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Special Article

Pancreaticogastrostomy Versus Pancreaticojejunostomy After Pancreaticoduodenectomy: Critical Analysis of Prospective Randomized Trials

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Prospective randomised studies Pancreaticojejunostomy Pancreaticoduodenectomy Pancreaticogastrostomy Complications ABSTRACT

This is a critical analysis of prospective randomised trials that compare pancreatic reconstruction techniques with the stomach and the intestine, after pancreatic oduode nectomy. A questionnaire with questions from the Evidence Based Medicine Centre of Oxford University (PICO analysis) was used, following the criteria for the evaluation of randomised prospective studies for surgical interventions of the McMaster University in Ontario. It was found that the studies differed in methodological aspects, the most important being the lack of a uniform definition of a pancreatic fistula. The techniques for performing pancreaticogastrostomy and pancreaticojejunostomy were not homogeneous. There were no differences in the percentage of pancreatic fistula in three of these studies; one which modified the pancreaticogastrostomy technique had more favourable results. New comparative studies should use new definitions of the complications of pancreaticoduodenectomy and standardise the pancreatic reconstruction technique.

Pancreaticogastrostomía versus pancreaticoyeyunostomía después de pancreaticoduodenectomía: análisis crítico de los ensayos prospectivos aleatorizados

RESUMEN

Palabras clave:
Estudios prospectivos aleatorizados
Pancreaticoyeyunostomía
Pancreaticoduodenectomía
Pancreaticogastrostomía
Complicaciones

Este es un análisis crítico de los ensayos prospectivos aleatorizados que comparan las técnicas de reconstrucción pancreática con el estómago y con el intestino, después de pancreaticoduodenectomía. Se utilizó un cuestionario de preguntas del Centro de Medicina Basada en Evidencias de la Universidad de Oxford (análisis PICO), y se han seguido los criterios en la evaluación de estudios prospectivos aleatorizados para intervenciones quirúrgicas de la Universidad de McMaster de Ontario. Se encontró que los

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estudios difieren en aspectos metodológicos, el más importante la falta de una definición uniforme de fístula pancreática. Las técnicas de realización de la pancreaticogastrostomía y pancreaticoyeyunostomía no fueron homogéneas. No existen diferencias en el porcentaje de fístula pancreática en tres de estos estudios; uno que modifica la técnica de pancreticogastrostomía presentó resultados más favorables. Los nuevos estudios comparativos deberán utilizar las nuevas definiciones de las complicaciones de la pancreaticoduodenectomía y estandarizar la técnica de reconstrucción pancreática.

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Introduction

Pancreaticoduodenectomy (PD) remains one of the most complex abdominal operations, requiring extensive and intense training. Advances in the knowledge of surgical techniques has notably reduced mortality to less than 5%.¹⁻³ However, morbidity remains high, reaching figures of 30% to 50%, even in centres with high caseloads.⁴⁻⁷

For this reason, surgeons are paying increased attention towards finding the best technique for pancreatic reconstruction.8 Traditionally, pancreaticojejunostomy (PJ) has been the most widely used form of reconstruction, with multiple variants published, including invagination, single-layer, double-layer end-to-end9-12 and duct-to-mucosa end-to-side (the most common technique in hospitals with high caseloads) techniques, 13-18 with or without internal or external stents. 19-22 In the search for techniques that significantly reduce morbidity in this operation, the use of the stomach as a means for restoring pancreatic continuity has also been employed.²³⁻³¹ Currently, four prospective randomised studies (PRS) have been published comparing the results of pancreaticogastrostomy (PG) versus PJ. 32-35 Three of these studies failed to demonstrate the advantage of one technique over the other.³²⁻³⁴ The most recent study demonstrated a low percentage of pancreatic fistulas (PF) and general complications for PG,35 using a new technique that included the creation of a gastric segment (gastric partition), partially separated from the rest of the stomach, which joins it to the pancreas through a duct-to-mucosa connection and using an internal stent.

The aim of this article is to perform a critical analysis of PRS, comparing techniques for pancreaticogastric and pancreaticojejunal reconstruction after PD, assessing methodological parameters, techniques and results presented in each study.

