Original Article

A Randomized Comparative Study of the Use of Individual Modality and Combination of Endoscopic Retrograde Cholangiopancreatography (ERCP) and Digital Single-Operator Cholangioscopy (DSOC) for Diagnosis of Indeterminate Biliary Strictures

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Abstract

Background: To determine the superiority of the combination of endoscopic retrograde cholangiopancreatography (ERCP) and digital single-operator cholangioscopy (DSOC) in the same sitting over the individual modality alone in patients with indeterminate biliary strictures.

Materials and Methods: A randomized study enrolled 60 adult patients with biliary strictures who were randomized into two groups: ERCP + DSOC and ERCP/DSOC. Histopathologic or cytologic assessment was performed in terms of benign, indeterminate, or malignant nature of the strictures. Procedural adverse events were documented. Accuracy in terms of sensitivity (Sn), specificity (Sp), and predictive value [positive (PPV) and negative (NPV)] were noted.

Results: As per final diagnosis, in ERCP/DSOC group, there were 12 (40%) benign cases and 18 (60%) malignant cases, and in group ERCP + DSOC, there were 8 (26.67%) benign cases and 22 (73.33%) malignant cases. ERCP/DSOC labeled 16 (53.33%) patients as benign, 8 (26.67%) as malignant, and 6 (20%) as indeterminate, while ERCP + DSOC labeled 8 (26.67%) as benign, 17 (56.67%) as malignant, and 5 (16.67%) as indeterminate. The Sn, Sp, PPV, and NPV of ERCP/DSOC were 44.4%, 75%, 100%, and 56.25%, and for ERCP + DSOC was 77.27%, 62.50%, 100%, and 62.5%, respectively ($P = 0.033$). Side effects were statistically similar in both the groups ($P > 0.05$).

Conclusion: To conclude, the combination of ERCP with DSOC is safe and effective with higher diagnostic sensitivity (77.27%) in comparison to standard ERCP or DSOC alone (44.4%) for the diagnosis of biliary strictures.

Keywords: Biliary tract, biopsy, cytology, diagnosis, endoscopy, pathology, sensitivity, specificity

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Introduction

Up to 20% of the biliary strictures remain indeterminate after extensive clinical and imaging investigations.[1] Since such indeterminate biliary strictures may be malignant in nature, the correct diagnosis remains important to plan an apt management strategy.[2,3]

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Initial investigative approach to indeterminate biliary strictures involves the use of non-invasive imaging and serum blood test. In non-invasive imaging, trans-abdominal ultrasound examination is the primary modality which

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locates the biliary strictures but fails in aligning the detailed anatomic description. In serum blood test, markers like carcinoembryonic antigen (CEA) and CA 19-9, i.e., carbohydrate antigen 19-9, are used to rule out malignancy. Other imaging tests involve computed tomography (CT) and MRI which provide wide comprehensive evaluation of the biliary strictures. However, these does not allow the sampling of the strictures. So, on a traditional note, ERCP is the first test which is used for the evaluation of indeterminate biliary strictures so that sampling can be taken by either blood cytology or biopsy.[4,5]

Research over the time shows that ERCP-guided brush cytology holds a low sensitivity of 15–60%.[6] This has been mainly ascribed to the fact that direct visualization is not possible, and secondly, cholangiocarcinomas have a hypervascularized endoplasmic stroma, thus not allowing an adequate sampling by brush cytology.[2] Superseding ERCP, a tool named DSOC was developed, which provides a high-resolution visualization of the bile duct directly, thereby allowing for biopsy sampling and intervention.[2]

Studies have shown that sensitivity of DSOC ranges from 66% to 72% for diagnosing malignant nature in indeterminate cases.[7] Moreover, the use of DSOC also decreases the cost for evaluation of indeterminate strictures. Still, overall, there is lack in complete sensitivity of detection of malignant nature of strictures even with DSOC.[4-7]

Thereby the research continues, and it has been shown that the sensitivity of the individual investigative modality can be improved further beyond 60%–70% if they are used in combination.[3,8] This seems logical also because the limitations of either investigative modality can be covered by the other investigative modality. Moreover, the cytology and biopsy reports can be combined and assessed by the pathologists, and they can be discussed by the endoscopists so that minimal malignancies are missed out while investigating the patients with indeterminate biliary strictures.[9]

Till date, to our knowledge, no previous studies have compared the combination of ERCP-guided brush cytology and DSOC-directed biopsy combination against the sensitivities of individual modalities for diagnosing the patients of indeterminate biliary strictures.

