The value of transdermal Glyceryl Trinitrate in the prevention of post-ERCP pancreatitis in comparison to Octreotide and Diclofenac injection.

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Abstract: Background: Post-ERCP pancreatitis **(PEP)** is the most common complication of endoscopic retrograde cholangiopancreatography **(ERCP).** A universally applicable, inexpensive, effective and safe intervention that ameliorates this complication has not yet been identified. Various forms of pharmacologic prophylaxis have demonstrated modest reduction in PEP in some randomized controlled trials. Glyceryl trinitrate is an inexpensive and easily administered agent. Octreotide have shown encouraging results. **Aim of the study:** To study the effect of **Glyceryl trinitrate** in the prevention of PEP in comparison to **Octreotide** and **Diclofenac** I.M injection. Also, we aimed to detect the risk factors associated with PEP. **Patients and methods:** The study included 160 patients who were candidates for ERCP and divided into four groups: Group I: 40 patients who did not receive any prophylactic drug. Group II: 40 patients received transdermal Glyceryl trinitrate75 mg. Group III: 40 patients received Dilofenac75 mg by I.M injection. Group IV: 40 patients received Octreotide 0.1 mg S.C. injection. ERCP was performed for all patients by two endoscopists under propofol. Both baseline serum amylase and lipase were measured. Also, they were measured 24 hours and 72 hours after ERCP. **Results:** The incidence of PEP in our patients was 12.5%. No statistically significant difference between the studied groups as regards this incidence. Although, there was significant difference between the groups regarding the cannulation time, duration of the procedure and difficulty of cannulation, the difference was not significant on comparing GTN group to the control groups regarding the cannulation technical parameters. Univariate analysis revealed five risk factors for PEP: non-dilated CBD, long cannulation time, lengthy procedure, pancreatic duct visualization and poor drainage of dye. **Conclusion:** The used drugs in the study were not effective in the prophylaxis against PEP. Glyceryl trinitrate may have facilitatory effect on the cannulation technical parameters but did not reach statistical significance. Large scale trials are still needed. [Nature and Science 2010;8(6):27-35]. (ISSN: 1545-0740).

Keywords: transdermal Glyceryl Trinitrate, post ERCP pancreatitis, octeriotide, diclofenac.

1. Introduction

Post-ERCP pancreatitis is a common serious complication of ERCP that continues to disturb endoscopists since the introduction of this technique. PEP has been reported in up to 40% of patients, depending on the criteria used for diagnosis, differences in patient populations, endoscopic techniques used, and accuracy of the follow-up ***(Andriulli et al., 2007).***

There have been several efforts to develop an effective preventive strategy that will reduce the risk or severity of PEP. Most of the pharmacological agents tested are not universally effective, hence a combined strategy is being advocated to minimize the occurrence of PEP. This includes the identification of patient -and procedure- related factors associated with high risk, refinement of endoscopic methods, search for an effective drug for prophylaxis and prophylactic placement of a pancreatic duct stent in high-risk patients ***(Bhasin et al., 2008).***

Various pharmacological interventions have been tested in various studies but the results were conflicting ***(Foster and Leung, 2007).*** For the prevention of PEP: somatostatin, octreotide, gabexate mesylate, ulinstatin, allopurinol, corticosteroids, diclofenac, indomethacin, nifedipine, glyceryl trinitrate, antibiotics, botulinum toxin, interleukin-10 and β-carotene have been tried in clinical studies ***(Xiong et al., 2007).*** Infusion of a high dose of octreotide has shown encouraging results ***(Choudhary et al., 2008).*** Glyceryl trinitrate (GTN) is an inexpensive and easily administered agent ***(Kaffes et al., 2006).***

Aim of the study:

To study the role of transdermal Glyceryl Trinitrate in the prevention of post-ERCP pancreatitis in comparison to the use of Octreotide and Diclofenac injections and also to detect the risk factors associated with PEP.

Patients and methods:

The study was conducted at the ERCP unit in Internal Medicine Department, Ain Shams University Hospitals over a period of 21 months, from January 2008 to September 2009. A total of 160 patients who were candidates for ERCP were enrolled in the study. Patients were assigned randomly and divided into 4 groups:

Group I (control group)**:** 40 patients who did not receive any prophylactic drug.