Material and Method

In order to analyse the four PRS that compare the results of PG against PJ after PD (published in the literature and identified through a systematic search of MEDLINE), we used a questionnaire designed based on tools supplied by the Centre for Evidence Based Medicine of Oxford University (http://www.cebm.net). These tools were designed

to determine the validity of PRS (PICO analysis) and the information provided by the systematic review for the methodology analysis of prospective randomised studies on the assessment of surgical interventions published by the University of McMaster, Ontario, Canada. This analysis was carried out using questions relevant to the assessment of the various methodological aspects and the results of each study (Table 1).

Analysis - Results

Was The Aim of the Study Sufficiently Described?

Yeo et al and Bassi et al do not sufficiently explain in their objectives the parameters they used to establish the comparison between the two techniques. However, Duffas et al and Fernandez-Cruz et al did, although the French study adds one more objective: determining morbidity and mortality risk factors after PD, independently of the comparison of techniques.

Were the Criteria for Admitting Patients to the Study Properly Established?

Yeo and Bassi did not specify any criterion for the inclusion of patients in the study. However, the latter indicated a selection criterion that was not performed in the other studies, which was to include only those patients who were intraoperatively considered carriers of soft pancreas with Wirsung's duct diameter of less than 5 mm. Duffas et al indicated that they included patients with benign or malignant pancreatic tumours, chronic pancreatitis and extrapancreatic tumours (ampullary, biliary and duodenal). Also, Fernandez-Cruz et al mentioned that patients were subjected to PD for benign and malignant ailments of the pancreas and the periampullary region.

Were the Treatments well Defined? Was there a Detailed Description of the Surgical Technique and the Postoperative Management? (Table 2) Yeo et al described the technique of double-layer pancreatic anastomosis for all their patients. They are unclear as to whether the internal plane is duct-to-mucosa, but it is assumed that this was not the case at least in PG since the size of the subsequent gastrostomy was 2.5 cm to 3 cm. In the PJ group, the technique loses homogeneity since the choice was left up to the surgeon, with end-to-end more frequently performed (n=48) than end-to-side (n=24). In this study, a standard technique was not used for PD, in terms of

Table 1 - Questionnaire for the Critical Assessment of Prospective Randomised Studies.

Questionnaire (PICO Analysisa)

Was the aim of the study sufficiently described?

Were the criteria for including patients in the study properly established?

Were the treatments well defined? Was there a detailed description of the surgical technique and the postoperative management?

Was random assignment used for the interventions being evaluated? How close to the time of surgery was this randomisation conducted? Was the study blind to some degree?

Were the measure criteria for the results satisfactorily established? Was the primary outcome measure identified?

Were the result analysis methods appropriate?

Was the calculation for the necessary sample size for the study indicated?

Was the duration of the post-treatment follow-up period established?

Were the treatment groups comparable in terms of relevant parameters?

Were a high proportion of patients monitored?

Were all the statistical procedures properly established or referenced?

Were additional analyses performed to determine if there were prognostic factors that influenced the results?

^aC indicates comparability; I, interventions; O, outcome; P, participants.

pyloric preservation (82%) or not (18%) for both groups, with the location of PG always 7 cm proximal to either the pylorus or the suture line when gastric resection was performed. All hepaticojejunal anastomoses were decompressed with either preoperative percutaneous drainage or with T-tubes placed during the operation. The number, characteristics and biliary drainage technique applied to each patient were not specified. Two to four silicone closed suction drains were used, although the time when they were removed was not specified. As for the use of drugs in the postoperative period, it was reported that octreotide was not used prophylactically in any patient, but was used postoperatively at the surgeon's discretion. However there was no mention as to the number of patients in each branch of the study in whom octreotide was ultimately used. Similarly, 'most' patients were administered erythromycin lactobionate (200mg IV every 6 h) from postoperative day 3 to day 10, although there is no mention as to how many or to which group this majority corresponds. For postoperative management for the diagnosis of pancreatic fistula, liquid samples of the drained peripancreatic fluid were taken between the third and seventh day, or contrasted imaging studies were obtained using the T-tube or the percutaneous catheter. However, the definition of fistula used was a radiologically detected leak or drainage of more than 50 ml of amylase-rich liquid during or after the 10th postoperative day. It is unclear whether samples were taken during every indicated postoperative day or whether a single sample was taken between those days. It is also unclear whether more samples were taken from the 10th day, which would be the only way to comply with its own definition, apart from the radiological demonstration.

