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Research Paper

Efficacy of octreotide for various pathological diagnosis in patients undergoing PD procedure: Meta-analysis

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ABSTRACT:-
Background: The aim of this meta-analysis was to analyze the efficacy of octreotide for different histopathological diagnosis in patients undergoing PD.
Methods: A systematic literature search was performed using Pubmed, Embase, and Cochrane library on all those studies published between 1995 to 2015 about the efficacy of octreotide in patients undergoing pancreaticoduodenectomy procedures. 105 studies were identified and 4 studies were included after matching with our inclusion criteria. The primary end points analyzed were octreotide efficacies for patients with pancreatic adenocrcinoma, ampullary carcinoma and other benign pancreatic lesions. The secondary end points analyzed were complication rate and mortality rates.
Results: 4 trials have been included comprising 633 patients in octreotide group and 896 patients in control group. In both the groups, there was no statistically significant difference in the pancreatic adenocarcinoma (P=0.50), Ampullary carcinoma (P=0.16), other benign lesion (P=0.45), Complications (P=0.36) and Mortality rate (P=0.20).
Conclusions: Octreotide has shown no role as a prophylactic treatment for patients undergoing PD who are diagnosed with different pathological diagnosis and thus, the routine use of octreotide as a prophylactic treatment before undergoing PD should not be recommended.

Keywords:- *Pancreaticoduodenectomy, Octreotide, Pancreatic adenocarcinoma, Ampullary carcinoma, Complications, Mortality, Meta-analysis*

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I. INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the major surgical and curative procedure performed for the resectable tumors such as pancreatic carcinoma, ampullary carcinoma and other benign lesion of the hepatobiliary tumors. Although it may be a curative procedure, it has a considerable rate of post operative morbidity and mortality. PD surgical methods have been evolved much largely in recent years with advanced technologies such as surgical techniques, management and post operative care but the concern for the clinicians when considering the complication rate which is about 35 to 65% [1], and the mortality rate which is about 5 to 10 % [2, 3]. With the recent advances in technologies, the mortality rate has been declined but not the complications rate. The most common complication associated after PD is the pancreatic fistula (Pancreatic anastomotic leak), this complication puts a great impact on the patient such as longer stay in the hospital after the surgery, high hospital cost, reoperation, intravenous hyper-alimentation and prolonged placement of intra-abdominal drain which itself increases the chance of infection such as intra-abdominal abscess etc [4,5,6]. Pancreatic fistula is defined as the persistent presence of 50 mL or more amylase rich fluid in the drainage after postoperative day 3. Despite of Various surgical techniques have been proposed in an attempt to prevent or to reduce the risk of the pancreatic fistula occurring after PD, the condition still remains as a complication with little or no improvement. Other two most common complications after PD are delayed gastric emptying and wound infection. In order to reduce the risk of the complication to occur, pharmacologic treatment before undergoing PD surgery may be effective. This type of treatment includes the inhibition of pancreatic exocrine secretion which as a result, the pancreatic enzyme will not be available to drive the fistula. The most common

medication used is octreotide, a somatostatin analogue [7, 8, 9, 10]. Several studies have been studied on the octreotide efficacy for the complication rate, hospital stay, reoperation, and blood loss etc in patients who are a candidate for PD surgery showed that octreotide may not be effective in reducing the risk of fistula and prophylactic octreotide administration should not be used, although some studies conducted in Europe showed that octreotide administration before undergoing PD surgery was associated with lower incidence of pancreatic fistula [11, 12, 13]. Many contradictory results have been obtained for the octreotide efficacy for its usage [14, 15, 16). This meta-analysis is conducted for the efficacy of the octreotide with regard to pathological diagnosis, complication and mortality rate. As to our knowledge, no meta-analysis has been conducted based on our outcomes and so further meta-analysis must be required to support our study.

II. MATERIALS AND METHODS

STUDY SELECTION

A systematic literature search was performed using Pubmed, Embase, and Cochrane library on all those studies published between 1995 to 2015 about the efficacy of octreotide in patients undergoing pancreaticoduodenectomy procedures. The medical subject headings (MeSH) used for the searching the studies was " Pancreaticoduodenectomy and octreotide, Octreotide efficacy for the pancreaticoduodenectomy, complication, pathological diagnosis". All the related article's abstract were reviewed.

DATA EXTRACTION

Three reviewers (RMN, MAH AND SMS) independently abstracted the date from each study. The following data were abstracted: first author, year of publication, study population characteristics, study design, pathologic diagnosis and number of subjects encountered complications more than one. Jadad scoring system was not applied to assess the quality of the studies as two of the included studies in this meta-analysis were not a Randomized Controlled Trials (RCTs). However, flow diagram of the studies has been reported in this meta-analysis as shown in figure 1.

