A Randomized Trial Comparing Empirical and Guided Therapy for Unexplained Non-Cardiac Chest pain

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List of abbreviations

BMI	Body mass index
FDA	Food and Drugs Administration
GERD	Gastroesophageal Reflux Disease
GERDQ	Gastroesophageal Reflux Disease Questionnaire
HRM	High Resolution Manometry
LES	Lower Esophageal Sphincter
NCCP	Non Cardiac Chest Pain
OTC	Over the Counter
PPI	Proton Pump Inhibitor
QOLRAD	Quality of Life Reflux and Dyspepsia
RM-ANOVA	Repeated measures analysis of variance
USM	Universiti Sains Malaysia
VAS	Visual Analogue Scale

ABSTRACT ~~IN ENGLISH~~

Background Non-cardiac chest pain (NCCP) is prevalent in Malaysia with almost two-thirds a result of gastroesophageal reflux disease. Treatment approach to NCCP is currently unclear. We aimed to determine if therapy guided by results of 24-hour pH-impedance test would be better than empirical trial of PPI.

Methods Consecutive participants with chest pain and normal angiogram or negative stress test were consented. Participants were randomized into guided group or empirical group. In guided group, all underwent 24-hour pH-impedance test (Sandhills, US) and if GERD then eight weeks of Dexlansoprazole 30mg OD but if functional chest pain or reflux hypersensitivity then four weeks of Theophylline SR 250mg OD were prescribed. In empirical group, two weeks of Dexlansoprazole 60mg OD were prescribed. Visual analog scale assessment (VAS) of chest pain, Gastroesophageal Reflux Disease Questionnaire (GERD Q), and Quality Of Life in Reflux And Dyspepsia (QOLRAD) questionnaire were evaluated during each visits at weeks 0, 2 and 8. Differences between visits were analyzed with Repeated Measures ANOVA.

Results Of 200 screened patients, 145 did not meet inclusion criteria, and 55 randomized (26 empirical and 29 guided). A further 9 withdrew (5 empirical and 4 guided). No participants experienced serious adverse events. With RM-ANOVA, the results demonstrated that guided therapy did better than empirical therapy in mean VAS at week 2 vs. 0 and at week 8 vs. 0. The mean values of guided group were outside the confidence intervals of empirical group.

Therefore, the mean VAS were significantly different. The results also demonstrated significant improvement of mean QOLRAD at week 8 vs. 0 in the guided therapy with p value=0.007, MD (95%CI) -3.2(-5.7,-0.8).However, no significant improvement in GERD Q were observed.In within-group analysis, mean QOLRAD was significantly better at week 8 vs. 0 (*P*=0.007) for guided group and for empirical group, mean QOLRAD was better at week 2 vs. 0 (*P*=0.004) and week 8 vs. 0 (*P*=0.01). On the other hand, mean GERDQ was better at week 8 vs. 0 (*P*=0.02) for empirical group only. We also observed that duration of treatment was the factor associated in the improvement of VAS in guided group. A duration of one week treatment would result in reduction of VAS scores by 0.7 points (95% CI -1.2, -0.2; p=0.007).

Conclusion In this analysis, guided therapy ~~seems~~ better than PPI trial in relieving chest pain symptom of NCCP patients. Both therapies improved QOL but those with GERD symptoms are better with PPI trial.

ABSTRAKCT IN MALAY

Latar belakang kajian: Sakit dada bukan berpunca jantung di Malaysia lazimnya dua per tiga berpunca daripada penyakit refluks gastroesofagus.Perawatan untuk sakit dada bukan berpunca jantung buat masa ini masih kurang jelas.Kajian ini bertujuaan membandingkan jika perawatan berpanduan berdasarkan keputusan ujian 24 jam PH impedance lebih baik daripada perawatan empirical dengan percubaan PPI.