Duffas et al designed their trial on a multicentre platform in which fourteen surgical centres participated (eight universities and six community hospitals), with a median of eight patients included per centre (range 2-27). Therefore, the PD results from centres with very low caseloads were combined with hospitals with very high caseloads, employing a diversity of pancreatic reconstruction techniques. PD was performed according to each surgeon's preference, including cases with resections combined with other organs (colon, small intestine, portomesenteric confluence, liver, biliary tree). PJ

was performed in an end-to-end or end-to-side manner, with or without preservation of the pylorus, with or without vagotomy. They did not specify whether an invagination, double or single-layer, or duct-to-mucosa technique was used, in either the PJ or PG. Surgeons were free to choose whether or not to inject fibrin glue, use a stent, perform an omentoplasty, or use octreotide. This study did not indicate the method for carrying out postoperative monitoring in order to detect complications and did not specify whether a systematic strategy was implemented for detection of amylase in the fluid by perianastomotic drainage or by imaging studies. It only states that the use of drainage was recommended, but apparently this was also at the surgeon's discretion.

In the Bassi et al study, the single-layer reconstruction technique is reported for both types of anastomosis. The telescoping technique was used for PG, but the level at which the gastrostomy was subsequently made was not specified. For the PJ, the duct-to-mucosa technique was conducted in addition to the single-layer technique, although the number of patients and the group to which they belonged was not specified. There was also no homogeneity in the use of pyloric preservation (Table 2). Furthermore, it was reported that two drains were used in the PJ and only one in the PG, without indicating the reason. Octreotide was used prophylactically in all patients one hour before the procedure, with a specified dose (0.1 mg three times a day for seven days). There was no mention of methods for control, detection and postoperative follow-up of complications. Ten consecutive cases were performed with PG reconstruction before starting the study as a learning and standardisation series.

Fernandez-Cruz et al present a detailed description with figures that demonstrate the surgical technique, not only for the new technique presented for PG (gastric partition), but also for PJ. This was the only study that maintained complete homogeneity in the technique used both for PG and PJ. In both groups, the duct-to-mucosa connection method was performed, with internal stent placement in all patients. PD with pyloric preservation was completed in both groups. This new technique of gastric partition was performed in 10 consecutive cases before starting the study to demonstrate its safety and reproducibility. Two Jackson-

Table 2 – Description of Surgical Techniques Used for Pancreatic Anastomosis.						
Author	PD	PG	PJ	Stent		
Yeo et al (1995) ³²	PPPD (82%); traditional (18%)	Double-layer; posterior gastric wall (2.5 cm to 3 cm)	Double-layer; end-to-end (48) or end-to-side (24) ^a	No		
Duffas et al (2005) ³³	PPPD (25%); traditional (75%)	Not described	Not described; end-to-end or end-to-side ^a	Yes (20%); No (80%) ^a		
Bassi et al (2005) ³⁴	PPPD (90%); traditional (10%)	Single-layer; posterior gastric wall; telescoping	Single-layer or duct-to-mucosa end-to-side	Not described		
Fernandez-Cruz et al (2008)35	PPPD (100%); traditional (0%)	Duct-to-mucosa; gastric partition	Duct-to-mucosa end-to-side	Yes		
^a According to surgeon preference.						

Pratt silicone drains were left in all cases. Furthermore, the study details the postoperative follow-up, indicating that somatostatin and octreotide were not used prophylactically in any patient. They state that drainage volume was measured daily and that the quantity of amylase was measured between the third and seventh postoperative day. This is consistent with the consensus definition of fistula established by the International Study Group Pancreatic Fistula (ISGPF)³⁷ (more than three times the normal serum value of amylases during or after the third postoperative day). They specified when the drains were withdrawn as well as the times when they withdrew the nasogastric probe and initiated oral feeding. They also specified the actions that were taken when presented with a complication. However, some patients were subjected to PD with venous vascular resection, without specifying how many or to which group they belonged.

Was Random Assignment Used for the Interventions Being Evaluated? How Close to the Time of Surgery was this Randomisation Conducted? Yeo et al indicated that randomisation was conducted during surgery but do not specify the details of the technique used.