Thus, the present study was conducted where we compared the efficacy of combined ERCP and DSOC against the individual modalities to accurately diagnose malignant nature of indeterminate biliary strictures, thereby allowing a better management of the patients.

Materials and Methods

We conducted an open-labeled non-blinded randomized interventional study over the period of one year (December 2021 to December 2022) in a tertiary care hospital of Bihar, India, wherein 60 consecutive patients of indeterminate biliary strictures were enrolled and divided randomly into two interventional groups by block randomization with sealed envelope system.

Every time for randomization, ten envelopes which were opaque and sealed were taken among which five were named as A and five were named as B, where A represented group ERCP/DSOC while B as group ERCP + DSOC. Every time a patient came, an envelope was selected and opened, and the group was allocated as per Group A and Group B written on the envelope. So, in the batches of 10 patients each, a total of 60 patients were randomized.

The two groups were ERCP/DSOC group (n = 30): ERCP visual impression and ERCP-guided brushing or DSOC-guided biopsy with one arm of ERCP-guided sphincterotomy and ERCP + DSOC group (n = 30): Combined ERCP-guided brush cytology and DSOC impression with DSOC-guided biopsy sampling.

Inclusion criteria were Age ≥ 18 years, Biliary obstructive symptoms like jaundice, cholangitis, pruritis, and not explained by other etiologies, Indeterminate biliary stricture – proximal to distal common bile duct (CBD) and intrinsic as per MRCP.

The patients who were contraindicated for endoscopy, pregnant patients, patients with coagulopathy, patients who had already undergone ERCP□guided transpapillary forceps biopsy (TPB) while evaluation of indeterminate biliary strictures and patients who had any extrabiliary cause of compression as diagnosed in the imaging were excluded.

Sample size calculation

The sample size was calculated for the present study based on the observation of the previous study by Kitajima *et al*.,[10] where sensitivity of ERCP + DSOC was 72.8%. This value was taken as reference and formula was applied, with 80% study power, 20% precision, and 5% alpha level. Minimum required sample was 30 patients for the study for one group. So taking 1:1 ratio, 60 patients were recruited for study with 30 patients in each group.

Procedure

Ethical clearance and patient consent were obtained. For the study, biliary strictures were classified as per Bismuth–Corlette classification[11] after doing MRCP. Malignancy (whether present or absent or indeterminate) was recorded by cholangiography. The ERCP brushing with minimum 9 passes was performed, and the sample was sent for cytology after fixing on the slide. For the procedure, RX cytology brush was used with dimensions of 2.1 mm × 8F or 3 mm × 6F Cytomax II Double Lumen Cytology Brush (Boston Scientific Corp, Marlborough, Massachusetts, United States).

For DSOC, three biopsy samples were taken to diagnose whether malignancy was present, absent, or indeterminate through the DSOC miniscope (SpyBite; Boston Scientific Corp, Marlborough, Massachusetts, United States). The biopsy samples were processed and sent to histopathology lab. The final reports were obtained from the cytopathologist

or histopathologist at a center without any blinding. For the combination of ERCP + DSOC, both samples were sent together to the laboratory for a single final report.

A 30-day follow-up was kept for every patient after the procedure by either telephonically or personal visit. The follow-up continued further till 6 months after the procedure on confirming whether the malignancy was present or absent.

Statistical analysis

Data recorded was entered in the Excel spreadsheet and analyzed by "Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0". Data was presented in n (%), means ± SD and as median with 25–75th interquartile. Specific tests used were Mann–Whitney test, independent *t*-test, Chi-square test, and Fisher's exact test.

Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were calculated for both interventions for predicting malignancy. Inter-rater kappa agreement was used to find out strength of agreement between visual impression and diagnosis. *P* value of less than 0.05 was considered statistically significant.

