Evaluation of the Role of Allopurinol in Prevention of Post-Endoscopic Retrograde Cholangio Pancreatography (ERCP) Pancreatitis

Thesis

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Contents

List of Abbreviations

Abb.	Mean
ALT	Alanine transaminase.
AST	Aspartate transaminase.
BUN	Blood urea nitrogen.
CBD	Common bile duct.
CLD	Chronic liver disease
COPD	Chronic obstructive airway disease.
EPBD	Endoscopic papillary balloon dilation.
ERCP	Endoscopic retrograde cholangio-pancreatography.
ES	Endoscopic sphincterotomy.
EUS	Endoscopic ultrasound.
GA	General Anesthesia.
GGT	Gamma glutamyl transferase.
i.v.	Intra venous
IHBRD	Intra hepatic biliary radicals dilatation.
MRCP	Magnetic resonance cholangio-pancreatography.
n	Number
OJ	Obstructive jaundice.
PEP	Post ERCP pancreatitis.
PTC	Percutaneous transhepatic cholangiography.
SD	Standard deviation.
SOD	Sphincter of Oddi dysfunction.
WBCs	White blood cells.

List of Tables

List of Figures

Introduction

Since its introduction in 1968, endoscopic retrograde cholangio-pancreatography (ERCP) has become a commonly performed endoscopic procedure. The diagnostic and therapeutic utility of ERCP has been demonstrated for a variety of disorders ***(Mallery et al., 2003).*** ERCP is a technically demanding endoscopic procedure that varies from a simple diagnostic to a highly complex therapeutic procedure. It has variable degrees of technical success and many complications**,** such as pancreatitis, hemorrhage, perforation and infection ***(Mallery et al., 2003)..***

Pancreatitis is the most common ERCP complication ***(Freeman et al., 2001),*** with an incidence ranging from 1.8% to 7.2% in most prospective series ***(Williams et al., 2007).*** However, the reported incidence can go up to 30%, depending on the criteria used in diagnosis of pancreatitis, the type and the duration of patient follow-up ***(Freeman and Guda, 2004).*** More commonly, hyperamylasemia occurs up to 30% of the patients undergoing ERCP ***(LaFerla et al., 1986).*** An early step in the pathogenesis of acute pancreatitis is capillary endothelial injury manifested by an increase in capillary

permeability ***(Sanfey and Cameron, 1984).*** Subsequent research has suggested that this capillary injury might be mediated by oxygen-derived free radicals ***(Schoenberg et al., 1994).***

Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, which generates an oxygen-derived free radical ***(Masci et al., 2003).*** Xanthine dehydrogenase is converted to xanthine oxidase by the proteolytic cleavage of a peptide fragment. These findings have prompted attempts for prevention of pancreatitis by treatment with free radical scavengers (e.g. superoxide dismutase, dimethyl sulfoxide or catalase), protease inhibitors (e.g. gabexate) or xanthine oxidase inhibitors (e.g. allopurinol) ***(Masci et al., 2003).***

Some attempts have been made to find pharmacologic agent that could be used to reduce the incidence and severity of post-ERCP Pancreatitis **(**PEP). An ideal agent should be highly effective in reducing PEP, safe for the patient, well tolerated, relatively affordable and does not require a prolonged administration time ***(Cooper and Slivka, 2007).***

The efficacy of oral allopurinol to reduce PEP has been investigated in an in vivo animal model ***(Marks et al., 1998).***

Pretreatment was not only associated with a significant (six folds) reduction in the incidence of pancreatitis, but when pancreatitis did occur it was less severe. Other animal models using pretreatment with allopurinol have demonstrated a significant reduction in progression of the histological pancreatic injury and in the severity of experimental pancreatitis in dog and rat models ***(Isik et al., 2006; Shabanov et al., 2006; and Comert et al., 2007).***

These findings in animal research supported the need for human studies on the utility of allopurinol pretreatment to reduce the incidence of hyperamylasemia and PEP. One randomized clinical trial has reported positive clinical results ***(Katsinelos et al., 2005),*** whereas others have reported negative outcomes ***(Romagnuolo et al., 2008).***

Allopurinol is also an inexpensive generic drug with an excellent safety record and is not included among list of drugs inducing pancreatitis ***(Badalov et al., 2007).***

Aim of the Work

The aim of this study is to evaluate prospectively the use of allopurinol in the prevention of post – ERCP pancreatitis in patients undergoing ERCP.

Patients and Methods

A prospective study will be conducted on 100 patients of both sexes who will undergo ERCP procedure in Ain Shams University Hospitals will be enrolled into the study, their age ranges from 20-70 years old. They will be randomized and divided into **2 groups:**

Group 1: 50 patients who will receive allopurinol tablets before the ERCP procedure **(study group).**

Group 2: 50 patients will undergo ERCP without allopurinol prophylaxis **(control group).**

All the patients will sign a written informed consent

Study design:

A- Sample size:

EPI.Info program was used for sample size calculation guided by

1. Power of the test = 80%
2. Confedence level =95%
3. Alfa error = 5%
4. Expected response rate = 60%

The minimal total sample size that achieve significance will be 100 cases divided into 2 equal groups:

1. 1st group (50 cases): will receive allopurinol drug prior to ERCP.
2. 2nd group (50cases): will not receive the drug.

B- Type of the study:

Randomized controlled clinical trial (RCCT).

C- Sampling plan:

Cases will be allocated by *Systematic Random Sample* according to their number into:

1. Odd numbers: 50 cases of the first group.
2. Even number: 50 cases of the second group.

Inclusion criteria:

All patients candidate for ERCP will be included in this study for ERCP:

1. Patients with calcular obstructive jaundice.
2. Patients with malignant or benign obstructive jaundice.
3. Patients with any other indications for ERCP.

Exclusion criteria:

1. Patients refusing to undergo the procedure or signing the informed consent.

2. Patients with clinically evident acute pancreatitis or hyperamylesemia (>150 IU/L) before the procedure.
3. Patients had undergone previous endoscopic or surgical sphincterotomy.
4. Current or recent use of allopurinol (within the last 48 hours).
5. Patients who are allergic or hypersensitive to allopurinol or hydro soluble contrast solutions.
6. Current use of drugs with a known interaction with allopurinol, including cyclophosphamide, chlorpropamide, azathioprine, mercaptopurines, or probenecid.
7. Patients receiving NSAIDS within a week prior to assessment.
8. Severe co-morbid conditions (eg. cardiovascular, renal failure or patients with decompensated cirrhosis).
9. Female patients with a known or suspected pregnancy lactating ***(Martinez et al., 2009).***

End points: Patients having any of the complications such as hemorrhage, perforation, etc, will end up their study.

Drug safety: The following adverse effects might happen during the procedure due to use of allopurinol such as diarrhea;