Treatment of malignant biliary stenosis : which stent to use ?

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Abstract

The insertion of a biliary endoprosthesis has become standard therapy in the palliative treatment of a malignant biliary stenosis. For plastic stents, stent occlusion results from clogging caused by the adherence of proteins, bacteria, and sludge to the inner stent wall, resulting in a median stent patency of about 4 to 5 months. No major gain in stent patency can be obtained by the omission of side holes, nor by changes in stent material. Putting the stent inside the bile duct, in a suprapapillary position, does not lead to a longer stent patency. The prophylactic administration of antibiotic agents such as ciprofloxacin or norfloxacin, that are active against the gram-negative enterobacteriaceae leading to stent clogging, could have potential advantages but still needs further study. The insertion of a straight 10 French gauge polyethylene Amsterdam-type of prosthesis in a normal transpapillary position, and without the administration of any prophylactic antibiotic treatment, can still be regarded as state-of-the-art therapy with a plastic stent. This mainly holds true for those patients with a low life expectancy of only a few months, such as it is often the case in patients in a poor clinical condition, with liver metastasis, or with a large primary tumor. Patients with a longer life expectancy can be treated with a self-expandable metallic stent. At present, there is no major indication that coated metallic stents will perform any better than the uncoated ones. (Acta gastroenterol. belg., **2001**, 64, **309-313**).

Key words : stent, biliary tract neoplasms, bile duct obstruction, extrahepatic, sludge, biliary.

Introduction

Insertion of a biliary prosthesis has become standard therapy in a number of biliopancreatic disorders. In benign conditions such as postoperative biliary strictures and leaks, large bile duct stones, chronic pancreatitis, and pancreatic pseudocysts, plastic stents are indicated. For the treatment of a malignant stenosis, plastic as well as metallic stents can be inserted. Plastic stents, that may consist of different types of polymers such as polyethylene, teflon, or polyurethane, are characterized by a small diameter, but are efficient for the short-term relief of cholestasis. These stents are prone to rapid occlusion by biliary sludge, leading to recurrent jaundice and cholangitis, and significantly limiting quality of life in patients with an already life-threatening malignant disease. The overall incidence of plastic stent clogging is 42% with a median stent patency of 4,8 months (1). The mechanism of stent clogging can be considered as a complex interplay between biliary constituents and the polymeric materials that make up these plastic stents. Occlusion starts off with the absorption of biliary proteins to the stent surface, followed by the adhesion and multiplication of bacteria within a protective glycocalix or biofilm, that shields the bacteria from white blood cells, immunoglobulins and antibiotics (1). Bacterial glucuronidases and phospholipases, by their deconjugation of biliary lipids, further lead to the formation of biliary sludge components such as calcium bilirubinate and calcium palmitate (2-5). Adherence of proteins and bacteria is influenced by stent characteristics such as stent diameter, stent material, stent position, and the presence or absence of side-holes (4,6-9). Therefore, measures to prevent stent clogging are aimed at changes in bile composition or at changes in plastic stent characteristics.

Metallic self-expandable stents are characterized by a larger diameter and by a significantly longer median stent patency of about 10 months (1). This type of prosthesis, however, is characterized by a much higher cost that amounts to 10 to 20 times the cost of a plastic stent. Moreover, stent occlusion may still occur resulting from tumor ingrowth through the meshes of the metallic stent or from tumor overgrowth above or below the stent. Therefore, coated-metallic stents have recently been developed in order to prevent tumor ingrowth.

It is the purpose of the present paper to critically evaluate the attempts that have been made to prolong patency rates of plastic as well as of metallic stents, and to give recommendations as to which stent to use in patients with a malignant biliary obstruction.

Measures to prevent plastic stent occlusion by changing stent characteristics

The most widely accepted approach to the prevention of stent blockage is the use of large diameter plastic stents, providing more room for sludge to accumulate before the lumen becomes occluded. A clear advantage of 10 French over smaller 8 French stents has been shown (10), but there is no further gain by the use of larger 11.5 French gauge stents (11,12).

The standard type of plastic stent that is most widely used is the straight 10 French polyethylene Amsterdam-type prosthesis that is characterized by the presence of side holes, and that, on scanning electron microscopic examination (SEM), shows an irregular aspect with tiny lumps and barbs on its inner surface (9).

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From in-vitro experimental work, it appears that the omission of side holes leads to a significantly lower amount of sludge formation as compared to side hole containing stents (4,6). In in vivo conditions, however, and as shown in a prospective randomized study, a clear benefit of the omission of side holes from the polyethylene stent on the occurrence of stent occlusion could not be substantiated (13).