Results

In the group ERCP/DSOC, the mean age of the patients was 56.07 ± 4.91 years with 19 (63.33%) males; 7 (23.33%) smokers, and 4 (13.33%) alcoholics. The commonest clinical symptom was jaundice in 16 (53.33%) patients, and on examination, pallor was seen in 10 (33.33%), icterus in 16 (53.33%), and edema in 2 (6.67%) patients. In comparison, in the ERCP + DSOC group, the mean age of the patients was 56.73 ± 5.08 years with 20 (66.67%) males; 7 (23.33%) were smokers, and 4 (13.33%) were alcoholics. The commonest clinical symptom was jaundice in 19 (63.33%) patients, and on examination, pallor was seen in 10 (33.33%), icterus in 19 (63.33%), and edema in 3 (10%) patients. There was no significant difference in the baseline demographic and clinical characteristics of the two study groups ($P > 0.05$) [Table 1].

Procedure wise, compared to ERCP/DSOC group, the patients with ERCP + DSOC group had comparable use of metal stent (6.67% vs. 3.33%) and plastic stents (93.33% vs. 96.67%, $P = 1$) and significantly higher procedural duration (57.23 ± 5.39 vs. 29.87 ± 6.37 minutes, $P < .0001$) [Table 1]. All the patients underwent sphincterotomy.

Distribution of bismuth classification was comparable between ERCP/DSOC and ERCP + DSOC (Bismuth classification:- 1:- 66.67% vs 53.33% respectively, 2:- 13.33% vs 20% respectively, 3a:- 10% vs 13.33% respectively, 3b:- 6.67% vs 6.67% respectively, 4:- 3.33% vs 6.67% respectively (*P* value = 0.894)) [Figure 1].

As per final diagnosis, in ERCP/DSOC group, there were 12 (40%) benign cases and 18 (60%) malignant cases, and in group ERCP + DSOC, there were 8 (26.67%) benign cases and 22 (73.33%) malignant cases. Among them, procedurally, ERCP/DSOC labeled 16 (53.33%) patients as benign, 8 (26.67%) as malignant, and 6 (20%) patients as indeterminate; while ERCP + DSOC labeled 8 (26.67%) as benign, 17 (56.67%) patients as malignant, and 5 (16.67%) cases as indeterminate [Table 2].

The combination (ERCP + DSOC) had a Sn, Sp, PPV, NPV and diagnostic accuracy of 77.27%, 62.5%, 100%, 62.5%, and 73.33%; while either ERCP/DSOC procedure had a Sn, Sp, PPV, NPV and diagnostic accuracy of 44.44%, 75%, 100%, 56.25%, and 56.67%, respectively. In prediction of malignancy, ERCP/DSOC had significantly lower sensitivity than ERCP + DSOC (44.44% vs 77.27%, $P = 0.033$) [Table 3].

For ERCP as individual procedure in the group ERCP/DSOC, overall concordance rate was 80% (K = 0.668, $P < 0.0001$).

Table 1: Clinical and procedural characteristics of the study groups

Characteristics	ERCP/DSOC (*n*=30)	ERCP + DSOC (*n*=30)	*P*
Mean age	56.07±4.91	56.73±5.08	0.607
Males	19 (63.33%)	20 (66.67%)	0.787
Smoking	7 (23.33%)	7 (23.33%)	1
Alcohol	4 (13.33%)	4 (13.33%)	1
Clinical symptoms			
Pain abdomen	10 (33.33%)	14 (46.67%)	0.292
Nausea/vomiting	8 (26.67%)	10 (33.33%)	0.573
Jaundice	16 (53.33%)	19 (63.33%)	0.432
Loss of appetite	11 (36.67%)	10 (33.33%)	0.787
Fever	7 (23.33%)	5 (16.67%)	0.519
Pruritus	11 (36.67%)	13 (43.33%)	0.598
Weight loss	3 (10%)	3 (10%)	1
Clinical examination			
Pallor	10 (33.33%)	10 (33.33%)	1
Icterus	16 (53.33%)	19 (63.33%)	0.432
Edema	2 (6.67%)	3 (10%)	1
Stent			
Metal	1 (3.33%)	2 (6.67%)	1
Plastic	29 (96.67%)	28 (93.33%)	
Mean duration of procedure (minutes)	29.87±6.37	57.23±5.39	<.0001