Metodologi: Penyertaan adalah daripada pesakit yang mempunyai sakit dada tetapi keputusan angiogram normal atau ujian tekanan larian jantung negative yang bersetuju.Peserta dirawakan kepada dua kumpulan iaitu perawatan berpanduan dan perawatan empirical.Di dalam kumpulan perawatan berpanduan,kesemua peserta melalui ujian 24 jam PH impedance (Sandhills, US).Berdasarkan keputusan ujian ini,jika sakit dada bukan berpunca jantung adalah disebabkan oleh penyakit refluks gastroesofagus,Tablet Dexlansoprazole 30 mg sekali sehari dipreskripsi untuk tempoh 8 minggu.Manakala jika ia berpunca daripada penyakit refluks esofagus hipersensitif, tablet Theophylline SR 250 mg sehari sekali dipreskripsi untuk tempoh 4 minggu.Untuk peserta didalam kumpulan perawatan empirical,tablet Dexlansoprazole 60 mg sehari sekali dipreskripsi untuk tempoh 2 minggu.Seterusnya, skor tahap kesakitan sakit dada (VAS), soalselidik penyakit refluks gastroesofagus (GERD Q) dan soalselidik kualiti hidup pesakit refluks dan dispepsia (QOLRAD) dinilai pada setiap lawatan pada minggu 0, 2 dan 8.Perbezaan disetiap lawatan dianalisa menggunakan “Repeated Measures ANOVA”.

Keputusan: 200 pesakit sakit dada bukan berpunca jantung dinilai.145 tidak memenuhi kriteria.55 peserta memenuhi kriteria dan dirawakan kepada dua kumpulan iaitu 26 didalam kumpulan perawatan empirikan dan 29 didalam kumpulan perawatan berpanduan.Seterusnya 5 peserta daripada perawatan empirikal dan 4 peserta daripada perawatan berpanduan digugurkan daripada kajian.Tiada peserta mengalami komplikasi akut didalam kajian ini.Dengan RM-ANOVA,keputusan menunjukkan perawatan berpanduan mempunyai tindakbalas yang lebih baik berbanding perawatan empirical didalam purata VAS pada minggu ke 2 berbanding minggu 0 dan pada minggu 8 berbanding minggu 0.Keputusan juga menunjukkan purata kemajuan didalam QOLRAD pada minggu ke 8 berbanding minggu 0 (p =0.007, MD (95%CI) -3.2(-5.7,-0.8) didalam kumpulan perawatan berpanduan.Walaubagaimanapun,tiada purata kemajuan dilihat untuk soalselidik GERD Q.Analisa didalam kumpulan berpanduan menunjukan purata QOLRAD lebih baik pada minggu ke 8 berbanding minggu 0 (p=0.007).Manakala didalam kumpulan perawatan empirical purata QOLRAD dilihat lebih baik pada minggu ke 2 berbanding 0(p=0.004) dan pada minggu ke 8 berbanding minggu 0 (p=0.01).Untuk analisa didalam kumpulan, purata GERD Q hanya dilihat lebih baik di dalam kumpulan perawatan empirical pada minggu ke 8 berbanding minggu 0(p=0.02).Tempoh rawatan juga dilihat memainkan peranan dalam kesembuhan sakit dada didalam kumpulan perawatan berpanduan.Penambahan sebanyak seminggu tempoh rawatan,membolehkan pengurangan skor VAS sebanyak 0.7%(95% CI -1.2, -0.2; p=0.007).

Kesimpulan: Di dalam analisa ini,perawatan berpanduan dilihat lebih baik berbanding percubaan PPI dalam mengurangkan simptom sakit dada pesakit sakit dada bukan berpunca

jantung(NCCP).Kedua-dua rawatan meningkatkan kualiti hidup pesakit,tetapi simptom refluks dilihat lebih baik didalam kumpulan percubaan PPI.

CHAPTER 1:

INTRODUCTION AND LITERATURE REVIEW

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 BACKGROUND OF STUDY AND LITERATURE REVIEW

Non-cardiac chest pain (NCCP) is very common in the general population but symptom alone or patient's characteristics do not adequately differentiate cardiac and esophageal causes [1]. Cardiologists are usually consulted first to exclude life-threatening acute coronary syndrome. Tests that are performed to exclude ischemic heart disease include exercise stress test and the more invasive coronary angiography. A negative stress test or angiogram or the presence of mild blockage of a single vessel disease will usually be adequate to exclude significant ischemia as a cause for chest pain.