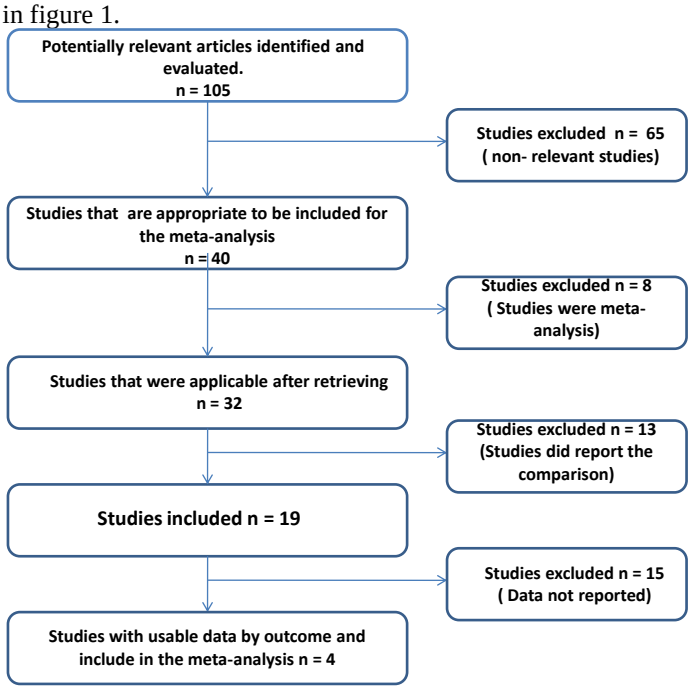

Fig.1: Flow diagram of the studies included in the meta-analysis

INCLUSION AND EXCLUSION CRITERIA

We have included 4 studies (n=4) out of 105 studies (n=105) that compared octreotide Vs. control for patients undergoing PD surgery. Only studies that reported the data of our outcomes were eligible for this meta-analysis. All our parameter must not be given in mean or standard deviation (STD). 65 studies (n=65) were excluded from this analysis as they were review articles and case reports, 8 studies (n=8) were excluded because they were meta-analysis, 13 studies (n=13) were RCTs but not related to our topic so as a results were excluded, 15 studies (n=15) were excluded due to lack of data. 4 studies (n=4) met our eligibility criteria and thus were included to perform this meta-analysis.

III. STATISTICAL ANALYSIS

Outcome data of our parameters were entered into digital database meta-disc spread sheet. The analysis was conducted using the free software program RevMan (review manager (RevMan) version 3.0; the Nordic Cochrane center, Copenhagen Denmark). All our data outcomes were not reported as mean and standard deviation. Dichotomous data, Mantel-Hansel method was applied for the analysis of the outcomes. The results with no heterogeneity a fixed effect model with 95% confidence interval (CI) was used, where as random effects model with 95% CI was used if heterogeneity existed. Results were considered statistically significant if P value < 0.05 provided 95% CI did not include the value 1. The data of our outcomes were entered into the software and the forest plot was generated accordingly for eat parameter. The funnel plot was roughly symmetrical with some minimal publication bias.

IV. RESULTS

ANALYSIS OF THE OUTCOMES

After carefully interpreting each study that compared the efficacy of octreotide Vs. control included for this meta-analysis, a set of outcome measure were identified. Our primary outcome was available to assess the efficacy of octreotide compared with control for patients with pancreatic adenocarcinoma, ampullary carcinoma and other benign pancreatic lesions. Our secondary outcomes were for the complication rate and the mortality rate. The analytical results for the pancreatic adenocarcinoma and other benign pancreatic lesion showed heterogeneity (I^2>50%), as a result, random effect model was applied with Odds Ratio (OR). Other outcomes did not show any heterogeneity and so fixed effect model was applied with OR. The demographics and the outcomes of the study population are listed in table 1. Results of the outcomes for the efficacy of octreotide are illustrated in table 2.

Octreotide efficacy for Pancreatic Adenocarcinoma, Ampullary carcinoma and other benign lesions in patients undergoing PD.