Group II: 40 patients, each of them treated with transdermal glyceryl trinitrate (GTN) 75 mg to deliver 15 mg. The patch was applied 2 hours before

the procedure and removed 24 hours after the procedure.

Group III: 40 patients received diclofenac 75 mg by IM injection 1/2 hour before the procedure.

Group IV: 40 patients received Octreotide 0.1 mg by S.C. injection 1/2 hour before the procedure.

All patients signed an informed written consent.

Exclusion criteria:

1- Known hypersensitivity to any of the used drugs.
2- Active acute pancreatitis.
3- Hypotension (BP less than 100/60).
4- Patients with renal impairment (serum creatinine > 1.5 mg/dl)
5- Patients known to have peptic ulcer.
6- Patients with chronic liver disease.
7- Pregnant and lactating females.
8- Concomitant intake of calcium channel or β-blockers.
9- Post-ERCP complication other than acute pancreatitis such as perforation, bleeding, septic complications … etc.
10- Patients with surgically altered anatomy (e.g. Billroth II).
11- Patients with previous sphincterotomy, ampullary or pancreatic cancer invading the papilla.

Methods:

I- Clinical and laboratory evaluation:

1- History taking and physical examination.
2- Baseline, 24 hours and 72 hours serum amylase (normal value 25 – 125 IU/L)
3- Baseline, 24 hours and 72 hours serum lipase (normal value 31 – 186 IU/L)
4- Complete liver profile.
5- Renal function tests.
6- S. triglycerides
7- Complete blood count.

II- ERCP:

Patients were fasting for at least 8 hours. The three drugs were randomly given to the patients. The procedure was performed by two experienced endoscopists under propofol using videoduodenoscope Olympus TJF 240. The distal common bile duct diameter was measured within 2 cm of the papilla. Pancreatic stents were not used and pancreatic sphincterotomy was not done in any case. The used electrocautery current was the blended one. Either 35% sodium and meglumine ioxitalamate or non-ionic low osmolarity contrast agent was used.

III- Statistical tests.

1- $\overline{X}$ = mean.
2- SD = standard deviation.
3- X^2 = Chi-square test.
4- Student independent t-test.
5- ANOVA = Analysis of variance.
6- Stepwise Regression Analysis.

Results:

A total of 160 patients were included in the study and divided into four groups as mentioned above. They were also divided into two groups according to post-ERCP pancreatitis:

Group A: 20 patients who had post-ERCP pancreatitis.

Group B: 140 patients with no post-ERCP pancreatitis.

Table (1): Comparison between the 4 studied groups as regard age using ANOVA test.

	Control (n=40)	GTN (n=40)	Diclofenac (n=40)	Octreotide (n=40)
$\overline{X}$ (mean)	46.6	44.78	49.82	51.17
SD	± 14.65	± 12.01	± 12.88	± 14.87
F	1.37			
P	> 0.05			

Table (2): Comparison between the pancreatitis group (group A) and non pancreatitis group (group B) as regards age using independent t-test.

	Pancreatitis group A (n=20)	Non pancreatitis group B (n= 140)
$\overline{X}$ mean	43.25	47.64
SD	± 12.5	± 13.76
t value	1.822	
P value	> 0.05	

There were 20 out of 120 patients (12.5%) who developed post-ERCP pancreatitis (PEP).

Table (3): Comparison between the 4 studied groups as regards patient-related risk factors for post-ERCP pancreatitis.