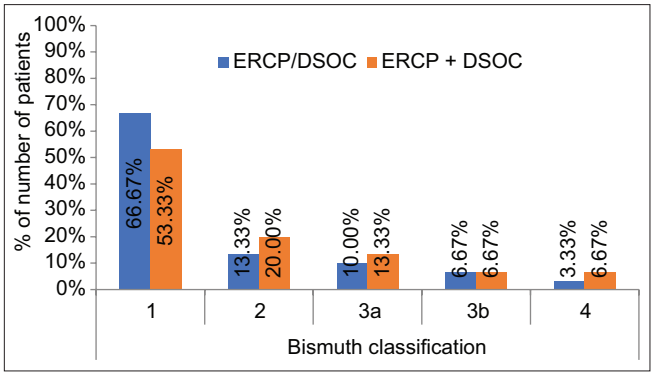

Figure 1: Comparison of bismuth classification between ERCP/DSOC and ERCP + DSOC, Fisher's exact test

Table 2: Association of procedural and final diagnosis

Diagnosis on ERCP + DSOC	Final diagnosis		Diagnosis on ERCP/DSOC	Final diagnosis	
	Benign ($n=8$)	Malignant ($n=22$)		Benign ($n=12$)	Malignant ($n=18$)
Malignant	0	17	Malignant	0	8
Benign	5	3	Benign	9	7
Indeterminate	3	2	Indeterminate	3	3

Table 3: Predictive ability of ERCP + DSOC and ERCP/DSOC for malignancy

Measure	ERCP + DSOC	ERCP/DSOC	*P*
Sensitivity	77.27% (17/22)	44.44% (8/18)	0.033†
Specificity	62.50% (5/8)	75% (9/12)	0.642*
Positive predictive value	100% (17/17)	100% (8/8)	-
Negative predictive value	62.50% (5/8)	56.25% (9/16)	1*
Diagnostic accuracy	73.33% (22/30)	56.67% (17/30)	0.176†

†Chi-square test, *Fisher's exact test

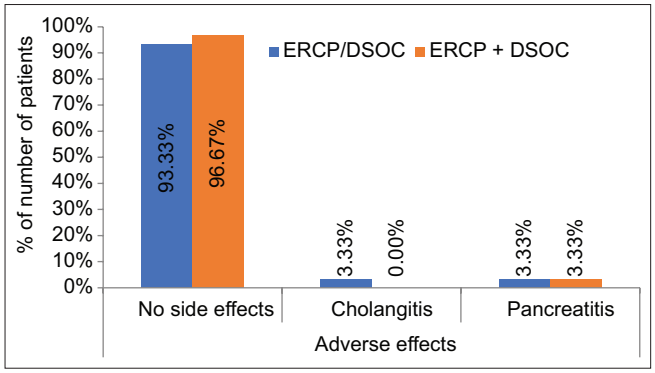

Figure 2: Comparison of adverse effects between ERCP/DSOC and ERCP + DSOC. Fisher's exact test

For DSOC as individual procedure in the group ERCP/DSOC, overall concordance rate was 80% (K = 0.692, $P = 0.001$). For the combination of ERCP + DSOC, overall concordance rate was 90% between diagnosis and visual impression (K = 0.833, $P < 0.0001$) [Table 4].

Distribution of adverse effects was comparable between ERCP/DSOC and ERCP + DSOC. (cholangitis:- 3.33% vs 0% respectively, pancreatitis:- 3.33% vs 3.33%, respectively) (*P* value = 1) [Figure 2].

Discussion

The present study was a randomized study where we compared the use of ERCP/DSOC and ERCP + DSOC among 30 cases each for diagnosis of biliary strictures. The randomization procedure in the present study ensured that baseline demographic characteristics like age, gender, history of addiction, clinical symptoms, and clinical examination findings were comparable among the patients of two groups who presented with biliary strictures, and the outcomes were purely due to differential intervention, thereby increasing the validity and power of the study.[12]

Biliary strictures remain complicated as it may be due to benign causes or malignant causes, and brushing cytology and biopsy are the methods that may determine whether the stricture is because of malignant or benign causes.[2-4] A correct malignant diagnosis is very essential as the management totally depends on it. Research over the period of time continues to increase the sensitivity of diagnosis, and this study is one of the first attempts to use the combination of ERCP with DSOC to further increase the diagnosis for malignancy.[3-6]