Duffas et al specify that randomisation was also intraoperative. The Bassi et al study only mentions that the patients were randomised but does not specified how or when this was conducted.

Fernandez-Cruz et al used the method of sealed envelopes containing randomised numbers that were assigned to patients in one group or the other. This assumes, therefore, that it was conducted preoperatively, since it is not mentioned.

Was the Study Blind to Some Degree?

Duffas et al indicated that postoperative complications were evaluated by a doctor who did not know the reconstruction performed on each patient.

Bassi and Fernandez-Cruz, as well as the Baltimore group, did not mention any attempt at designing a blind study.

Were the Measure Criteria for the Results Satisfactorily Established? Was the Primary Outcome Measure Identified?

Yeo et al clearly defined their primary outcome measure, which was the percentage of pancreatic fistula (whose

definition is mentioned above), as the most important measure for comparing each pancreatic reconstruction technique. However, secondary outcome measures, i.e., other postoperative complications (abdominal and extraabdominal), as well as the postoperative hospital stay, were not defined, except for delayed gastric emptying, which was clearly specific at the foot of Table 3 of this article.

Duffas et al established their primary outcome measure as the percentage of patients with one or more postoperative intra-abdominal complications (IAC) diagnosed during the postoperative period, specifying this period as the total hospital stay and 30 days after discharge for patients hospitalised for less than one month. They define the diagnostic criteria for each complication, using a pancreatic fistula definition different from that of Yeo et al (fluid obtained through drainage or percutaneous aspiration, with an amylase content of at least four times the normal serum value for three days, regardless of the volume of fluid and the day of appearance, or through radiological study) (Table 3). However, their secondary outcome measures, extra-abdominal complications (EAC), are not defined, and this is not considered in their objectives. The definition of IAC severity was adequately specified and includes the mortality rate.

Bassi et al stated that their primary outcome measure was to compare the 2 groups of treatment on the base of the development of single or multiple postoperative abdominal complications. However, when they report the statistical analysis, it is more precise and ultimately establishes the pancreatic fistula rate (with or without other complications) and the impact of abdominal complications for the 2 techniques as the primary outcome measure. Furthermore, they include a table where the definitions used for each complication are specified in detail, using a different definition for pancreatic fistula (any volume of fluid with clinical significance, rich in amylases, confirmed by fistulography). The concept of hospital mortality is also not defined.

Fernandez-Cruz et al establish two primary outcome measures, the percentage and severity of pancreatic fistulas. As secondary outcome measures, they use general postoperative complications, hospital stay and death. They do not specify the concept of mortality but they do specify hospital stay. This is the only study that uses the ISGPF³⁷ consensus

Table 3 – Differences in the Definition of Pancreatic Fistula				
Author	Definition of Pancreatic Fistula			
Yeo et al	>50 ml of amyiase-rich fluid from drainage during or after the 10 th postoperative day or failure of anastomosis shown radiologically			
Bassi et al	Amylase-rich fluid with clinical significance and confirmation by fistulography			
Duffas et al	Biochemical tests, symptoms and radiography			
Fernandez-Cruz et al	ISGPF definition (see text)			

definition for pancreatic fistulas referred to previously, although they eventually use the modification proposed by Reid-Lombardo.³⁸ This modification states that grade A fistulas without clinical significance are not considered complications. They also use the classification proposed by Strasberg³⁹ to measure the severity of pancreatic anastomosis failure, and establish a comparison between the stratification established by the ISGPF (grades A, B and C). They also clearly specify the definitions of other complications (intraabdominal abscess, pneumonia, delayed gastric emptying), but not for biliary fistula, abdominal haemorrhage or surgical wound infection.

Were the Result Analysis Methods Appropriate?

Yeo et al clearly identified this point and used the rate of PF as a primary outcome measure, and make the effort to relate this complication to the rest of the postoperative complications.

Duffas et al establish all IAC as a primary outcome measure, perhaps not taking into account that what is being evaluated is the pancreatic reconstruction technique, and that complications secondary to failure of the biliary (3), colonic (2), gastrojejunal or jejunal (5) anastomosis may not be related to the surgical treatment (PG or PJ) being assessed.