Variables \ Groups		Control (n=40)		GTN (n=40)		Diclof (n=40)		Octr (n=40)		X^2	P value
Sex	Male	20	50%	20	50%	22	55%	24	60%	1.106	>0.05 (N.S)
	Female	20	50%	20	50%	18	45%	16	40%		
Previous cholecystectomy	Yes	6	15%	11	27.5%	5	12.5%	8	20%	3.44	>0.05 (N.S.)
	No	34	85%	29	72.5%	35	87.5%	32	80%		
Previous acute Pancreatitis	Yes	3	7.5%	5	12.5%	3	7.5%	2	5%	1.59	>0.05 (N.S.)
	No	37	92.5%	35	87.5%	37	92.5%	38	95%		
Presence of chronic pancreatitis	Yes	0	0%	1	2.5%	0	0%	2	5%	3.73	>0.05 (N.S.)
	No	40	100%	39	97.5%	40	100%	38	95%		
Prophylactic antibiotics	Yes	21	52.5%	25	62.5%	18	45%	19	47.5%	2.87	>0.05 (N.S.)
	No	19	47.5%	15	37.5%	22	55%	21	52.5%		
Shape of papilla	Normal	37	92.5%	32	80%	35	87.5%	36	90%	3.20	>0.05 (N.S.)
	Enlarged	3	7.5%	8	20%	5	12.5%	4	10%		
Periamp diverticulum	Yes	1	2.5%	7	17.5%	4	10%	6	15%	5.25	>0.05 (N.S.)
	No	39	97.5%	33	82.5%	36	90%	34	85%		
Dilated IHBR	Yes	28	70%	38	95%	36	90%	31	77.5%	11.18	<0.05 (S.)
	No	12	30%	2	5%	4	10%	9	22.5%		
Non dilated CBD (<8mm)	Yes	4	10%	4	10%	10	25%	2	5%	8.22	<0.05 (S.)
	No	36	90%	36	90%	30	75%	38	95%		
Panc duct stricture	Yes	3	7.5%	3	7.5%	4	10%	3	7.5%	0.25	>0.05 (N.S.)
	No	37	92.5%	37	92.5%	36	90%	37	92.5%		

Comparison between the 4 studied groups showed significant difference as regards the presence of dilated intrahepatic biliary radicles and non-dilated common bile duct (<8 mm) while showed insignificant difference regarding the other patient-related risk factors for PEP (Table 3).

Table (4): Comparison between the 4 studied groups regarding cannulation-related factors

Factors \ Groups		Control (n=40)		GTN (n=40)		Diclof (n=40)		Octr (n=40)		X^2	P value
Cannulation	Short	28	70%	29	72.5%	26	65%	18	45%	8.02	<0.05 (S)
	Long	12	30%	11	27.5%	14	35%	22	55%		
Duration of procedure	Short	17	42.5%	26	65%	12	30%	10	25%	15.8	<0.01 (H.S.)
	Long	23	57.5%	14	35%	28	70%	30	75%		
Difficulty of cannulation	Easy	26	65%	28	70%	20	50%	11	27.5%	17.5	<0.01 (H.S.)
	Difficult	14	35%	12	30%	20	50%	29	72.5%		
Precut sphincterotomy	Yes	2	5%	5	12.5%	5	12.5%	8	20%	4.11	>0.05 (N.S)
	No	38	95%	35	87.5%	35	87.5%	32	80%		
Guide-wire assisted cannulation	Yes	36	90%	28	70%	31	77.5%	27	67.5%	6.76	>0.05 (N.S.)
	No	4	10%	12	30%	9	22.5%	13	32.5%		

Table (5): Comparison between control group & GTN group regarding cannulation technical parameters.

		Control (n=40)		GTN (n=40)		X^2	P value
Cannulation time	Short	28	70%	29	72.5%	0.01	>0.05 (N.S)
	Long	12	30%	11	27.5%		
Duration of procedure	Short	17	42.5%	26	65%	3.21	>0.05 (N.S.)
	Long	23	57.5%	14	35%		
Difficulty of cannulation	Easy	26	65%	28	70%	0.057	>0.05 (N.S.)
	Difficult	14	35%	12	30%		
Sphincterotomy	Yes	33	82.5%	36	90%	0.42	>0.05 (N.S.)
	No	7	17.5%	4	10%		
No. of panc duct cannulation	None	6	15%	4	10%	0.91	>0.05 (N.S.)
	≤2 times	22	55%	26	65%		
	>2 times	12	30%	10	25%		

There was significant difference regarding the cannulation time, duration of the procedure and difficulty of cannulation between the 4 studied groups (Table 4) but the difference was not significant on comparing GTN group to the control group as regards the cannulation technical parameters (Table 5).

Table (6): Comparison between the 4 studied groups as regards number of pancreatic cannulations using Chi-square test.

