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ORIGINAL ARTICLE

The effect of adding gentamicin to contrast media for prevention of cholangitis after biliary stenting for non-calculous biliary obstruction, a randomized controlled trial

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Abstract
Aim Cholangitis is the most common infectious complication of ERCP. In vitro studies showed that addition of aminoglycosides to contrast medium was effective in reducing cholangitis but the results of clinical trials are conflicting. We studied the effect of adding gentamicin to contrast medium in reducing the rate of post-ERCP cholangitis in patients with non-calculous obstructive jaundice.
Methods All patients with non-calculous obstructive jaundice who underwent endoscopic biliary stenting at the Shariati Hospital, Tehran, between December 2009 and October 2010 were enrolled in the study. Gentamicin (10 mg) or distilled water was added to each 10 cc contrast medium during ERCP. Intravenous antibiotics were administered before and after the procedure in all patients. After ERCP and stent deployment, patients were followed for 72 h for symptoms and signs of cholangitis.
Results A total of 114 patients were eligible for the study. Of these, 57 patients were included in each group. Cholangiocarcinoma was the most prevalent diagnosis. The obstruction was relieved in all patients by stenting. Five patients in each group (8.8 %) developed cholangitis. There was no significant difference in the incidence of cholangitis between the two groups (p=1.000).
Conclusions With adequate drainage of the obstructed biliary tract by proper stenting, adding gentamicin to contrast media had no significant effect on incidence of post-ERCP cholangitis.

Keywords Cholangiopancreatography · Cholangitis · Cholestasis · Endoscopic retrograde · Stents

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a standard therapeutic modality in pancreatobiliary disorders. However, it is associated with some complications including pancreatitis, bleeding, perforation, and sepsis. Cholangitis is the most common infectious complication of ERCP [1]. Risk factors of post-ERCP cholangitis are failure to obtain adequate biliary drainage, Klatskin's tumor (range: 14 % to 53 %), primary sclerosing cholangitis (PSC), occlusion in biliary stents, jaundice, low annual case volumes, and both percutaneous and endoscopic procedures [2–9]. A few suggestions have been made to prevent post-ERCP cholangitis, including thorough disinfection of endoscope and accessories, use of low volume of contrast solutions, decompression of obstruction, prophylactic use of antibiotics, and percutaneous or surgical decompression in cases of ERCP failure [10]. In vitro studies have found that adding antibiotics to the contrast agent was useful, but only a few clinical studies have evaluated its use in ERCP with conflicting results [11–16]. Collen et al. [13] examined the efficacy of adding gentamicin to contrast agent and

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concluded that it did not reduce infectious complications. However, this study was done in simple pancreatobiliary disorders and many years before today's therapeutic ERCP. Recently, a retrospective study [14] on 6,695 ERCP in 2005 concluded that adding antibiotics to the contrast agent and intravenous antibiotics can reduce infectious complications of ERCP. In the present double-blind randomized controlled trial, we evaluated the effect of adding gentamicin to contrast media for preventing post-ERCP cholangitis, in non-calculous biliary obstruction.

Methods

Between December 2009 and October 2010, all patients with non-calculous biliary obstructions, e.g. cholangiocarcinoma, pancreatic cancer, sclerosing cholangitis, postsurgical benign biliary strictures, and biliary stenosis due to metastatic cancers to biliary tree who were candidates for palliative stenting, were included in this study. Patients with biliary stones, those who were candidates for surgical treatment, those who were already febrile, and those not consenting to the study protocol were excluded (Fig. 1).

Cholangitis was defined as the presentation of fever with or without chills within the first 72 h after ERCP. The primary pancreatobiliary disorder was documented by radiology, ERCP findings, endoscopic ultrasound, or surgery. Patients were randomized to receive either 10 mg (2 mL) gentamicin (intervention group) or distilled water (placebo group) in 10 mL contrast medium (Meglumine; Bracco Diagnostics Inc., China). Gentamicin or placebo (distilled water) was added just before the scheduled stenting based on the random table prepared by a physician who was not involved in the ERCP procedure and was not aware of the clinical status of the patient. Distilled water was added as placebo and the volume was similar to that of gentamicin. The dose of gentamicin was based on previous studies [11–13].

Randomization was done by a computer-generated randomization table. Based on an expected incidence of cholangitis of 25 % Rerknimitr et al. [4] in the placebo group and to detect a 20 % reduction in the incidence of cholangitis in the treatment group, we calculated a sample size of 57 patients in each group to give 80 % power to detect a significant difference between gentamicin and placebo. All the study personnel and participants were blinded to treatment assignment for the duration of the study. Only the study statisticians and data monitoring committee had access to allocation data, and these individuals did not have contact with the study participants. The study was approved by the institutional review board of the Digestive Diseases Research Center of Tehran University of Medical Sciences. Written informed consent was obtained according to the guidelines of the institute.

