Proceedings of the Tenth Islamic Countries Conference on Statistical Sciences (ICCS-X), Volume I,
The Islamic Countries Society of Statistical Sciences, Lahore: Pakistan, (2010): 98–105.

SESSION 3: A SYMPOSIUM ON MEDICAL META-ANALYSIS

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PRELIMINARY RESULTS OF META-ANALYSIS OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) VERSUS CONSERVATIVE TREATMENT FOR GALL STONE PANCREATITIS

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ABSTRACT

Objectives: The aim was to conduct a meta-analysis of randomised control trials (RCTs) investigating the treatment of gallstone pancreatitis (GSP) by early ERCP versus conservative management and subsequent patient outcomes.

Data Sources and Review Methods: A search of Medline, Embase, Science Citation Index, Current Contents, PubMed and the Cochrane Database of Randomised control trials identified all RCTs comparing early ERCP to conservative treatment in gallstone pancreatitis published in the English Language. The meta-analysis was prepared with reference to the guidelines given in the Quality of Reporting of Meta-analysis (QUOROM) statement. Variables that were considered the most objective to analyse were overall mortality, overall morbidity, severity of pancreatitis (mild or severe), pseudocyst formation, organ failure (renal, respiratory and cardiac), abnormal coagulation, development of pancreatic abscess/phlegmon and biliary sepsis.

Results: Six trials were identified totalling 997 patients. There were significantly fewer complications in the active treatment group OR 1.78 (1.19, 2.67) with two further variables (pseudocyst formation and biliary sepsis) strongly favouring treatment but not reaching statistical significance. The other outcome variables examined showed no strong trend for either treatment regimen.

Conclusions: Early ERCP in the setting of acute GSP significantly decreases the risk of complications and biliary sepsis.

Keywords: Endoscopic retrograde cholangiopancreatography (ERCP); Meta-analysis; Randomized controlled trials (RCT); Gallstone pancreatitis; Biliary pancreatitis; Conservative treatment; Human; English

1. INTRODUCTION

Acute pancreatitis is a condition that is responsible for around 220000 hospital admission in the United States (US) and 12700 in Australia (2007-08), with an estimated cost to the US health system of $2.2 billion dollars annually (Whitcomb, 2006; AIHW Principal Diagnosis**;** Fagenholz et al., 2007). There are many and varying causes that lead to this common pathological endpoint, however the vast majority of cases are caused by either alcohol or gallstones; in Australia this is 35% and 45% respectively (Baker, 2006). The spectrum of disease severity seen in acute pancreatitis also varies, 80% of individuals will have mild pathology with a relatively benign course, 20% will suffer a severe attack, and 5% will die (Whitcomb, 2006; Fagenholz et al. 2007; Pandol et al. 2007). Pancreatic inflammation caused by gallstones is likely related to biliary "hypertension" from obstruction and inappropriate activation of pancreatic enzymes, but the exact cause is not fully understood (Whitcomb, 2006; Pandol et al., 2007; Siva and Pereira, 2006; Wysoki and Carter, 2007). Relieving biliary obstruction in GSP by ERCP has been practiced since 1973, and advocated as an early intervention in an attempt to mitigate the morbidity and mortality of this condition (Classen, 2000; Kawai, 2000; Neoptolemos et al. 1988; Fan et al. 1993; Fölsch et al. 1997; Nowak et al. 1995; Acosta et al. 2006; Oria et al. 2007). Randomised controlled trials (RCT) have been conducted comparing conservative (supportive) treatment of GSP with early (usually within 24-72hrs of presentation) ERCP, and the results have been conflicting (Neoptolemos et al. 1988; Fan et al. 1993; Fölsch et al. 1997; Nowak et al. 1995; Acosta et al. 2006; Oria et al. 2007). Meta-analyses performed on these trials have also delivered conflicting results contributing to the uncertainty surrounding the optimum management of these patients (Sharma et al. 1999; Ayub et al. 2004). Since the publication of the last meta-analysis in 2004, 2 further RCTs examining this question have been published, and it is hoped that with this additional data a clearer picture of the appropriate management of these patients will emerge (Acosta et al., 2006; Oria et al., 2007).