Manipulation \ Groups		Group I	Group II	Group III	Group IV	X^2	P value
Number of pancreatic cannulation	Non	6 (15%)	4 (10%)	4 (10%)	9 (22.5%)	16.7	<0.05 (S.)
	≤2 times	22 (55%)	26 (65%)	14 (35%)	24 (60%)		
	>2 times	12 (30%)	10 (25%)	22 (55%)	7 (17.5%)		

It has been found that pancreatic cannulation more than 2 times was highest in the diclofenac group (55%) and the difference between the study groups was significant regarding the number of pancreatic cannulation.

Table (7): Comparison between the 4 groups regarding incidence of post-ERCP pancreatitis (PEP) & post-ERCP hyperamylasemia (PEH).

Variables \ Groups		Control (n=40)		GTN (n=40)		Diclof (n=40)		Octr (n=40)		X^2	P value
Incidence of PEP	Yes	4	10%	7	17.5%	4	10%	5	12.5%	1.37	>0.05 (N.S)
	No	36	90%	33	82.5%	36	90%	35	87.5		
Incidence of PEH	Amylase ≤125 IU/LL	9	22.5%	13	32.5%	20	50%	22	55%	11.45	<0.01 (H.S)
	Amylase >125 IU/L	31	77.5%	27	67.5%	20	50%	18	45%		

Table (7) shows insignificant difference between the 4 groups as regards the incidence of PEP but shows a highly significant difference regarding the incidence of hyperamylasemia (P<0.01). The overall incidence of post-ERCP pancreatitis in the study was 2 of 160 patients (12.5%) and 20 of the 96 patients who had post-ERCP hyperamylasemia (20.8%).

Table (8): Comparison between the 4 groups regarding pancreatic enzyme levels.

Factors \ Groups		Control (n=40)	GTN (n=40)	Diclof (n=40)	Octr (n=40)	X^2	P value
Baseline amylase IU/L	$\overline{X}$	100.45	99.62	92.92	74.97	3.68	<0.05 (S)
	SD	±40.06	± 53.08	±32.82	± 24.97		
24 hrs amylase IU/L	$\overline{X}$	216.2	379.02	260.9	247.47	1.05	>0.05 (N.S.)
	SD	± 168.84	± 624.32	± 416.12	± 419.98		
72 hrs amylase IU/L	$\overline{X}$	138.15	190.85	167	158.62	0.36	>0.05 (N.S.)
	SD	± 81.98	± 279.21	± 208.53	±284.71		
Baseline lipase IU/L	$\overline{X}$	136.05	143.67	124.95	113.67	2.51	>0.05 (N.S)
	SD	±47.78	± 63.89	±41.76	± 52.84		
24 hrs lipase IU/L	$\overline{X}$	286.2	572.4	317.72	368.97	2.12	>0.05 (N.S.)
	SD	± 221.73	± 927.8	± 381.41	± 439.88		
72 hrs lipase IU/L	$\overline{X}$	227.5	430.35	264.42	293.05	1.69	>0.05 (N.S.)
	SD	± 176.99	± 697.44	± 325.79	± 339.96		

No significant difference between the 4 groups as regards 24 hrs and 72 hrs amylase, baseline lipase, 24 hrs and 72 hrs lipase (Table 8).

Table (9): Comparison between patients with post-ERCP pancreatitis (group A) & patients with non post-ERCP pancreatitis (group B) regarding patient-related factors for post-ERCP pancreatitis (Chi-square test).

		Pancreatitis group (group A) (n=20)		Non pancreatitis group (group B) (n=140)		X^2	P value
		No	%	No	%		
Sex	Male	9	45%	77	55%	0.7	>0.05 (N.S)
	Female	11	55%	63	45%		
Previous cholecystectomy	Yes	6	30%	24	17.1%	1.89	>0.05 (N.S.)
	No	14	70%	116	82.9%		
Previous acute Pancreatitis	Yes	1	5%	12	8.6%	0.29	>0.05 (N.S.)
	No	19	95%	128	91.4%		
Presence of chronic pancreatitis	Yes	1	5%	2	1.4%	1.21	>0.05 (N.S.)
	No	19	95%	138	98.6%		
Prophylactic antibiotics	Yes	14	70%	69	49.3	3	>0.05 (N.S.)
	No	6	30%	71	50.7%		
Shape of papilla	Normal	18	90%	122	87.1%	0.13	>0.05 (N.S.)
	Enlarged	2	10%	18	12.9%		
Periamp diverticulum	Yes	2	10%	16	11.4%	0.03	>0.05 (N.S.)
	No	18	90%	124	88.6%		
Dilated IHBR	Yes	17	85%	116	82.9%	0.05	>0.05 (N.S.)
	No	3	15%	24	17.1%		
Non dilated CBD (<8mm)	Yes	8	40%	12	8.6%	15.8	<0.01 (H.S.)
	No	12	60%	128	91.4%		
Pancreatic duct stricture	Yes	4	20%	9	6.4%	4.31	>0.05 (N.S.)
	No	16	80%	131	93.6%		

