially over the time (Arts et al., 2005). SOFA; originally referred to as the "Sepsis – related Organ Failure Assessment Score" developed by a panel of expert from the European Society of Intensive Care Medicine, based on review of the literature (Cabré et al., 2005).

The SOFA score is graded from 0 (normal) to 4 (most abnormal) according to the degree of dysfunction / failure. This tool composed of scores from six organ systems. These organ systems are respiratory (PaO2 / FiO2), cardiovascular (blood pressure, vasoactive drugs), renal (creatinine), hematological (platelet count), neurological (Glasgow Coma Scale) and liver (bilirubin) (Cabré et al., 2005).

An initial SOFA score up to 9 predicted a mortality of less than 33%, while an initial SOFA score of greater than 11 predicted a mortality rate of 95%. Independent of the initial value, an increase in SOFA score during first 48 hours of ICU admission predicts a mortality rate of at least 50 % (Ferreira et al., 2001)

2.5 Normal gastrointestinal motility

The gut has not only the most extensive immune system in the body but also the largest collection of neurons (up to 108 cells) outside the central nervous system in order to maintain fluid, electrolyte, and energy homeostasis by the assimilation of food (Holzer et al., 2001)

This enteric nervous system (ENS) is located within the bowel wall, covering from the esophagus to the internal anal sphincter. It is well organized in such a way that it can operate independently of the brain. The neurons of the ENS are organized in two main plexuses (Figure 2.4).

The myenteric plexus which is mainly regulates motility located between the longitudinal and circular muscle layers. Meanwhile the submucous plexus which is located between the circular muscle and the mucosa is involved in the regulation of mucosal processes (electrolyte and fluid secretion, mucus secretion, mucosal blood flow and neuroimmune interactions) (Schemann et al., 1999).

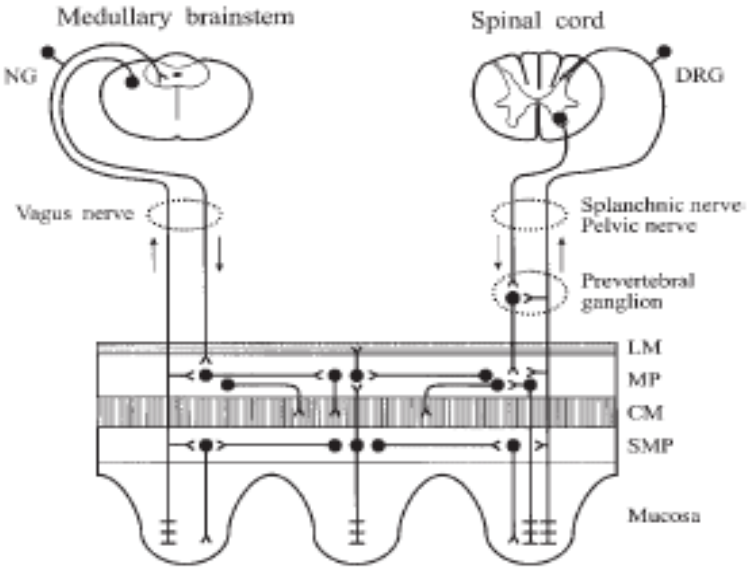

Figure 2.4:. Schematic diagram showing the multiple innervation of the gastrointestinal (GI) tract by intrinsic enteric neurons originating in the myenteric plexus (MP) and submucosal plexus (SMP), extrinsic sensory neurons originating from the nodose ganglia (NG; vagal afferents) and dorsal root ganglia (DRG; spinal afferents), and autonomic efferent neurons of the parasympathetic nervous system (vagus and pelvic nerves) and sympathetic nervous system (splanchnic nerves). (Schematic diagram from Holzer et al. 2001).(Holzer et al., 2001)