2. METHODS

RCTs that compared early ERCP + ES with conservative (supportive) treatment, and were published in full in peer-reviewed journals in the English language between 1970 and 2007, were included. Unpublished studies and abstracts presented at national and international meetings were also included. Published studies that contained insufficient information were also excluded, but only after an effort had been made to obtain unpublished or missing data from the original authors. Six trials were identified by conducting a comprehensive search of Medline, Embase, Science Citation Index, Current Contents and PubMed databases, using medical subject headings 'Endoscopicretrogradecholangiopancreatography (ERCP)'; 'Meta-analysis'; 'Randomized controlled trials'; 'Gallstone pancreatitis'; 'Biliary pancreatitis'; 'Conservative treatment'; 'Human'; 'English' (Neoptolemos et al. 1988; Fan et al. 1993; Fölsch et al. 1997; Nowak et al. 1995; Acosta et al. 2006; Oria et al. 2007). Manual search of the bibliographies of relevant papers was also carried out to identify trials for possible inclusion. Data extraction and critical appraisal were carried out by two authors (MJB and MAM). Standardised data extraction forms were used by these authors to independently and blindly summarise the randomised controlled trials meeting the inclusion criteria. The authors were not blinded to the source of the document or authorship for the purpose of data extraction. The data was compared and discrepancies were resolved by consensus. The primary author also contacted the original authors of some of the trials for clarification of data and to obtain unpublished, missing or additional information on various outcome measures. Variables that were considered the most objective to analyse were overall mortality, overall morbidity, severity of pancreatitis (mild or severe), pseudocyst formation, organ failure (renal, respiratory and cardiac), abnormal coagulation, development of pancreatic abscess/phlegmon and biliary sepsis. The quality of the randomized clinical trials was assessed using Jadad's scoring system and the meta-analysis prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement (Jadad et al. 1996; Moher et al., 1999).

3. STATISTICAL ANALYSIS

Meta-analyses were performed using odds ratios (ORs) for binary outcome and weighted mean differences (WMDs) for continuous outcome measures. The slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values in the calculation of the original OR (Agresti, 1996). Random effects models, developed using the inverse variance weighted method approach, were used to combine the data (Sutton et al. 2000). Heterogeneity among studies was assessed using the Q statistic proposed by Cochran and $I2$ index introduced by Higgins and Thompson (Sutton et al., 2000; Cochran, 1954; Hedges and Olkin, 1985; Higgins and Thompson, 2002; Huedo-Medina et al., 2006). If the observed value of Q is larger than the critical value at a given significant level (α), in this case 0.05, we conclude that there is statistically significant between-studies variation. In order to pool continuous data, mean and standard deviation are required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median and range. Using these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo et al. Funnel plots were synthesized in order to determine the presence of publication bias in the meta-analysis. Both total sample size and precision (1/standard error) were plotted against the treatment effects (OR of outcome variable) for re-operation rate, failure rate and complication rate (Sutton et al., 2000; Egger et al., 1997; Tang et al., 2000). All the resulting funnel plots are asymmetrical, suggesting the existence of publication bias (Egger et al., 1997; Tang et al., 2000). The number of studies included in the

funnel plots, indicated by the number of plotted points, is not large enough for the detection of study bias (Egger et al., 1997, Span, 2006). All estimates were obtained using a computer program written in R (R: Version 1, 2008) All plots were obtained using the meta-package (Lumley T. The rmeta Package, Version 2.14).

4. RESULTS

Six prospective RCTs were identified by the authors as meeting the inclusion and exclusion criteria for meta-analysis. The studies include 997 patients, 532 treated supportively and 465 having early ERCP +/- ES. Patient demographics and selection methods were detailed in all of the available studies. The design of each RCT was slightly different, namely in time to ERCP in the treatment group (varying from 24-72hrs), and in the specific aspects of the complications reported; the primary endpoints in each study were morbidity and mortality.