In the Bassi et al study, the definition of pancreatic fistula used requires this complication be shown by fistulography, whose sensitivity for detection is not very high, and must also be clinically significant, while not clearly specifying to what this refers.

The study by the Hospital Clínic of Barcelona, as with the Yeo et al study, uses the most important primary objective: the rate of PF, using an international consensus definition and comparing the results by applying variants of this definition. It establishes the stratification by fistula grades, as proposed by the ISGFP.

Was the Calculation of the Necessary Sample Size for the Study Indicated?

Yeo et al calculated the sample size based on the premise of improving the percentage of PF from 20% to 5%. Duffas et al calculated their sample on the premise of reducing the percentage of patients with one or more IAC from 40% to 20%. Bassi et al also made the calculation on the premise of reducing the percentage of complications (single and multiple) from 25% to 5%. Fernandez-Cruz et al calculated the sample

size based on previous studies that used similar definitions of PF, to detect a difference of 20% in the percentage of PF.

Was the Duration of the Post-Treatment Follow-up Period Established?

The duration of the follow-up was not mentioned in any of the studies.

Were the Treatment Groups Comparable in Terms of Relevant Parameters?

In all studies, both treatment groups were comparable. No significant differences were found in patient characteristics, or in the multiple preoperative and intraoperative parameters analysed.

Were a High Proportion of Patients Monitored?

It is noteworthy that none of the trials mentioned whether or not there were hospital readmissions. If there were none then it should have been reported. Additionally, the follow-up period should be specified, considering a prudent time period from which complications from the surgery are not expected, a minimum of 30 days.

Were all the Statistical Procedures Properly Established or Referenced? Statistical analyses and tests were properly described and referenced in the four studies, establishing 95% confidence intervals for submitted results.

Were Additional Analyses Performed to Determine if There Were Prognostic Factors That Influenced the Results?

The Yeo and Duffas studies made additional efforts to analyse risk factors for the development of pancreatic fistulas and other complications, and try and explain the observed results. Yeo et al, in their univariate analysis, found the following risk factors of PF: operative time, transfusions, soft texture of the pancreas, ampullary or duodenal disease and the low caseload per surgeon. In the multivariate analysis, surgical caseload and ampullary or duodenal disease appeared as predictors of risk.

Were the Conclusions Justified Based on the Statistical Analysis?

Yeo et al concluded that their data did not support the hypothesis that PG was safer than PJ or was associated with a lower incidence of PF, which agrees with the results of the statistical analysis.

Bassi et al concluded that PG did not show any significant differences in the overall postoperative complication rate or incidence of pancreatic fistula. However, the risk for related complications, biliary fistula, postoperative collections and delayed gastric emptying were significantly reduced in patients treated by PG.

Duffas et al similarly conclude that the type of pancreaticenteric anastomosis does not influence, in a statistically significant manner, the percentage of patients with one or more IAC, the percentage of PF or the severity of complications.

Fernandez-Cruz et al concluded that pancreatic anastomosis failure was significantly lower with the PG technique, in accordance with their statistical analysis.

Table 4 – Results of Postoperative Morbidity and Mortality of Randomised Prospective Trials Comparing Pancreaticogastrostomy Against Pancreaticojejunostomy.							
Mortality, %							
PG							
0							
1							
12							
0							

Discussion

PRS in surgery has several methodological problems inherent in surgical treatment, which threaten its internal validity and thus the possibility for its generalisation and applicability (external validity). Systematic errors or biases are among the most common errors that skew study results away from what is sought: the truth. These include pseudo-randomisation (randomising alternately by birth date, day of the week, medical record number), assignment that is not hidden from the patients (coin toss, closed envelope, etc.), not using a blind study on participants, not applying the principle of intent to treat, the lack of complete patient follow-up and post-randomisation exclusion of patients. 36,40-49 There is also the difficulty of properly selecting outcome measures for analysing the results that will later define the differences or not between one treatment or the other, as well as the appropriate calculation of the sample size in order to ultimately obtain a clinical and statistical difference. 40-50