The next most important cause of unexplained chest pain would be gastro-esophageal reflux disease (GERD). GERD and its complications of Barrett's oesophagus and oesophageal adenocarcinoma have increased markedly in recent decades, not just in the developed countries but also in Asia [2]. Although relatively less common among populations in Malaysia [3], there are data to suggest an increasing prevalence of reflux disease largely a result of obesity and increased intra-abdominal pressure [4,5].

Numerous studies have shown the association between NCCP and GERD. There is approximately 37 to 61.5% of patients with NCCP have experienced GERD symptoms [6–8].Likewise, half of patients with NCCP have abnormal ambulatory 24-hour pH studies [9,10].Only one study from Asia has shown that 34.3% of patients with NCCP have at least 1 abnormal pH parameter [11].

Functional chest pain due to esophageal hypersensitivity is the next common cause for unexplained NCCP [12, 13]. Only a minority of patients with NCCP have esophageal dysmotility disorders that include nutcracker esophagus, diffuse esophageal spasm and achalasia [1].

It is unknown what would be the next recommended approach once cardiac causes of chest pain are excluded. A proton-pump inhibitor (PPI) test may be tried and has been found to be effective in 60 to 90% of patients [14–16]. The wide range in response may be attributed to heterogeneity of study population and differences in the dose and types of PPI used. Cytochrome CYP2C19 polymorphisms may affect metabolism of PPI and those who are "poor metabolizers" particularly among Asians may experience more adverse effects. However among the Malays poor metabolizers are reported in only 5.6% compared to 19.1% among the Chinese [17].

Dexlansoprazole (Takeda Pharmaceuticals, Japan) is a novel dual delayed release system recently approved by the FDA for treatment of heartburn associated with non-erosive and erosive reflux disease [18]. It is unknown if dexlansoprazole is effective as an empirical therapy for NCCP.

Another approach would be therapy guided by investigations including high resolution (HR) esophageal impedance manometry and 24-hour pH-impedance studies. Study of esophageal function has greatly evolved with the recent availability of high resolution multi-channel solid state manometer and impedance [19]. Water swallows are commonly used in esophageal manometric studies to evaluate for peristaltic abnormalities. Esophageal pH monitoring does not detect all gastroesophageal reflux (GER) events but with the combination of impedance, this technique allows detection of GER of gas and acid or non-acid liquids [20]. These tests would enable diagnosis of GERD and functional chest pain and thereby allow targeted therapy.

For treatment of GERD, dexlansoprazole is effective [21] and for functional chest pain, nonspecific adenosine antagonist, theophylline is proven to improve symptoms in patient with hypersensitive esophagus [22]. A selective serotonin reuptake inhibitor (SSRI) is also effective for functional chest pain [23], however it is not known if theophylline is more effective than any other SSRIs.It is unknown about the response rates based on the guided therapy approach compared to the empirical PPI therapy and therefore this forms the basis for this study.

1.2 DEFINITION AND EPIDEMIOLOGY OF NON CARDIAC CHEST PAIN

Non cardiac chest pain is defined as recurrent chest pain is indistinguishable from ischemic heart pain after a reasonable workup has excluded a cardiac cause. (Fass & Achem, J Neurogastroenterol Motil 2011; 17:110-123).

It is significantly resulting in high healthcare utilization and significant work absenteeism. However, despite its chronic nature, non-cardiac chest pain has no impact on patients' mortality.

The main underlying mechanisms include gastroesophageal reflux, esophageal dysmotility and esophageal hypersensitivity.

NCCP is common in Asia but information about the epidemiology of NCCP in the Asia and around the world is relatively limited. The mean annual prevalence of NCCP in 6 population based studies was approximately 25%. However, these studies differ in many aspects such as NCCP definition, geography, sample size, sampling order and ethnic disparities.