A highly significant difference was found between patients with PEP (group A) and patients who did not develop PEP (group B) as regards non dilated CBD (<8 mm) while the difference was insignificant as regards the other patient-related risk factors as shown in table (9).

Table (10): Comparison between group (A) and group (B) regarding cannulation-related factors (Chi-square test).

		Pancreatitis group (group A) (n=20)		Non pancreatitis group (group B) (n=140)		X^2	P value
		No	%	No	%		
Cannulation time	Short	8	40%	93	66.4%	5.25	<0.05 (S)
	Long	12	60%	47	33.6%		
Duration of procedure	Short	4	20%	61	43.6%	4.03	<0.05 (S)
	Long	16	80%	79	56.4%		
Difficulty of cannulation	Easy	8	40%	77	55%	1.58	>0.05 (N.S.)
	Difficult	12	60%	63	45%		
Precut sphincterotomy	Yes	5	25%	15	10.7%	3.26	>0.05 (N.S.)
	No	15	75%	125	89.3%		
Guide-wire assisted cannulation	Yes	17	85%	105	75%	0.96	>0.05 (N.S.)
	No	3	15%	35	25%		

Comparison between the patients with PEP and those without showed a significant difference as regards cannulation time and duration of the procedure (Table 10).

Table (11): Comparison between group (A) and group (B) regarding pancreatic manipulations.

		Pancreatitis group (group A) (n=20)		Non pancreatitis group (group B) (n=140)		X^2	P value
		No	%	No	%		
No. of panc duct cannulation	None	5	25%	18	12.9%	5.42	>0.05 (N.S)
	≤ 2 times	6	30%	80	57.1%		
	> 2 times	9	45%	42	30%		
No. of panc duct injection	None	5	25%	25	17.9%	1.52	>0.05 (N.S.)
	≤ 2 times	10	50%	90	64.3%		
	> 2 times	5	25%	25	17.9%		
Pancreatic visualization	None	5	25%	22	15.7%	9.51	<0.05 (S.)
	Main duct	5	25%	81	57.9%		
	1ry branches	8	40%	34	24.3%		
	Acinarization	2	10%	3	2.1%		

A significant difference as regards pancreatic duct visualization was found on comparing patients with PEP and those who did not develop PEP (Table 11).

Table (12): Comparison between group (A) and group (B) regarding contrast-related factors (Chi-square test)

		Pancreatitis group (group A) (n=20)		Non pancreatitis group (group B) (n=140)		X^2	P value
		No	%	No	%		
Type of contrast	Ionic	18	90%	132	94.3%	0.54	>0.05 (N.S)
	Non ionic	2	10%	8	5.7%		
Amount of contrast	≤ 50 ml	10	50%	97	69.3%	2.93	>0.05 (N.S)
	> 50 ml	10	50%	43	30.7%		
Intramural injection of dye	Yes	0	0%	4	2.9%	0.58	>0.05 (N.S.)
	No	20	100%	136	97.1%		
Drainage of dye	Good	12	60%	130	92.9%	18.9	<0.01 (H.S)
	Poor	8	40%	10	7.1%		

Table (12) shows insignificant difference as regards the type of contrast, its amount and intramural injection of dye while the difference was significant as regards the drainage of dye on comparing pancreatitis group to non-pancreatitis one.

Univariate analysis of the factors associated with PEP in tables 9-12 revealed five significant risk factors

which are mentioned in table (13).