The analysis showed no statistically significant difference for the octreotide efficacy in patients with the diagnosis of pancreatic adenocarcinoma [OR 0.70 (95% CI 0.25 to 1.96); P=0.50] as shown in figure 2. The results for the patients with ampullary carcinoma for the octreotide efficacy was also not statistically significant [OR 0.79 (95% CI 0.56 to 1.10); P=0.16] as shown in figure 3. Efficacy of octreotide for other benign pancreatic lesions also showed no statistical significant difference seen between the two groups [OR 1.62 (95% CI 0.47 to 5.54); P=0.54] as shown in figure 4. Although the analysis showed no significant results for all the primary outcomes, the meta-analysis results of pancreatic adenocarcinoma and ampullary carcinoma favored octreotide group slightly where as for other benign pancreatic lesions, the analysis favored slightly the control group. This shows that octreotide may be effective but not to the significant level for the first two primary outcomes and octreotide may not be effective at all for other benign pancreatic lesions.

Prophylactic preoperative octreotide efficacy for complication and mortality rates.

There was no significant difference observed for the complication rate in figure 5 [OR 1.10 (95% CI 0.87 to 1.37); P=0.36], and for the mortality rate in figure 6 [OR 1.61 (95% CI 0.78 to 3.35); P= 0.20]. The analysis favored same efficacy between the two groups for complication rate and favored control group for the mortality rate. This shows that octreotide has no any efficacy neither in complication rate reduction nor in mortality rate and octreotide must not be used as a prophylaxis treatment before PD surgery.