Not only the omission of side holes but also the use of other polymeric materials has been studied. Again, in in-vitro conditions, Teflon stents, that show a low friction coefficient, performed significantly better and accrued less sludge material than did polyethylene stents in similar conditions (4,6). These in vitro findings, however, could not be translated into a significant clinical benefit. In the prospective randomized trial performed by van Berkel *et al.* (14), comparing side hole containing Teflon and polyethylene stents in a group of patients with malignant distal common bile duct lesions, no improvement in stent patency by the use of Teflon could be shown. The combination of the use of Teflon material and of the omission of side holes has led to the concept of the so-called Tannenbaum stent, that initially showed promising results and even compared favourably with published results of metallic self-expandable stents (15,16). Again, in a prospective randomized trial comparing the Tannenbaum stent with the standard polyethylene stent in a group of patients with malignant distal bile duct obstruction, a significant advantage of the Tannenbaum stent on the length of stent patency could be not be shown (17). Differences between the theoretical advantages of Teflon stents and their actual disappointing results in controlled comparative studies can best be explained by the SEM results of van Berkel *et al.* (9), demonstrating that the inner surface of Teflon Amsterdam-type and of Teflon Tannenbaum stents also showed marked irregularities with shallow pits, ridges, and particles protruding into the stent lumen, favoring protein and bacterial adherence and thus the formation of sludge. Hydrophilic polymer (Hydromer)-coated polyurethane stents are characterized by a low friction coefficient, an ultrasmooth surface, and by a low bacterial adhesion (6,9,18). Even with these "optimal" stent conditions, no significant increase in stent patency could be observed when this type of stent was compared to the Amsterdam-type polyethylene prosthesis in a randomized trial (19). Reasons for the marked differences between in vitro and in vivo results are not yet clear. Damage to the stent surface occurring during the mechanical process of stent insertion, as well as ascending infection by the standard position of stents across the papilla of Vater, overcoming the bacteriological barrier of the sphincter of Oddi, could play a major role in the process of stent occlusion.

Animal studies have shown that stents placed entirely within the bile duct ("inside-stents") remain patent longer than stents placed across the sphincter (20,21). However, a randomized trial comparing stents placed above and across the sphincter of Oddi in patients with malignant bile duct obstruction failed to show any beneficial effect from placing the stent inside the common bile duct (22). Furthermore, an inside-position of the stent would only be possible in about one third of the patients with malignant bile duct stenosis, and would lead to a higher percentage of stent dislocation (22,23). Another option to prevent stent occlusion is to use antimicrobial agents such as in silver-coated or benzalkonium chloride impregnated stents (24,25) ; clinical studies in patients, however, have not yet been performed.

From the foregoing, it appears that no major measures can be taken to significantly prolong plastic stent patency. Therefore, the policy of "prophylactic" stent exchange in which a routine prophylactic stent exchange every 3 to 4 to six months could be applied, has been studied (1). According to Frakes *et al.*, the time interval for prophylactic stent replacement could be prolonged to 6 months, resulting in decreased patient discomfort and cost, and obviating any replacement in that significant percentage of patients who expire within the first six months after endoscopic palliation (26). Recent prospective randomized studies, comparing "prophylactic" stent exchanges with "on-demand" replacements that were required by the clinical evolution, showed no apparent benefit of prophylactic exchanges, neither on patient survival nor on the number of ERCPs or of stents per patient (27,28).

Measures to prevent plastic stent occlusion by changing bile characteristics

One of the most important mechanisms leading to stent occlusion is the adherence of bacteria to its inner surface. Isolates from blocked stents usually reveal a mixed infection. Two thirds of the bacteria are gram-negative Enterobacteriaceae, the most common being Eschericia coli and Klebsiella species. The remaining one third consist of gram-positives including Enterococcus and a small number of anaerobic bacteria (29,30). Thus, the Enterobacteriaceae appear to be appropriate targets for prophylactic antibiotic therapy in the prevention of sludge formation. Reported clinical trials of antibiotic prophylaxis to prevent stent occlusion have yielded conflicting results. The discrepancies in outcome may be the result of different factors such as the choice of antibiotics with a varying spectrum of activities against the bacterial flora, the duration of drug treatment, and the concurrent use of choleretic agents. Negative results in the studies of Smith *et al.* (31) who used doxycycline, and of Ghosh and Palmer (32) who used cyclical antibiotic therapy with ampicillin, metronidazole, and ciprofloxacin given in monthly cycles and started only two weeks after stent insertion, could be explained by inadequate antibacterial coverage against the enteral bacteria colonising the biliary tree after stenting. From animal models, evidence arises that

ciprofloxacin eliminates the presence of gram-negative bacteria from biliary stents and leads to a significant prolongation in stent patency (33,34). A small pilot study found that treatment with norfloxacin and ursodeoxycholic acid was effective in prolonging stent patency, but did not give any information about the relative roles of the antibiotic and the bile acid (35). Luman *et al.* reported that the combination of ciprofloxacin and the choleretic agent Rowachol did not prolong stent patency (36). However, the number of patient recruited was small and the negative result might represent a type II error.