There was a significant decrease in overall complications in the treatment group as compared with supportive management (OR 1.78, 95% confidence interval (CI) 1.19, 2.67; *P* 0.0053). Mortality was not shown to be significantly improved by early biliary decompression, however, there was a trend favouring intervention (OR 1.5, CI 0.59, 3.83; *P* 0.39). Other parameters that favoured the treat group without achieving statistical significance were pseudocyst formation (OR 1.57, CI 0.81, 3.01; *P* 0.17) and biliary sepsis (OR 3.77, CI 0.74, 18.99; *P* 0.10). No strong trend favouring either hypothesis was shown for renal failure (OR 0.86, CI 0.34, 2.18; *P* 0.75), cardiac failure (OR 1.29, CI 0.62, 2.69, *P* 0.49), respiratory failure (OR 1.04, CI 0.41, 2.64; *P* 0.93) or coagulation abnormalities (OR 0.91, CI 0.35, 2.36; *P* 0.85).

5. DISCUSSION

The pancreas (Greek *pan,* all; *kreas,* flesh or meat), so named by Rufus of Ephesus around 100 AD, was first connected to the alcohol induced phenomenon of epigastric pain and vomiting by Reginald Fitz, a Harvard pathologist. In 1878 he noticed pancreatic inflammation was associated with this constellation of symptoms, which could progress to severe suppurative and haemorrhagic complications (Townsend et al., 2007; Beger et al., 2007). Biliary calculi were first associated with pancreatitis in 1901 by Opie, also a pathologist, who worked at Johns Hopkins University. He discovered an impacted stone at the Ampulla of Vata during a post-mortem on a patient who had succumbed to severe pancreatitis (Townsend et al., 2007). Acute pancreatitis is still diagnosed clinically by the characteristic epigastric pain, nausea and vomiting, now augmented with tests for serum pancreatic enzyme levels and imaging studies to determine both the cause of pancreatic inflammation and its severity (Whitcomb, 2006; Pandol et al., 2007; Baron et al., 2007). Clinically, acute pancreatitis is categorised according to severity (mild or severe) and aetiology (Whitcomb, 2006; Pandol et al., 2007). The two scoring systems most commonly used to predict severity are Ranson's criteria and The Acute Physiology and Chronic Health Evaluation (APACHE II) score (Whitcomb, 2006; Pandol et al., 2007). A Ranson's score ≥ 3 or an APACHE II score ≥ 8 indicates severe acute pancreatitis, and in these individuals more intensive monitoring is crucial (Whitcomb, 2006; Pandol et al., 2007; Baron et al., 2007; Swroop et al., 2004). The overall mortality in acute pancreatitis is 5%, but of the 20% of people who suffer a severe attack 10-30% will die, and in patients requiring ICU admission mortality increases to 30-50%, with outcomes further worsening as the severity scores increase (Whitcomb, 2006; Swroop et al., 2004; Nathens et al., 2004). In 70-80% of individuals, the primary cause of acute pancreatitis is either ethanol ingestion or cholelithiasis; others include drugs, trauma, systemic illness, congenital causes with around 20% classed as idiopathic (Whitcomb, 2006; Pandol et al., 2007; Swroop et al., 2004). However despite the high

prevalence of gallstone acute pancreatitis and ever increasing biochemical and imaging investigations, the exact mechanism responsible for the pathological process is still unknown (Pandol et al., 2007). Although the pathogenesis is almost certainly related to aberrant activation of pancreatic enzymes and biliary obstruction, no current animal model adequately explains this, and detailed human data is not available (Whitcomb, 2006; Pandol et al., 2007).

