

Title: Balloon dilation itself may not be a major determinant of post-ERCP pancreatitis: review of endoscopic papillary balloon dilation and endoscopic papillary large balloon dilation

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The manuscript has been improved according to the suggestions of reviewers:

Reviewer-2

For reviewer

I appreciate your kind and careful comment of our paper.

Evaluations:

Comments To Authors

This is a review article about EPBD and EPLBD. It was well written, but the conclusion was not widely acceptable from this review.

Major Comments;

1, Title should be changed. It could not be concluded that EPBD itself was not a major risk contributor of PEP, except for EPLBD and PTPBD.

→ This review article focused on the causes of post-ERCP pancreatitis (PEP) following balloon dilation (EPBD, EPLBD and PTPBD). Although the precise

mechanisms underlying PEP following balloon dilation are unclear, we aimed to demonstrate that the principal determinant of severe PEP is edema or spasm caused by irritation of the pancreatic orifice while performing difficult selective cannulation and concomitant difficult removal of the stone, rather than balloon compression of the pancreatic flow in EPLBD or EPBD. The results and conclusions of the present review article accord with those of a previous comparative study.^[1] We request that you take this point into consideration, and we also wish to retain the original title of the article.

1 Seo YR, Moon JH, Choi HJ, Kim DC, Lee TH, Cha SW, Cho YD, Park SH, Kim SJ. Papillary balloon dilation is not itself a cause of post-endoscopic retrograde cholangiopancreatography pancreatitis; results of anterograde and retrograde papillary balloon dilation. *Journal of gastroenterology and hepatology* 2013; **28**(8): 1416-1421 [PMID: 23701518 DOI: 10.1111/jgh.12277]

2, In page 5, you mentioned that ‘EPBD is performed in patients with a mostly normal, non-dilated CBD.’ It was not true. The indications for EPBD did not depend on the size of CBD. Please revise it.

→ EPBD has been used in the treatment of dilated CBD in many studies, as we described. The size of the CBDs also differed across these studies (Table 1). However, the size of the balloon in EPBD is less than 10 mm, such that its use is applicable to small CBD stones only. Balloon dilation is not required for enlargement of the sphincter

of Oddi to a size greater than that of the stone itself. We referred to the mini-review published in WJG^[2] to define the indication for EPBD (Figure 1). Another study^[3] suggested that the ideal patients for EPBD are those with a smaller number of CBD stones (≤ 3), of a maximum diameter of ≤ 10 mm, and with a minimally dilated bile duct. We therefore altered our text accordingly per your recommendation.

EPBD is performed in patients with a non- or minimally dilated CBD

Table 1.

Year	Author	Nation	Stone size(mm)	Duct size(mm)	Balloon size(mm)	Indication
1995	Minami	Japan	<12	NA	8	
1995	Mathuna	Ireland	8		8	
1996	Tytgat	REVIEW			8-10	
1997	Bergman	Netherland	10		8	
1997	Kodama	Japan			10	
1999	Ueno	Japan			4 atm	
2001	Arnold	Germany	<20		8	Small CBD stone
2001	Bergman	Netherland	9		8	
2001	Yasuda	Japan		15.1	8	
2003	Vlavianos	UK	5~10	>7 (80%)	10	
2003	Fujita	Japan	7~7.3	11.8~12.7	4~8	Coagulopathy B-II
2003	Sugiyama	Japan	<10	>9 (76%)	8	Caution in patients with non-dilated

Year	Author	Country	Small Balloon Diameter (mm)	Large Balloon Diameter (mm)	Number of Patients	Notes
2004	Disario	USA	6 (0.5~10)	10 (4~20)	8	duct
2004	Tanaka	Japan	10.2(5~15)		8	
2004	Baron	REVIEW				Stone number<3 Stone size<10mm Minimal dilated CBD
2005	Tsujino	Japan	2~32	9.8	8	
2007	Tsujino	Japan	7.8±4.5	11.5±4.6	8	Anatomic variation Diverticulum Cirrhotic patients
2008	Ito	Japan	7.3~10.3	10.8~13.2	8	
2011	Chung	Korea(review)		6~15	6~15	Coagulopathy Periampullary diverticulum B-II GJstomy Prior EST status

Figure 1.