All patients were administered 2 g ceftriaxone intravenously 30 min before ERCP and daily for 3 days. After ERCP, patients were admitted for 72 h. Blood culture was performed if they developed fever (oral temperature >37.2 °F). Any fever, chills,

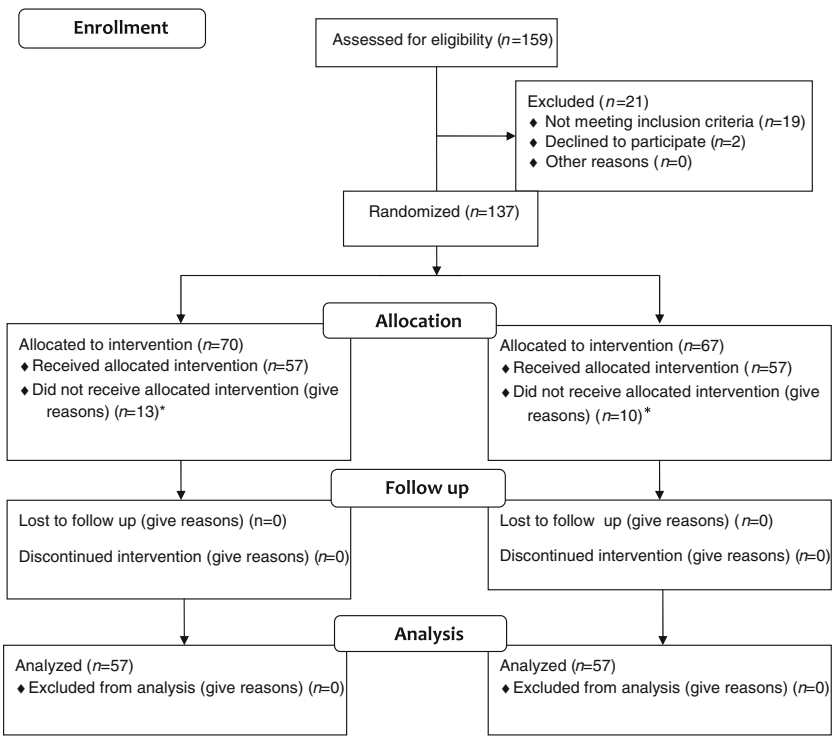

Fig. 1 CONSORT 2010 Flow Diagram

* attempts for cannulation were failed

Table 1 Clinical characteristics of patients in placebo and intervention groups

Patients demographics	Placebo group; No (%)	Intervention group; No (%)	*p*-value
Male gender	36 (63.2)	42 (73.7)	0.23
Mean age (SD)	66.42 (14.20)	62.82 (14.76)	0.18
Clinical diagnosis			0.86
Cholangiocarcinoma	17 (29.8)	18 (31.6)	
Pancreas tumor	17 (29.8)	16 (28.1)	
Ampullary tumor	11 (19.3)	11 (19.3)	
Others	12 (21.1)	12 (21.0)	
Nausea	23 (40.4)	16 (28.1)	0.16
Abdominal pain	36 (63.2)	37 (64.9)	0.84
Weight loss	42 (73.7)	39 (68.4)	0.53
Jaundice	52 (91.2)	54 (94.7)	0.71
Pruritus	42 (73.7)	41 (71.9)	0.83

or positive blood culture was recorded. The study end point was developing cholangitis within 72 h after the procedure.

Data on patients' demographics, ERCP findings, and complications were analyzed with SPSS version 16 (SPSS Inc., Chicago, IL, USA) using chi-square or Fischer's exact test.

Results

A total of 114 patients were eligible for inclusion in the study; 57 patients were allocated to each group. The mean age of patients in the intervention and placebo groups was 66.4 and 62.8 years, respectively, and most patients were male. Cholangiocarcinoma was the most prevalent diagnosis in both groups, and jaundice was the most frequent symptom. Demographics of subjects are presented in Table 1. There was no significant difference at baseline between the study groups.

Details of ERCP data are given in Tables 2 and 3. Median number of cannulation attempts was 2, and volume of contrast injection was 10 mL in both groups ($p=0.70$ and 0.14, respectively). For most patients, only a single stent was deployed (56 in placebo group, 57 in intervention group). Metallic stent was deployed for 22 (38.6 %) patients in the placebo group and 15 (26.3 %) in the interventional group ($p=NS$).