In the United States assessed the prevalence of GERD in Olmsted County, Minnesota and reported an overall NCCP prevalence of 23%. Gender distribution among NCCP patients was similar (24% among males and 22% among females).

A nationwide population-based study from South America found that the annual prevalence of NCCP was 23.5% and that NCCP has been equally reported by both sexes.

Another epidemiologic study demonstrated that the annual prevalence of NCCP in a Chinese population was 19%.In Asia population reported that 66.7% of NCCP prevalence is due to gastroesphageal reflux (Hanizam Mohd, 2008).

NCCP patient in comparison with cardiac origin chest pain patient are more younger in view of they are consume greater amount of alcohol, smoke more often, and more likely suffer from anxiety which attribute to NCCP.

These prove by several studies which shown a decrease in the prevalence of NCCP with increasing age (Chiocca JC,Olmos JA,2005).

1.3 PATHOPHYSIOLOGY AND MECHANISM OF NON CARDIAC CHEST PAIN

Pathophysiology of non-cardiac chest pain is remains to be fully unclear. It may be attributed to multiple gastrointestinal, musculoskeletal, pulmonary and psychological causes (Leise et al., 2010). Esophageal disorders can also be the etiology of chest pain (Lemme, Moraes-Filho,Domingues, Firman, & Pantoja, 2000). Gastroesophageal reflux disease (GERD) is the main underlying mechanism of NCCP, accounting for up to 60 % of cases (Leise et al., 2010). NCCP can also be caused by esophageal motor dysfunction; and the frequency may be underestimated. Motor disorders are observed in almost 50% of patients with NCCP who ultimately undergo conventional manometry evaluation (Gambitta et al., 1999).

The close anatomical relationship between the esophagus and the heart contributes to the similarity in symptoms and the difficulty in distinguishing the origin of chest pain (Figure1).

The esophagus is located posterior to the heart and is separated from the left atrium by the pericardium. Both the heart and the esophagus share the same common path of pain fibers from the sympathetic trunk (Heatley, Rose & Weston, 2005).

Esophageal pain has many patterns. Patients usually describe it as burning, gripping, stabbing, and pressing in the anterior chest. The pain is also usually in the throat or epigastrium and sometimes radiates to the neck, back or upper arms. These symptoms may also apply to cardiac pain (Bennett, 2001).

The specific mechanisms for esophageal-induced NCCP are poorly understood (Fang & Bjorkman, 2001).The potential for an esophageal etiology for recurring NCCP was originally hypothesized by William Osler in 1892 (Castell, Talley, & Travis, 2010).

For GERD, it is widely understood that the characteristic pain is burning epigastric, and related to recent food intake, lying down or bending (Bennett, 2001).Pain as a result of esophageal spasms is retrosternal, deep and often labeled as burning, squeezing or aching, usually radiating to the arms, jaw, and back (Heatley, Rose & Weston,2004).

However, a few possible mechanisms have been identified and include: irritant stimuli to the esophageal mucosa, mechanical effects on the muscular wall, and visceral hypersensitivity (Castell et al., 2010).

1.3a: Mucosal stimulation.

Chest pain arises from esophageal mucosal irritation by acid exposure. This causes discomfort in most patients. It usually resolves when acid perfusion ceases (Bennett, 2001).

1.3b: Mechanical changes.

Alterations in esophageal motility can be a cause of chest pain. This includes achalasia (absent distal peristalsis or abnormal relaxation of the LES), diffuse esophageal spasm (DES) (simultaneous contractions or intermittent peristalsis), nutcracker esophagus (increased contraction amplitude of over 180 mm Hg with normal peristalsis), hypotensive LES, and ineffective esophageal motility (contractions of low amplitude or failed and non-transmitted) (Bennett, 2001).

1.3c: Visceral hypersensitivity

Chest pain caused by alterations in visceral receptor sensitivity; the prevalence is higher in patients with anxiety, depression, somatization, and neuroticism (Bennett, 2001).