Similarly, reported clinical trials with ursodeoxycholic acid yield no clear results as to the role of this bile acid in the prevention of stent clogging. The use of different doses of 10 mg/kg/day (32) and of 13-15 mg/kg/day (35), as well as the concurrent administration of prophylactic antibiotics (32,35) do not allow to draw any firm conclusion about the preventive role of this choleretic agent.

Prevention of recurrent cholestasis by self-expandable uncoated and coated metallic stents

Self-expandable uncoated metallic stents, characterized by a much larger stent diameter of 30 French, have a longer median stent patency of about 10 months but a much higher cost up to 10 to 20 times the cost of a plastic stent (1). For these stents, mechanisms of stent occlusion consist of tumor ingrowth into the meshes of the prosthesis or tumor overgrowth above and below the stent.

Prospective randomized controlled studies, comparing metallic and plastic stents, have mainly been performed in patients with a distal malignant bile duct stenosis (37,38). Both stents have similar results with regard to regression of jaundice and patient survival. However, the use of metallic stents leads to a significantly lower percentage of stent occlusions, a longer median stent patency, and a lower number of repeated procedures necessary for the treatment of stent occlusion (37,38). From a cost-effectiveness point of view, insertion of a metallic stent seems indicated if life expectancy is expected to exceed 3 to 6 months (37-40). Predictions about life expectancy can be made based upon the general condition of the patient, the presence of metastatic lesions (12), and the size of the primary tumor (41). In Pereira-Lima's study, the median survival of patients with distant metastases was 2,5 months in contrast to 9 months in those without distant metastases ($p = 0.0015$) (12). In Prat's study, median survival was 3,2 months in patients with a tumor greater than 30 mm as compared with 6,6 months for patients with a tumor less than 30 mm ($p < 0.001$) (41).

For malignant strictures at the hilum of the liver, only one comparative study is available showing a significantly lower number of reinterventions to deal with stent-related problems in patients treated with metallic stents than in patients with plastic stents (42).

Coated metallic stents have recently been developed in an attempt to overcome occlusion of metallic stents by tumor ingrowth. Several coating materials are used such as polyurethane (43-46), silicone Permalume™ (47), and ePTFE in the so-called Gore stent. However, according to the first clinical trials, no significant differences in patency rates between coated and uncoated metallic stents could be observed, so that it still remains unclear whether the properties of covered stents are superior to those of uncovered stents (48). Occlusion of metal stents may be treated by the insertion of a plastic stent or of another metal stent through the original one (37,40,49)

Further developments in the use of expandable metal stents in patients with cancer include the application of stents that emit radiation (50) or that release chemotherapeutic agents (51) to cause tumor regression. Furthermore, the insertion of a biliary metal stent can be combined with the placement of an expandable metal stent in the duodenum in patients presenting with gastric outlet obstruction. Given the difficulties in obtaining access to the biliary tree through the mesh wall of a duodenal stent placed across the papilla, an expandable stent should first be placed before the duodenal stent if there is a known or impending biliary obstruction (49).

Conclusions

The insertion of a biliary endoprosthesis has become standard therapy in the palliative treatment of a malignant biliary stenosis. With this therapy, major problems with recurrence of cholestasis and cholangitis still exist. For plastic stents in general, stent occlusion results from clogging caused by the adherence of proteins, bacteria, and sludge to the inner stent wall, resulting in a median stent patency of about 4 to 5 months. No major gain in stent patency can be obtained by the omission of side holes, nor by changes in stent material such as by the use of Teflon or of hydrophilic-coated polyurethane. Putting the stent inside the bile duct, in a suprapapillary position, does not lead to a longer stent patency. The prophylactic administration of antibiotic agents such as ciprofloxacin or norfloxacin, that are active against the gram-negative enterobacteriaceae leading to stent clogging, could have potential advantages but still needs further study. Therefore, the insertion of a straight 10 French gauge polyethylene Amsterdam-type of prosthesis in a normal transpapillary position, and without the administration of any prophylactic antibiotic treatment, can still be regarded as state-of-the-art therapy with a plastic stent. This mainly holds true for those patients with a low life expectancy of only a few months, such as it is often the case in patients in a poor clinical condition, with liver metastasis, or with a large primary tumor. Patients with a longer life expectancy can be treated with a self-expandable metallic stent. At present, there is no major indication that coated metallic stents will perform any better than the uncoated ones.

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