Table 1 Comparison of endoscopic balloon dilation methods according to balloon diameter

	Small-balloon EPBD	Large-balloon EPBD
Balloon diameter used	≤ 10 mm (6-10 mm)	≥ 12 mm (12-20 mm)
Target stone	Small to moderate sized stones in no or minimally dilated CBD	Large stones in considerably dilated CBD
Endoscopic biliary sphincterotomy	Not performed	Mostly, in conjunction with a small EST ¹

¹Preceding small-endoscopic biliary sphincterotomy (EST) use may shift the expansile force more toward the common bile duct (CBD) rather than the pancreatic orifice. EPBD: Endoscopic papillary balloon dilation.

2 Jeong SU, Moon SH, Kim MH. Endoscopic papillary balloon dilation: revival of the old technique. *World journal of gastroenterology : WJG* 2013; **19**(45): 8258-8268 [PMID: 24363517 PMID: 3857449 DOI: 10.3748/wjg.v19.i45.8258]

3 Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. *The American journal of gastroenterology* 2004; **99**(8): 1455-1460 [PMID: 15307859 DOI: 10.1111/j.1572-0241.2004.30151.x]

Reviewer-3

This study evaluated the clinical efficacy of EPBD and EPLBD for large CBD stones.

This manuscript was well written. However, there are some problems to be resolved.

1. Page 5, lines 18-19:

“EPBD is performed in patients with a mostly normal, non-dilated CBD”

The indications of EPBD did not depend on the diameter of CBD. The authors should revise specific indication of EPBD in the revised manuscript.

→ EPBD has been used in the treatment of dilated CBD in many studies, as we described. The size of the CBDs also differed across these studies (Table 1). However, the size of the balloon in EPBD is less than 10 mm, such that its use is applicable to small CBD stones only. Balloon dilation is not required for enlargement of the sphincter of Oddi to a size greater than that of the stone itself. We referred to the mini-review

published in WJG^[2] to define the indication for EPBD (Figure 1). Another study^[3] suggested that the ideal patients for EPBD are those with a smaller number of CBD stones (≤ 3), of a maximum diameter of ≤ 10 mm, and with a minimally dilated bile duct. We therefore altered our text accordingly per your recommendation.

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2004	Tanaka	Japan	10.2(5~15)		8	
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2. Page 7, line 12:

“Gradual dilation”

How slow is the speed of inflation? Is there a standard or recommendation for it?

Besides, how long should we inflate the balloon after disappearance of the waist? The authors should cite concrete dilation methods in the revised manuscript.

→ The velocity and duration of balloon inflation varies across studies, ranging between a few seconds to minutes. Although guidelines pertaining to the optimal velocity of balloon inflation have yet to be established, the most important consideration is that the balloon should be inflated slowly, to allow for detection of any resistance during ballooning; inflation should be discontinued when resistance is discerned to avoid complications including perforation. We refer to this process as ‘gradual dilation’. Guidelines pertaining to the duration of balloon inflation also remain to be established. Although a previous comparative study^[4] reported that 5-minute ballooning improves the efficacy of stone extraction and reduces the risk of pancreatitis compared with

conventional 1-minute ballooning, a different study^[5] showed that 30-s papillary balloon dilation was equally effective to 60-s dilation. Therefore, we cannot yet confirm the optimal parameters for balloon inflation velocity and duration. Based upon our observations and experience, however, we recommend that balloon inflation velocity and duration proceed according to the parameters delineated as follows:

The velocity and duration of balloon inflation vary across studies, ranging from a few seconds to minutes. Although guidelines pertaining to the optimal velocity of balloon inflation have yet to be established, the following guidelines for safe EPLBD were proposed based on the current knowledge.