2.5.1 Oesophageal motility

The musculature of the oesophagus is consisting of skeletal muscle in the upper third, a mixture of skeletal and smooth muscle in the middle, and smooth muscle only in the lower third. It's given task is to transport the swallowed food into the stomach. The two (upper and lower) oesophageal sphincters will relax and open after swallowing the food (a voluntary act) while a peristaltic contraction propels the food bolus (Mittal and Bhalla, 2004). The sphincters close after the contraction has swept through the entire length of the oesophagus. Peristalsis in the upper skeletal muscle part of the oesophagus is the consequence of the sequential activation of neurons in the nucleus ambigus, one of the vagal motor nuclei. Peristalsis in the smooth muscle part of the esophagus is mediated at the level of the dorsomotor nucleus of the vagal nerve and at the level of the myenteric plexus (Mittal and Bhalla, 2004).

2.5.2 Gastric emptying

The fundus, the upper part of the stomach, is involved mainly in the accommodation of food. The underlying relaxation of the proximal gastric wall seems to be mediated by inhibitory vagal neurons. This is because the reflex is abolished in vagotomy patients. Digestible substances reached an essentially liquid form when they are emptied from the stomach (Minami and McCALLUM, 1984).

The antrum which is the distal part of the stomach, responsible for reducing solids form to the required fluid form. The antrum is also controlled by neuronal and humoral mechanisms. The rate of gastric emptying influences by the composition of the gastric contents. Neutral, isoosmolar, and calorically inert fluids empty fast.

Meanwhile hypertonic fluids containing acid, fat or certain amino acids delay gastric emptying (Minami and McCALLUM, 1984).

2.5.3 Gastrointestinal motility

Regarding the small bowel motility, it can be subdivided into interdigestive (fasting) and digestive (feeding) motility patterns (Fruhwald et al., 2007).

The interdigestive motility pattern, the migrating motor complex (MMC), starts several hours after a meal. It has passed through the stomach and small intestine, progresses to the distal ileum. It consists of three distinct phases that are repeated approx. every 2 h: phase I is a period of quiescence (45–60 min), phase II a period of irregular contractions with a duration of 30–45 min, and phase III a period of regular, propulsive activity that lasts 5–15 min (Fruhwald et al., 2007). However, the duration of these MMC periods demonstrates enormous inter and intraindividual variability. Now all three phases of interdigestive motility are referred to as the MMC where previously only the phase III was subsumed under this term.

A new one MMC begins in the stomach, by the time one ends in the ileum. A typical MMC pattern is important for the purging of the small bowel. Remaining food particles and indigestible residues are swept to the distal part of the small bowel and into the colon during phase III. An undisturbed MMC also important play a role in protection against bacterial overgrowth of remaining food particles in the small bowel (Fruhwald et al., 2007). The MMC is controlled by the ENS and modulated by regulatory peptides. Disconnection of the extrinsic nerve supply does not interrupt the MMC pattern (Sana, 1985). Motilin is one of the MMC-regulating peptides. Intravenous administration of motilin or the motilin receptor

agonist erythromycin initiates phase III activity in the antroduodenal region. Meanwhile somatostatin and other substances can initiate phase III activity in the duodenum (Husebye, 1999). An absence of the MMC indicates severe enteric dysfunction, while the presence of the MMC is thought to predict a successful outcome of enteral feeding (Schippers et al., 1991).

Interdigestive motility pattern disrupted by meal ingestion and replaces it with accommodation, stationary motility (segmental contractions and pendular movements) and propulsive peristalsis (Holzer et al., 2001). Accommodation denotes to an active relaxation of the fundus in response to food intake. Accommodation is also present in the small bowel and colon. Filling of the bowel initiates a descending inhibitory reflex pathway (Costa et al., 2000). Stationary contractions mix the food with the secretions of the gut and subsequently improve its contact with the mucosa of the small intestine to allow absorption of luminal contents. These stationary contractions are due to pendular movements of the longitudinal muscle and segmental contractions of the circular muscle (Fruhwald et al., 2007). Their rhythm derives from the interstitial cells of Cajal. These cells are innervated by excitatory and inhibitory motor neurons Therefor important as transducers of the ENS output to the musculature (Huizinga et al., 2000). Their oscillating membrane potential, transmitted electrically to the adjacent smooth muscle layers then initiates slow waves with a frequency of 10/min. These slow waves determine the frequency of the muscular contractions.