We observed that the combination procedure enhanced the sensitivity of detecting malignancy by a significant amount from 44.4% with either procedure to 77.27% with the combination ($P = 0.033$). To the best of our knowledge, no previous study has been conducted that compared the diagnostic accuracy of ERCP + DSOC with either ERCP/DSOC. However, some of the previous studies compared brushing/biopsy with brushing + biopsy taken during ERCP. In one of such study, Weber A *et al*.[13] compared diagnostic accuracy of ERCP brush cytology/forceps biopsy and combination of ERCP brush cytology + forceps biopsy for biliary strictures, and it was found that out of 58 patients, brush cytology spotted malignancy in 24 (41.4%) patients and forceps biopsy in 31 (53.4%) patients, while the combination increased the diagnostic sensitivity to 60.3% (35 out of 58 patients). They found combination to be better than either technique alone, which is similar to the present study. However, they did not compare DSOC that is latest technique, and thus, our study is superior as it compared ERCP/DSOC with ERCP + DSOC.

In a similar systematic review, Navaneethan *et al*.[8] found that brushings had Sn, Sp of 45%, and 99%, intraductal biopsies had Sn, Sp of 48.1% and 99.2%, while combination of the two had diagnostic sensitivity of 59.4% for the diagnosis of malignant biliary strictures. Our study further adds to this notion where combination of ERCP-guided brush cytology and DSOC-guided biopsy increases the sensitivity to detect malignant biliary strictures. Jang S *et al*.[14] also supported the fact that combination of DSOC-guided biopsy and ERCP-guided brush cytology (80.6%) supersedes guided brush cytology accuracy alone (47.1%). The higher accuracy with DSOC was ascribed to better biliary lumen visualization by using better optics.

Particularly in relation to indeterminate biliary strictures, in the present study, it was seen that two malignant and three benign cases were diagnosed as indeterminate as per ERCP + DSOC, while in ERCP/DSOC, three malignant and three benign cases were diagnosed as indeterminate ($P > 0.05$)

Table 4: Inter-rater kappa agreement between visual impression and diagnosis

Procedure	Benign (visual/diagnosis)	Indeterminate (visual/diagnosis)	Malignant (visual/diagnosis)	Kappa, *P*
ERCP (*n*=20)	9/12	5/5	2/3	0.668, *P*<0.0001
DSOC (*n*=10)	3/4	1/1	4/5	0.692, *P*=0.001
ERCP + DSOC (*n*=30)	6/8	5/5	16/17	0.833, *P*<0.0001

with no significant difference. When conventional diagnostic techniques (endoscopy or transabdominal imaging) are unable to identify a specific etiology, a biliary stricture is labeled as "indeterminate." An accurate diagnosis in such cases is crucial, especially if the case is of an early stage malignancy which can be treated.[14] Moreover, overall, the concordance rate between visual impression and biopsy/brushing was higher with ERCP + DSOC (90%) in comparison to ERCP or DSOC alone (80%), adding to the further advantages of the combination procedure.

While noting the efficacy of the procedure, it is always mandatory to observe the side effects, and in that aspect, both procedures had comparable side effects such as cholangitis (3.33% vs. 0%) and pancreatitis (3.33% vs. 3.33%) ($P = 1$). Among other previous studies, Jang S *et al*.[14] reported that adverse outcomes were seen in 7 (6.7%) patients: pancreatitis in 3 (2.9%), cholangitis in 3 (2.9%), and bile duct injury in 1 (1%) patient. Kitajima *et al*.[10] found that mild pancreatitis developed in 5 (3.7%) patients. Wen LJ *et al*.[15] reported that the pooled adverse event rate was 7% where the main complications included cholangitis, post-ERCP pancreatitis, perforation, and bleeding. Overall, the side effects profile does not deter the use of the combination procedure over the single procedure.

Limitations of the study

- In the combination group of ERCP + DSOC, hemorrhage caused due to ERCP might have restricted the visual analysis on DSOC.
- Experience of the endoscopist was not taken into account.
- The study did not conduct a cost-effectiveness analysis.
- Although the randomization ensured the comparable baseline characteristics of the patients of both groups, we could not do blinding of the procedures for the operator.

Conclusion

To conclude, the combination of ERCP with DSOC is safe and effective with higher diagnostic sensitivity (77.27%) in comparison to standard ERCP or DSOC alone (44.4%) for the diagnosis of biliary strictures. The effectiveness of ERCP/DSOC in evaluating indeterminate biliary strictures does not seem to show improvement by ERCP + DSOC. ERCP + DSOC diagnosis showed a superior visual agreement with the diagnosis with concordance rate of 90%.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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