4 Liao WC, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, Lin JT, Wu MS, Wang HP. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. *Gastrointestinal endoscopy* 2010; **72**(6): 1154-1162 [PMID: 20869710 DOI: 10.1016/j.gie.2010.07.009]

5 Paspatis GA, Konstantinidis K, Tribonias G, Voudoukis E, Tavernaraki A, Theodoropoulou A, Chainaki I, Manolaraki M, Chlouverakis G, Vardas E, Paraskeva K. Sixty- versus thirty-seconds papillary balloon dilation after sphincterotomy for the treatment of large bile duct stones: a randomized controlled trial. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2013; **45**(4): 301-304 [PMID: 23195665 DOI: 10.1016/j.dld.2012.10.015]

3. Page 10, lines 5-6:

“Dormia basket and retrieval balloon catheter are unnecessary”

What does the authors usually use for removal of stones after EPBD? The authors should describe concrete stone extraction method in the revised manuscript.

→ We agree with your comment. Although the ampulla was dilated by EPLBD, a Dormia basket or retrieval balloon is required to remove CBD stones. We had intended to describe sufficiently the opening of the ampulla for stone removal following EPLBD; however, because the original paragraph was not adequate for this purpose, it was altered as follows:

Moreover, and in contrast to EPBD, EPLBD dilates the ampullary orifice sufficiently to allow for straightforward removal of a large CBD stone, using a Dormia basket or retrieval balloon, and so that it is wide enough to reduce the need for MLT.

4. Page 10, line 15:

“PEP after EPLBD was not reported as a problem.”

The authors should delete this sentence on the basis of duplication.

→ We agree with your comment and have deleted the sentence in question.

5. Page 12, lines 6-10:

“According to a report..... widened ampullary orifice.”

This explanation is very difficult to understand. The authors should exchange it for understandable other words, or omit this paragraph itself.

→ We agree with your comment, and have deleted the paragraph accordingly.

6. Page 12, lines 12-13:

“in a state of nnothing per os”

The authors should delete this expression, because it is not understandable.

→ We agree with your comment and have deleted the sentence in question.

7. Page 13, line 3:

“no difference”

The authors should replace “no difference” into “no significant difference”.

→ We agree with your comment and have modified the sentence accordingly.

8. Page 13, lines 9-10:

“In addition,.....duration time of EPBD.”

Because of duplicate expression, the authors should omit this sentence.

→ We agree with your comment and have deleted the sentence in question.

9. Page 13, line 13:

“Therefore, the cause.....”

The authors should omit this word and exchange it for ‘and’.

→ We agree with your comment and have modified the sentence accordingly.

10. Page 13, line 14:

‘PTPBD’ is not appropriate abbreviation. The reviewer recommend ‘AGPBD’. Or percutaneous papillary balloon dilation should be used as a full expression.

→ We agree with your comment and have modified the sentence accordingly; moreover, the paragraph this sentence is in was also altered as follows:

The incidence of pancreatitis, using percutaneous papillary balloon dilation (PTPBD) for CBD stone removal, is extremely low (0-1.4%)

11. Page 13, lines 15-16:

“The incidence of acute pancreatitis.....stone removal”

Because of duplicate expression, the authors should delete this sentence.

→ We agree with your comment and have deleted the sentence in question.

12. Page 13, line 25 to page 14, line 1:

“this procedure.....the cause of pancreatitis.”

Because of duplicate expression, the authors should omit this sentence.

→ We agree with your comment and have deleted the sentence in question.

13. Table 1, 2 and 3:

The authors should replace ‘Overall’ to ‘Overall’.

→ We agree with your comment and have corrected the word accordingly.

14. There was a wide discrepancy between “WORKS CITED” and “REFERENCE

lists”. The authors should revise concretely based on these points in therevised manuscript.

→ We agree with your comment and checked and revised the “WORKS CITED” and “REFERENCE” sections as suggested.