In this critical analysis, we wanted to show that PRS must be properly interpreted based on currently available tools, since the results of these studies may also not conform to reality (Table 4, Table 5). The meta-analysis that compares PJ with PG^{51,52} unfortunately does not allow for a breakdown of methodological details in each study design. The lack of homogeneity in many of the fundamental aspects of the design prevents, in some cases, the quality of this type of analysis from complying with the rigour necessary for making actual conclusions.⁵⁰

The four trials analysed here differ in methodological issues. The most important is related to the definition of pancreatic fistula, a complication that as a primary outcome measure is directly related to pancreatic reconstruction techniques. Without a uniform definition of PF, the comparison of the various studies with similar objectives is very difficult. For this reason, the ISGPF³⁷ in 2005 published the consensus definition, which only Fernandez-Cruz et al used in their study. It should be noted, however, that the other three studies published their

Table 5 – Characteristics of the Centre, Patient and Diagnoses in Each Trial.					
Author	Centre	Patient	Diagnosis		
Yeo (USA) adenocarcinoma	Single	145 PD (73 PG/72 PJ)	80 ductal 18 ampulla of Vater 13 cholangiocarcinoma 9 duodenal cancer 25 others		
Bassi (Italy) adenocarcinoma	Single	151 PD (69 PG/82 PJ)	60 ductal 24 ampulla of Vater 3 cholangiocarcinoma 2 duodenal cancer 62 others		
Duffas (France) adenocarcinoma	Multicentre	149 PD (81 PG/68 PJ)	59 ductal 36 ampulla of Vater 19 cholangiocarcinoma 6 duodenal cancer 11 others		
Fernandez-Cruz (Spain) adenocarcinoma	Single	108 PD (53 PG/55 PJ)	54 ductal 22 ampulla of Vater 15 cholangiocarcinoma 2 duodenal cancer 18 others		

results before the consensus conference results emerged. In addition to the lack of a uniform definition for PF in the studies performed, most of them do not clearly specify the number, function and measurement of amylase content in the drainage fluid. We believe that amylase content in drainage fluids must be systematically measured in the same manner in all patients, regardless of the presence or absence of symptoms, and of course at least from the 3rd postoperative day. The discussion as to whether a PF, biochemically-defined according to the ISGFP with no clinical repercussions (grade A), should be considered a complication^{38,39} must be clearly defined during the study's design phase. It is also important to make it clear that the analysis of secondary outcome measures must be closely related to pancreatic anastomosis failure, as well as the complications arising from it, such as intraabdominal abscess, surgical wound infection, postoperative haemorrhage, pneumonia and possibly delayed gastric emptying. It is also directly related to mortality, hospital stay, re-interventions, hospital readmissions and costs.39 It is notable that these latter measures were not included in the analysis of results in most of the studies analysed. Furthermore, they also did not define the follow-up period needed for detection of complications related to the procedure, which are often detected after patients are discharged and require rehospitalisation.

There is no doubt that as much as we strive to homogenise and place all the studies in one 'bag' so as to metaanalyse them, the critical analysis of each study separately is of paramount importance. For example, the surgical techniques included in the four studies differ both for PG and for PJ (Table 2). Among the methodological differences between the four studies analysed are: the use of specific drugs (octreotide, erythromycin) in some studies, the use of stents at the surgeon' discretion and that one of the studies includes patients at risk of PF. Among the studies analysed, the hospital centres had a high caseload for PD, but the French study included centres with a lower caseload (less than 10 patients per year). In some of the studies, the randomisation techniques were not clearly explained. Study blinding was also not mentioned in most of the studies, leaving the impression that an effort was not made to include this important measure and thus avoid systematic methodological error.³⁶

Therefore, we currently have these four PRS that attempt to demonstrate whether a pancreatic reconstruction technique, PJ or PG, reduces the rate of PF after PD and thus the global impact of this complication. One of these shows a clear benefit using a new variant of the PG technique, while the other three fail to show statistically significant differences between these two interventions. Questions remain as to whether this problem is resolved, whether we should perform a PJ or a PG and whether we should keep searching for the technique that produces lower morbidity and mortality. If we perform a PJ, should we do a single-layer or double-layer end-to-side or duct-to-mucosa? If PG were preferred, what would be the choice: duct-to-mucosa anastomosis, the telescoping technique or gastric partition?

Conflict of Interest

The authors affirm that they have no conflict of interest.

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