Table (13): Summary of significant risk factors for post-ERCP pancreatitis concluded from univariate analysis done in tables 9-12.

Risk factor	P value	Significance
CBD <8 mm (non dilated CBD)	0.001	H.S.
Long cannulation time	0.022	S.
Long duration of procedure	0.045	S.
Pancreatic duct visualization (1ry branches or acinarization)	0.023	S.
Poor drainage of dye	0.000	H.S

Stepwise regression analysis of the 5 significant risk factors mentioned in table (13) showed that the most important 2 factors were:

1- Poor drainage of dye.

2- Non-dilation of CBD (< 8 mm).

Table (14): Stepwise Regression Analysis for the most important risk factors for post-ERCP pancreatitis.

Model	R2	F	(beta)	Sig.
Poor drainage of dye	0.118	21.192	-0.344	0.000
Non-dilated CBD (<8 mm)	0.177	16.939	-0.25	0.001

Discussion:

Post-ERCP pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Because of the potential risks and consequences of post-ERCP pancreatitis, considerable efforts have been made to define patient and procedure-related factors that may be associated with an increased risk of this complication, along with determining interventions that can be done to reduce PEP ***(Cooper and Slivka, 2007).***

Various forms of pharmacologic prophylaxis, usually administered before the procedure, have demonstrated modest reduction in PEP in some randomized controlled trials ***(Bailey et al., 2008).***

The present study included 160 patients who underwent ERCP. The patients were followed for 15 days after the procedure. Univariate and regression analysis were used to assess the impact of risk factors on the occurrence of PEP and to detect the benefit of patients from the drugs used.

There was significant difference between the four studied groups regarding the dilated intrahepatic biliary radicles (IHBR) and the normal diameter of common bile duct (CBD). Dilated IHBR was highest in GTN group (group II) and lowest in the control group (group I) (95% and 70% respectively). The percentage of patients with normal diameter of CBD was highest in diclofenac group and lowest in the octreotide group (25% and 5% respectively).

There was significant difference regarding short cannulation time (<15 minutes), short duration of the procedure (<30 minutes) and difficulty of cannulation among the 4 studied groups. The clinical and statistical significance was in favor of the GTN group when compared to octreotide group but on comparing GTN group to the control group alone, no statistical significance was found (Table 5).

These results agree with ***Kaffes et al. (2006)*** who did not find significant improvement in the ease of cannulation. Also, our study agree with ***Moreto et al. (2003)*** who used the same dose as we gave to patients and found no facilitation in cannulation but he explained this by the fact that they applied the GTN patch only 30 minutes before the procedure which may have not given enough time for the drug to peak in blood. In our study, we applied the patch 2 hours before the procedure but the result was the same as that reported by ***Moreto et al. (2003).***

Contradictory to the present study, ***Ghori et al. (2002)*** found that failure of cannulation was 7% in the GTN group versus 15.8% in his control group. These variable results obtained in the different studies were explained by ***Visvanathan and Priya (2006)*** who reported that mechanical factors such as the angle between the duct and ampulla and papillary stiffness were probably more important determinants of successful cannulation than the size and patency of papillary orifice.

The octreotide group in our study was associated with difficult cannulation and long cannulation time. This is similar to ***Di Francesco et al. (1996) and Testoni (2004)*** who stated that octreotide increase the basal pressure of sphincter of Oddi. On the contrary, ***Thomopoulos et al. (2006) and Li et al. (2007)*** found that octreotide did not cause difficult cannulation. Their results may be explained by the fact that they gave octreotide at least one hour before ERCP (away from the peak level in blood which is reached in 15 minutes).

It was worthy to note that the number of patients with good drainage of dye in the GTN group (group II) was 38 in comparison to 33 cases in the control group (group 1) which, although statistically insignificant, means that nitrate may have a role in relaxing biliary and pancreatic sphincters, thus minimizing the

potential pancreatic outflow obstruction after the procedure as mentioned by ***Kaffes et al. (2006).***

It was found in our study that there was highly significant statistical difference between the 4 groups as regards post-ERCP hyperamylasemia being highest in the control group (77.5%) followed by GTN group (67.5%), then diclofenac group (50%) and lastly octreotide group (45%). We have to mention that the main mechanism of action of octreotide was inhibition of pancreatic enzymes.