Distortion of the mucosal villi or distension of the gut wall initiates propulsive peristalsis. These propulsive peristalsis involves a contraction of the circular muscle orally and relaxation aborally of the site of the stimulus (Fruhwald et al., 2007). The propulsive peristaltic wave moves only a few centimeters in order to forward the chyme, but not as far

as phase III of the MMC in the interdigestive motility pattern. The digestive pattern is lasting for several hours after ingestion of a meal. The duration seems to depend primarily on the caloric load of the food: the higher the caloric load, the longer the duration is (Ouyang et al., 1989).

2.6: Classification of constipation

Constipation can be divided into primary and secondary causes.

2.6.1: Primary constipation

Primary constipation can be classified into three groups: normal transit constipation, slow transit constipation, and anorectal dysfunction. Normal transit constipation is the most common, also known as functional constipation (Rao, 2009).

Stool passes through the colon at a normal rate in patients with functional constipation. Second type of constipation - slow transit constipation is characterized by prolonged delay in the passage of stool through the colon (Rao, 2009). Patients may complain of abdominal bloating and infrequent bowel movements (Koch et al., 1997). The causes for slow transit constipation are unclear; therefore the postulation mechanisms include abnormalities of the myenteric plexus, defective cholinergic innervation, and anomalies of the noradrenergic neuromuscular transmission system (Rao, 2009). Anorectal dysfunction is the inefficient coordination of the pelvic musculature in the evacuation mechanism (Rao et al., 1998). These patients are more likely to complain of a feeling of incomplete evacuation, a sense of obstruction, or a need for digital manipulation.

2.6.2: Secondary constipation

Table 1 : Lists medical and psychiatric conditions that are potential causes of secondary constipation (Hsieh, 2005).

Causes of Secondary Constipation	
Endocrine and metabolic diseases	Myopathic conditions
Diabetes mellitus	Amyloidosis
Hypercalcaemia	Myotonic dystrophy
Hyperparathyroidism	Scleroderma
Hypothyroidism	
Uraemia	
Structural abnormalities	Neurologic diseases
Anal fissures, strictures,	Autonomic neuropathy
haemorrhoids	Cerebrovascular disease
Colonic strictures	Hirschsprung's disease
Inflammatory bowel disease	Multiple sclerosis
Obstructive colonic mass lesions	Parkinson's disease
Rectal prolapse or rectocele	Spinal cord injury, tumors
Psychological conditions	Other
Anxiety	Irritable bowel syndrome
Depression	Pregnancy
Somatization	

A thorough history and physical examination may exclude these conditions. A consensus guideline from the American Gastroenterological Association (AGA) also recommends that most patients have tests for a complete blood count and serum glucose, thyroid stimulating hormone, calcium, and creatinine levels. A sigmoidoscopy or colonoscopy to exclude colon cancer is indicated in patients older than 50 years who have not had a recent examination and in those with concomitant rectal bleeding or weight loss (Locke et al., 2000). The use of medications, especially those that affect the central nervous system, nerve conduction, and smooth muscle function are the important secondary causes of constipation. The most common medicines associated with constipation are listed in Table 2 (Prather and Ortiz-Camacho, 1998).

Table 2: Medications commonly associated with secondary constipation (Prather and Ortiz-Camacho,1998)

Medications commonly associated with secondary constipation	
Anticholinergics	Clonidine (Catapres)
Antidepressants	Diuretics
Antihistamines	Iron
Calcium channel blockers	Levodopa (Larodopa)
Opioids	Narcotics
Psychotropics	Nonsteroidal anti-inflammatory drugs
Sympathomimetics	

2.7 Constipation in Intensive Care Unit

2.7.1 Definition

Constipation was defined as 'failure of the bowel to open for three consecutive days'(Mostafa et al., 2003), (Dorman et al., 2004).