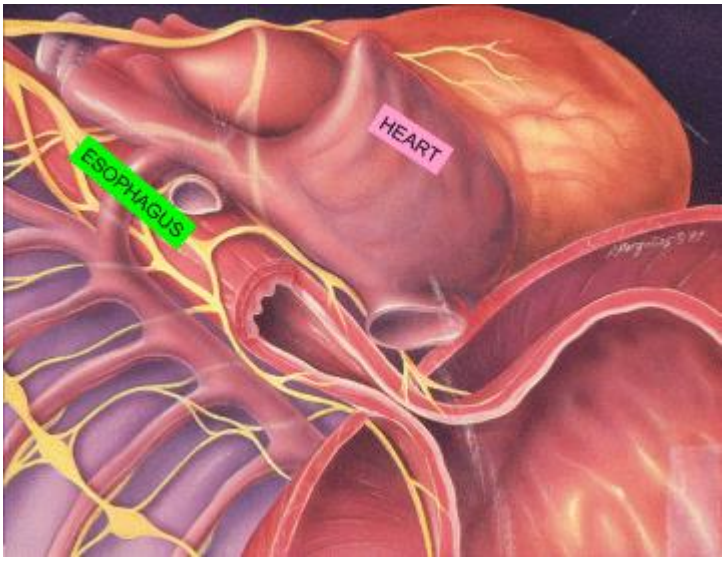

Figure1: Anatomical relation of heart and esophagus (Adopted from American College of Gastroenterology-Non cardiac chest pain)

1.4 THE USE OF HIGH RESOLUTION MANOMETRY AND PH STUDY AS A DIAGNOSTIC TOOL

High resolution manometry is a new technology used to measure intraluminal pressure activity within the gastrointestinal tract using a series of closely spaced pressure sensors within the esophagus. It uses a series of 36 1-cm-spaced pressure sensors that provides detailed pressure information that reveals the segmental nature of esophageal peristalsis. (Parkman, McCallum, &Rao, 2011, p. 22).

Esophageal manometry combined with acid perfusion has been found to be a safe and reliable technique for the diagnosis of patients with NCCP since 1991.In 2003 Lacima, Grande, Pera, Francino, and Ros found that ambulatory manometry had a small but perhaps important impact on the diagnosis of patient with NCCP compared to standard esophageal testing. However this study using conventional manometry but recent study by Hilal Imam

2012 prove that the use of HRM has changed the diagnostic approach to esophageal motility disorders.

It is the most specific and sensitive test for diagnosing motor disorders and a promising procedure in detecting motility disorders in patients with NCCP.

1.5 TREATMENT FOR NONCARDIAC CHEST PAIN

1.5.1 GERD RELATED NCCP

1.5.1a: Lifestyle Modifications

Lifestyle modifications like elevated of head of the bed, weight loss, cessation of smoking, avoidant of alcohol, caffeine, fresh citrus juice and other associated food products as well as few medication which can exacerbate reflux are commonly recommended to patient with GERD. However, at the moment there was no proven data to support their efficiency in treating patient with GERD related NCCP.

1.5.1b: Histamine-2 Receptor Antagonist (H2RAs)

Efficacy of H2RAs in controlling symptoms of patient with GERD related NCCP only showed around 42%, thus more potent agent like PPIs needed.

1.5.1c: Proton Pump Inhibitors (PPIs)

Base on few studies, it was recommended that in treating patient with GERD related NCCP, PPIs dose need to double than usual and to be continue until symptoms remit. Than followed by tapering dose until the lowest dose that can control the symptoms. NCCP patient may require long term treatment beyond 2 months for optimal symptoms control. Among all of PPIs, omeprazole has been the most frequently studied in clinical trial of GERD related NCCP.

1.5.1d Surgical Treatment

There are no studies of GERD related NCCP as a sole indication for surgical treatment. But there are a few studies in NCCP with symptoms correlation with reflux events at least 40% on pH study demonstrated better symptoms improvement after complete or partial fundoplication.

1.5.2 NON-GERD RELATED NCCP

The treatment for non GERD related NCCP is basically base on esophageal pain modulation. There for it is important to identify specific motor dysfunction by manometry test as specific treatment can be targeted.

1.5.2a: MUSCLE RELAXANTS