It is no surprise therefore that early surgical intervention in the patient with acute pancreatitis has long been considered and attempted. Specifically in relation to GSP, a study by Acosta found early biliary decompression by cholecystectomy, duct exploration and transduodenal sphincterotomy performed within 48hrs decreased mortality (16% vs. 2%) (Rocha et al., 2008). This finding however was contrary to the commonly held view at the time, that early surgical intervention in patients with GSP was associated with a high morbidity and mortality (Rocha et al., 2008). ERCP, although now routine, is a relatively young intervention in the history of medical and surgical practice. Reports of the first successful endoscopic retrograde cholangiography and endoscopic retrograde pancreatography date from 1968 and 1970 respectively (Goh, 2000). The first ERCP with endoscopic sphincterotomy (ES), was performed by Demling and Classen at Erlangen on June 6, 1973, closely followed by Kawai on August 10 1973 (Classen, 2000; Kawai, 2000). During this first sphincterotomy Drs Classen and Demling also performed a gallstone extraction using the Dorma basket; Dr Classen related that this first successful ERCP + ES resulted in a "massive response" from his autonomic nervous system (Classen, 2000). From these beginnings ERCP has been honed into a formidable diagnostic and therapeutic tool over the preceding forty years.

The utility of ERCP in relieving biliary obstruction in GSP is undoubted, despite this, there is still much controversy as to which patients benefit from this intervention. Both the AGA (American Gastroenterology Association) and ACG (American College of Gastroenterologists) guidelines agree that patients with GSP plus cholangitis should undergo immediate ERCP (Banks et al., 2006; AGA Institute Medical Position Statement on Acute Pancreatitis Gastroenterology 2007). The ACG adds that patients with severe GSP should also undergo early ERCP, however the AGA guidelines sight this as controversial, sighting the conflicting data (Banks et al., 2006; AGA Institute Medical Position Statement on Acute Pancreatitis Gastroenterology 2007). The BSG (British Society of Gastroenterology) further recommends that patients with jaundice, or a dilated common bile duct should also be considered for ERCP preferably within seventy-two hours, although no mention of the severity of pancreatitis is attached to this statement (UK Guidelines for the Management of Acute Pancreatitis. 2005).

Two previous meta-analyses (and their component studies) on which these guidelines have been based reached different conclusions (Sharma et al., 1999; Ayub et al., 2004). The first analysis performed on four RCTs including 834 patients found early (24-72hrs) ERCP significantly decreased complications in the treatment group (regardless of severity) (Neoptolemos et al., 1988; Fan et al., 1993; Fölsch et al., 1997; Nowak et al., 1995; Sharma et al., 1999). The second study focused on only three RCTs with 554 patients, and showed that the significant decrease in complications was found only in patients with severe pancreatitis, neither meta-analysis found that early ERCP significantly decreased mortality (Neoptolemos et al. 1988; Fan et al., 1993; Fölsch et al., 1997; Ayub et al., 2004). Interestingly, a caveat regard the Cochrane meta-analysis must be noted as the authors included data from one study (Fölsch et al) that was not originally included in the published version which enabled further stratification of patients into those with mild and those with severe acute pancreatitis (Ayub et al., 2004). This particular study was stopped early due to poorer patient outcomes in the experimental group both for mortality (in mild and severe GSP) and morbidity (again in both groups), although this was not statistically significant (Ayub et al., 2004). The findings of this meta-analysis support those of the first, that early ERCP +/- ES significantly decreases morbidity, but not mortality.

Unfortunately there is a paucity of data in the RCTs classifying disease severity, making useful analysis of this variable difficult, and thus affecting the consensus statements drawn from them.

6. CONCLUSIONS

This meta-analysis confirms the findings of a previous review, this being that early ERCP +/- ES decreases overall complications in patients with acute GSP. Mortality, biliary sepsis and pseudo-cyst formation favour intervention but do not reach the level of statistical significance. Examination of the data available indicates that further large prospective RCTs are required to confirm the utility of early ECRP +/- ES in mild and severe GSP.

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