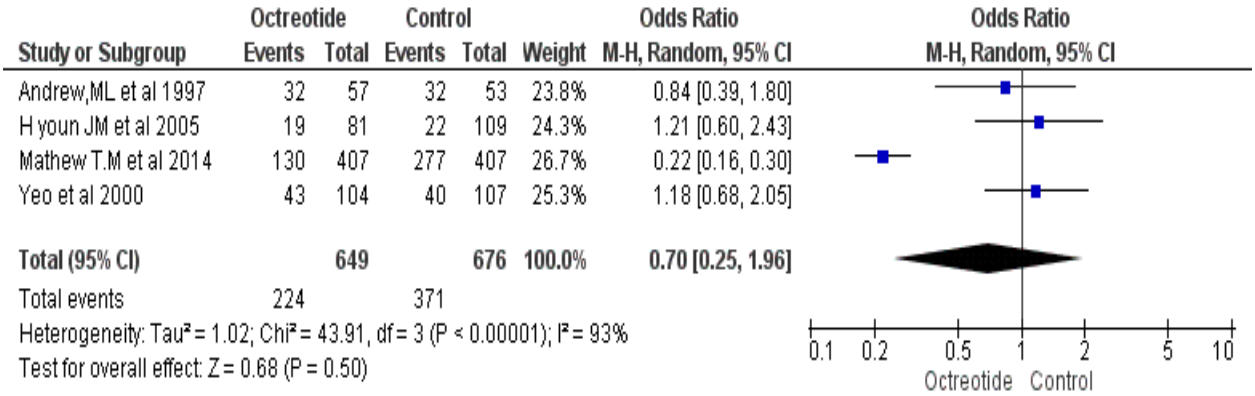

Fig2. Meta-analysis of octreotide efficacy for pancreaticoadenocarcinoma

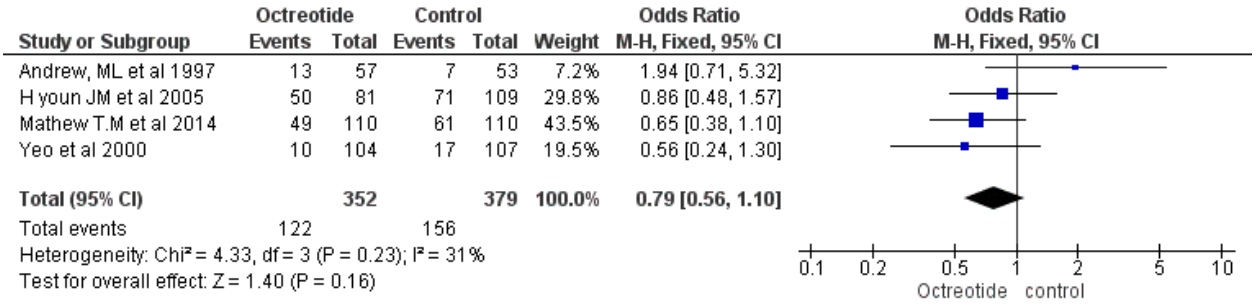

Fig3. Meta-analysis of octreotide efficacy for ampullary carcinoma

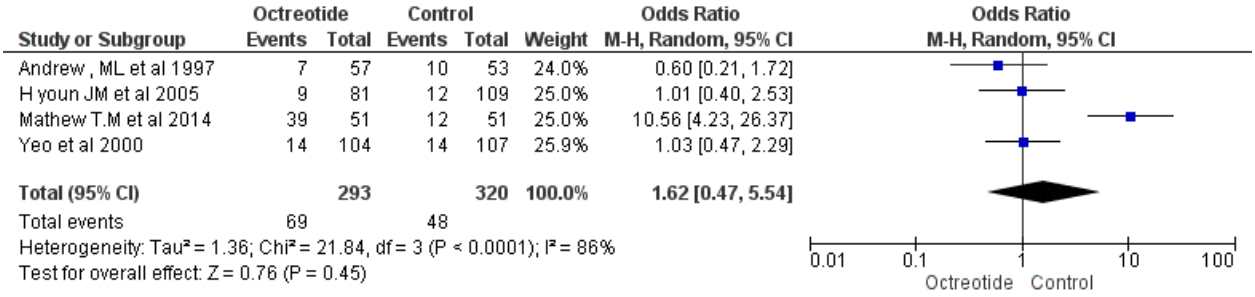

Fig4. Meta-analysis of octreotide efficacy for other benign pancreatic lesions

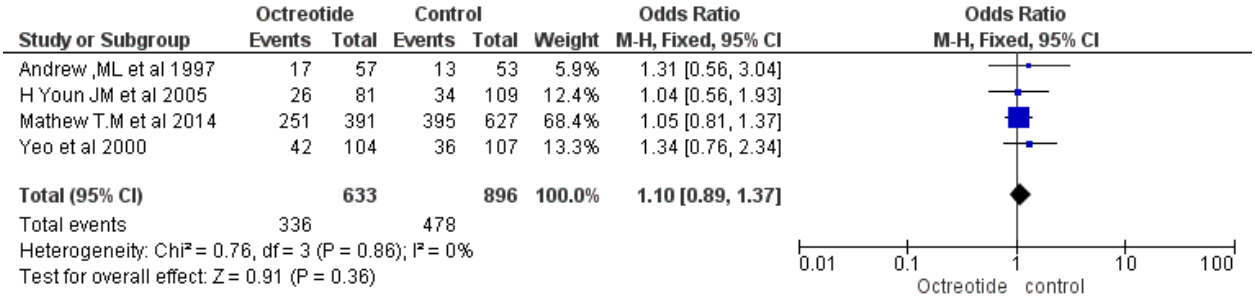

Fig5. Meta-analysis of octreotide efficacy for complications

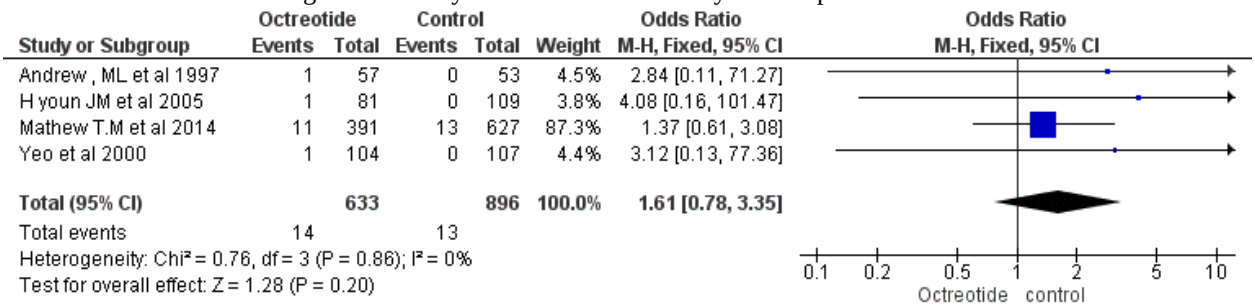

Fig6. Meta-analysis of octreotide efficacy for mortality rate.

Table 1: Demographics and the outcomes of the study population

Study	Intervention	N	Age (Mean)	Gender M/F	PAC	APC	Other BL	Comp.	Mortality
Andrew M.L et al (20)	Octreotide	57	63	32/25	32	13	1	17	1
1997,USA	Control	53	63	25/28	32	7	4	13	0
Hyoun JM et al (19)	Octreotide	81	58.8	49/32	19	50	9	26	1
2005, Korea	Control	109	57.7	64/45	22	71	12	34	0

Mathew et al (17)	Octreotide	391	–	–	130	49	39	251	11
2014, USA	Control	627	–	–	277	61	12	395	13
Yeo et al (18)	Octreotide	104	65	59 (M)	43	10	14	42	1
2000, USA	Control	107	67	52 (M)	40	17	14	36	0

M/F, Male, Female; M, male; PAC, Pancreaticadenocarcinoma; APC, Ampullary Carcinoma; BL, Benign Lesion; Comp, Complication