The overall incidence of PEP in the present study was 20 of 160 patients (12.5%). This finding was higher than reported by ***Vandervoort et al. (2002)*** (7.2%) and ***Johnson et al. (1995)*** (10.2%) while it was comparable to that reported by ***Hookey et al. (2006)*** (12.1%) and ***Cheng et al. (2006)*** (15.1%).

This variety in the incidence of post-ERCP pancreatitis among the different studies may be attributed to:

a- Variable threshold of amylase required to define pancreatitis.

b- Wide variation of included cases between centers.

c- Endoscopic expertise or the use of preventive techniques such as pancreatic stents.

In our study, no statistically significant difference was found between the 4 studied groups as regards the incidence of PEP which means that no benefit from the used drugs in reducing the incidence of PEP in comparison to the control group. Even, it was found that the number of PEP patients in our study was higher in the GTN group.

These results were similar to a clinical trial done by ***Nojgaard et al. (2008)*** and used the same dose of GTN as our study. It showed insignificant preventive effect of GTN against PEP.

Also, these results agree with ***Kaffes et al. (2006)*** who found no role of GTN in preventing PEP. On the contrary, ***Sudhindran et al. (2001) and Moreto et al. (2003)*** showed favorable outcome with GTN which may be explained by the high incidence of PEP in the control group of these two studies (18% and 15% respectively).

The incidence of PEP in the diclofenac group was equal to that in the control group (10%). This finding was in agree with ***Cheon et al. (2007)*** who found no benefit for diclofenac in reducing the incidence of PEP in high-risk patients.

On the other hand, ***Murray et al. (2003)*** found that diclofenac reduced the incidence of PEP in their patients. These different results may be due to high incidence of PEP in their control group of and the small number of patients in our study.

In our study, the difference between octreotide group and control group regarding the incidence of PEP was statistically insignificant and this was similar to ***Andriulli et al. (2007)*** who concluded in their meta-analysis that octreotide has no effect on PEP.

Contradictory to our results, ***Li et al. (2007)*** found that high dose octreotide (300 g and 500 g respectively) can prevent PEP. We have to mention that we used small dose of octreotide (100 g) in our study.

Our study revealed that, the most significant 5 risk factors for PEP in univariate analysis were:

Diameter of CBD $\leq$ 8 mm. This finding was in agreement with ***Boender et al. (1994)*** who found a statistically significant inverse relationship between CBD diameter and the occurrence of PEP.

Long cannulation time. It was found in our study that 12 of 20 (60%) patients who developed PEP underwent cannulation of CBD in > 15 minutes.

Duration of the procedure. The procedure lasted > 30 minutes in 16/20 (80%) of our patients with PEP. Our finding was similar to that obtained by ***Moneir (2000)*** who found that very difficult and lengthy procedure was a responsible factor for PEP.

The extent of pancreatic duct visualization. The present study showed that the difference between patients with and without PEP (Table 11) was statistically significant as regards the extent of pancreatic duct visualization. These results agree with ***Vandervoort et al. (2002) and Ciocirlan and Ponchon (2004).***

Poor drainage of dye was found in 40% of patients with PEP versus 7.1% in those without PEP. This finding agrees with ***Kaffes et al. (2006)*** who identified this factor as a risky one in multivariate analysis. This may reflect a higher volume of injected contrast or prolonged retention of dye.

Forward stepwise regression analysis of the previously mentioned 5 risk factors showed that 2 of them appeared to be the most important: Poor drainage of dye. Non-dilated CBD ($\leq$ 8 mm).

Conclusions:

Glyceryl Trinitrate, Diclofenac and Octreotide were not effective in the prophylaxis against post-ERCP pancreatitis. Further large scale trails are needed. Further studies are recommended to assess the role of GTN in cannulation time and its effect on the drainage of dye. Non dilated CBD, poor drainage of dye, long cannulation time, lengthy procedure and increasing the extent of pancreatic duct visualization are risk factors for PEP.

We recommend meticulous endoscopic techniques and inserting a prophylactic pancreatic duct stent in high risk patients until an ideal prophylaxis for PEP is reached.

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