This definition been used because it may be the most sensitive (Nassar Jr et al., 2009).

A 'normal' bowel function varies considerably. It is defined as 'the maintenance of the patients usual bowel habit; the easy passage of (normally soft) stool, as frequently as is usual for the individual (Shepherd, 2000). However, Powell and Rigby et al state that normal bowel function should be at least twice per week (Powell and Rigby, 2000). Action should be taken if the patient has not had their bowels opened in the last 3 days as constipation been occurred. A 3 days time frame permits for stabilization of the patient and the establishment of enteral feed (Dorman et al., 2004).

2.7.2 Incidence and risk factors

Constipation has received very little attention even though gastrointestinal motility disorders are common in critically ill patients. Incidence of constipation in ICU setting is variable, ranging from 50% to 83%.

Patanwala studied 50% of patient did not have a bowel movement during the first 96 hours of medical ICU admission (Patanwala et al., 2006). Meanwhile Nassar Jr presented that constipation occurred in 69.9% of the patients (Nassar et al., 2009).

Mostafa showed the higher result for incidence of constipation in critical care, which was 83% (Mostafa et al., 2003). The difference in term of incidence percentage most likely due to the sensitiveness of the chosen criteria.

Criteria that been used to look for incidence of constipation in intensive care are; all patients admitted to the ICU and who stayed for 3 or more days in ICU. This criterion because the previous study that addressed constipation in ICU setting defined constipation as a "failure of bowel to function for 3 consecutive days" (Mostafa et al., 2003). Patients were excluded if they did not stay in ICU for 3 or more days because of rapid recovery or death. Bowel surgery patients were also excluded (Nassar Jr et al., 2009).

There are many elements that may contribute to constipation in critically ill patients. Present of shock causes splanchnic hypoperfusion, which is associated with impaired gastrointestinal motility. More common condition which is electrolyte disturbances, mainly hypokalemia and hypomagnesemia, are also associated with decreased in intestinal motility. Meanwhile Chappell and colleague revealed that major contributing factors on constipation in the intensive care unit are parenteral nutrition, mechanical ventilation, hypoperfusion, shock, dehydration, secretion of inflammatory mediators as well as endogenous and exogenous opioids (Chappell et al., 2008)

Opioid-induced bowel dysfunction includes delayed gastric emptying accompanied by increased gastroesophageal reflux, as well as constipation (Thomas, 2008). Opioid such as fentanyl and morphine are the commonest prescribed analgesics in ICU. These opioids can inhibit intestinal motility and at the same time have a venodilator property. The venodilator

property can decrease venous return and, maybe, impair perfusion to a great level subsequently lead to constipation. (Fruhwald et al., 2007).

Meanwhile, immobility, lack of fibre in diet, dehydration and factors such as lack of access to appropriate facilities can also lead to constipation. In addition, in ICU critically ill patients cannot mobilize to the toilet, response to the urge or strain to defecate (Mostafa et al., 2003).

Martindale and Maerz et al had done the study which first to demonstrate that the early beginning of enteral nutrition is associated with a decreased incidence of constipation. Enteral nutrition demonstrated that better preserves the gastrointestinal mucosal structure and function based on experimental and clinical studies (Martindale and Maerz, 2006). Apart from that, defecation also may be seen as a sign of maintenance of gastrointestinal function. This is because there is a tendency to face impaired gastrointestinal motility as a manifestation of multiple organ dysfunctions. Therefore early enteral nutrition may be seen as a protective factor.

Other than that, antibiotic therapy was not associated with either increase or decrease in incidence of constipation (Nassar Jr et al., 2009).

2.7.3: Implication in the critically ill patient

Observational studies done by Nassar and colleague had found a correlation between constipation, organ dysfunction, prolonged length of stay and failure to wean from mechanical ventilation, although results diverge among studies (Nassar Jr et al., 2009). Mostafa et al said constipation can give rise few implications in patients such as more