Table 2: Results of the outcomes for the efficacy of the octreotide

outcomes	Number of studies	Participants	Odds ratio (M-H, 95% CI)	Statistical difference
Pancreatic adenocarcinoma	4	1325	[R] 0.70 (0.25, 1.96)	NS (P= 0.50)
Ampullary carcinoma	4	731	[F] 0.79 (0.56, 1.10)	NS (P=0.16)
Other benign lesions	4	613	[R] 1.62 (0.47, 5.54)	NS (P=0.45)
Complications	4	814	[F] 1.10 (0.89, 1.37)	NS (P=0.36)
Mortality	4	1529	[F] 1.61 (0.78, 3.35)	NS (P=0.20)

[R], Random effect model; [F], Fixed effect model; NS, non-significant

V. DISCUSSION

This meta-analysis was designed to evaluate the efficacy of prophylactic octreotide in patients undergoing elective PD. The primary end points analyzed were octreotide efficacies for patients with pancreatic adenocrcinoma, ampullary carcinoma and other benign pancreatic lesions. The secondary end points analyzed were complication rate and mortality rates. Nowadays, PD remains the only curative intervention for most of the tumors arising in the Common Bile Duct (CBD), Duodenum and pancreas. Most of the procedures when performed at high centers, the result is associated with improved outcomes [21], despite of this improved outcomes seen at high volume centers, the incidence of postoperative complications remains high. Various studies had been conducted for the efficacy of octreotide for the outcomes such as complications, operative time, hospital stay, blood loss etc, but our study does not address the above mentioned outcomes which is to our knowledge no meta-analysis have been reported based on our parameters.

Some studies have supported the use of prophylactic administration before undergoing PD and found that the incidence of the clinically relevant pancreatic fistula was lowered [22]. According to our analysis, octreotide does not appear to show any statistically significant result for both the primary and secondary outcomes. Prophylactic administration of octreotide in patients with pancreatic adenocarcinoma did not show any significant difference with the control group (P=0.50) even though forest plot (fig.1) favored octreotide group. In 2014, Matthew T.M et al [17] studied on 130 patients who received octreotide in patients diagnosed with pancreatic adenocarcinoma, 49 patients with ampullary carcinoma and 39 patients with other benign lesions where they obtained a significant result for pancreatic adenocarcinoma and for other benign lesions ($p<0.001$) and not for the ampullary carcinoma (P=0.161), but in a study, Yeo et al, [18] showed no significant results in patients who had received octreotide which is associated with our outcomes. The prophylactic octreotide administration conducted by various studies remained contradictory. In a study of Hyoun J.M et al [19], no any characteristically significant result (P=0.982) for patient with pancreatic adenocarcinoma, ampullary carcinoma and other benign lesions were obtained. All these studies showed that prophylactic octreotide was not effective and did not produce clinically significant results in terms of histopathological diagnosis. Regarding the effect of octreotide for the complications and mortality rates, the incidences were similar in both the groups and no statistically significant differences observed. The most common complication

encountered in both the groups was pancreatic anastomotic leak (pancreatic fistula). Number of deaths were encountered in octreotide group was almost similar to control groups as conducted by previous studies. In a study, Montorsi et al, found that the rates of pancreatic fistula had not differences between the octreotide and the control groups (23). Octreotide have been studied for the complications which showed that, the incidence of delayed gastric emptying was reduced, but not the pancreatic fistula [24].

Octreotide has the ability to inhibit the secretion of pituitary growth hormone (GH), insulin like growth factor-1 (IGF-1) and epidermal growth factor (EGF), all of which accelerate the wound healing [25, 26, 27, 28], so the healing of gastrointestinal ulcers may be delayed with the use of octreotide due to EGF inhibition [29]. Another major complication encountered with the octreotide administration (intravenously or subcutaneously) could decrease the splanchnic blood flow [31]. According to our study, prophylactic octreotide administration in patients undergoing PD not have a particular benefit in patients with different histopathological diagnosis, complications and mortality rates. Further, octreotide therapy did not have any influence in the rates of complications such as wound infections, intra-abdominal abscess, delayed gastric emptying etc, and also has no any other influences, such as post operative hospital stay, operative time etc.

In conclusion, we suggest that octreotide has no role as a prophylactic therapy in patients undergoing PD, thus, the routine use of octreotide as a prophylactic treatment before undergoing PD should not be recommended. Octreotide may be recommended in patients with high risk for pancreatic complications [30]. Further studies need to be done before applying in the routine clinical care.

COMPETING INTEREST

The authors declare that they have no any conflict of interest.

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