Table 3 Multivariate analysis for variables of post-ERCP cholangitis

	Placebo group	Intervention group	*p*-value
Male/female	2/3	4/1	0.72
Median cannulation attempt	3/2	1/4	0.13
Median volume of contrast	2/3	3/2	0.14
Metallic/plastic stent	4/1	1/4	0.29
One/two stents	5/0	5/0	1.000
CBD/other stenting sites	2/3	4/1	0.02

Ten patients (5 in each group; 6 males) developed post-ERCP cholangitis. Five of these patients with cholangitis had received less than 10 mL contrast media. Five patients with metallic stents and five with plastic ones developed cholangitis. No patient with two stents deployment developed cholangitis, and six patients with cholangitis had stent deployment in the common bile duct (CBD). Only location of stent deployment in CBD had significant correlation with incidence of post-ERCP cholangitis. After multivariable regression analysis for location of stent deployment, cannulation attempts, and volume of contrast injection, the site of stent still had significant statistical correlation with developing post-ERCP cholangitis ($p=0.02$, 95 % CI=0.038–0.768; Table 2).

One patient in intervention group with diagnosis of PSC died because of septic shock. In addition, one patient each died of myocardial infarction and severe pancreatitis (both in placebo group). Three patients developed mild pancreatitis and one had post-ERCP cholecystitis.

Discussion

The authors found that adding gentamicin to contrast media did not alter the incidence of post-ERCP cholangitis. Adding aminglycosides to contrast media was first introduced by Jendrzejewski et al. [11] in 1980. They found that in vitro

Table 2 ERCP characteristics in the study groups

Patients demographics	Placebo group	Intervention group	*p*-value
Median number of cannulation attempt	2 (range: 1–10) 34/23	2 (range: 1–20) 36/21	0.70
Median volume of contrast	10 (range: 2–60) 38/19	10 (range: 2–35) 45/12	0.14
Metallic/plastic stent (%)	22/35 (38.6/61.4)	15/42 (26.3/73.7)	0.16
One/two stents (%)	56/1 (98.2/1.8)	55/2 (96.5/3.5)	1.000
CBD/other stenting site (%)	50/7 (87.7/12.3)	50/7 (87.7/12.3)	1.000

addition of aminoglycosides to iodinated contrast agents and bile did not interfere with their antibactericidal activity and could prevent growth of organisms producing cholangitis. Ramirez et al. [12] studied the effect of adding gentamicin to contrast medium in artificial bile ducts resembling biliary ducts and added gentamicin-sensitive and -resistant pseudomonas to this medium. They found that contrast medium was bacteriostatic in itself and addition of gentamicin to it could eliminate sensitive bacteria and reduce the resistant-form colonies. This study supported the idea of theoretical benefit of intracontrast aminoglycosides, especially in resistant bacteria, which are prevalent in ERCP.

In 1980, Collen et al. [13] studied the addition of gentamicin to contrast media in a randomized controlled trial. They added gentamicin or placebo to Renograffin-60 for prevention of post-ERCP cholangitis. They did not use intravenous antibiotics before ERCP. They concluded that adding gentamicin had no significant effect on reducing the incidence of post-ERCP cholangitis, but this study was long before new era of therapeutic ERCP and also contained patients with low risk of post-ERCP cholangitis. The sample size in this study was also small.

In 2005, Bernadino et al. [14] reported their 14 years study of 6,695 ERCP in an abstract. In their study, patients were divided into high-risk (hilar obstruction, sclerosing cholangitis, pancreatic strictures and stones, or pseudocysts) and low-risk (noninfected cases) groups. All patients in high-risk group received intravenous and intracontrast antibiotics and low-risk patients did not. They concluded that with this selective adoption, infectious complications of ERCP could be reduced to near zero. Their study had a large sample size and long follow up for up to one month, but it was not randomized and all high-risk patients received both intravenous and intracontrast antibiotics, which made assessment of the role of intracontrast antibiotics difficult.

In the present study, the addition of gentamicin to contrast medium had no significant effect in reduction of post-ERCP cholangitis. Furthermore, the incidence of cholangitis had no association with gender, number of cannulation attempts, volume of contrast injected, or type and number of deployed stents. Only the location of stent deployment correlated with development of cholangitis, and patients with stents placed in CBD were more likely to develop cholangitis. There is no explanation for this finding.

To the best of our knowledge, this study is the first double-blind randomized controlled trial that studied intracontrast aminoglycosides for prevention of biliary stenting infectious complications. In this study, high-risk patients for post-ERCP cholangitis were included, and effect of prophylactic intravenous antibiotics was eliminated by administering them to all patients. Numbers of different diagnoses were almost similar in the two groups, again potentiating the results. The main limitation of this study is the small sample size.

In conclusion, in cases with adequate biliary drainage after ERCP, adding gentamicin to contrast media had no significant effect in reduction of incidence of post-ERCP cholangitis.

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