JOP. J Pancreas (Online) 2012 Nov 10; 13(6):651-653.

EDITORIAL

Consequences of Splenectomy in Pancreatic Surgery: Should We Really Plan a Prophylactic Strategy for Splenectomized Patients?

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Surgeons facing with benign, premalignant and malignant tumors of the body and the tail of pancreas utilize distal pancreatectomy that is worldwide considered to be a standardized procedure. Traditionally, this operation includes en-bloc splenectomy. As an alternative, a spleen-preserving distal pancreatectomy may be performed through conservation of the splenic artery and vein by ligating the pancreatic tributaries or through the Warshaw's technique which includes perfusion of the spleen by the short gastric vessels [1]. Both techniques are feasible with minimally invasive approaches, which are well described and safe to perform [2, 3]. Because of some important functions of the spleen such as immunological defenses, hypercoagulability and hematological malignancies after splenectomy, several authors [4, 5, 6] have recently pointed out the benefits in the long run of splenic preservation in distal pancreatectomy when compared with splenectomized patients.

Consequences of Splenectomy

The spleen was once considered unnecessary for life but it clearly serves extremely important hematologic and immunologic functions [7]. The spleen is separated into two major functional compartments: the white pulp and the red pulp. The white pulp contains a large mass of lymphoid tissue and serves a vital role in the recognition of antigens and production of antibodies. The red pulp of the spleen consists of a tight framework of sinusoids, which primarily serve as "filter" of the blood for aged or damaged red cells, ultimately removed by splenic macrophages. Antibody-coated cells and bacteria are also recognized and ingested by these phagocytic cells lining the sinusoids.

Key words Antibiotic Prophylaxis; Infection; Pancreas; Splenectomy; Surgical Procedures, Operative; Vaccination

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As a consequence, patients without a functioning spleen have a severe impairment in their ability to cope with specific infections where the spleen would normally play a prominent role in protection. In particular, the spleen is able to filter and clear encapsulated bacteria such as *Streptococcus pneumoniae* once bloodstream invasion has occurred. Its absence results in an increased risk of serious sepsis carrying considerable mortality. The overall incidence of septicemia remains low but death rates from the so-called "overwhelming postsplenectomy infection" have been reported to be up to 50 times greater than in the general population, with an estimated lifetime risk for overwhelming postsplenectomy infection of approximately 5% [8]. The term overwhelming postsplenectomy infection defines fulminating sepsis, meningitis or pneumonia mainly caused by encapsulated bacteria, such as *Pneumococcus*, *Meningococcus* and *Haemophilus influenzae type b* [9]. Overwhelming postsplenectomy infection is a medical emergency and represents the major clinical problem after splenectomy. It is characterized by a rapid worsening associated with arterial hypotension, alteration of consciousness or shock and a high mortality risk of approximately 50-70% [7, 10]. Bacteremia commonly has an unknown origin and septic shock develops in just a few hours with rapid progression to multiorgan failure. The highest overwhelming postsplenectomy infection risk lies not only within the first few years after surgery but it persists lifelong: almost the same number of cases occurred more than 40 years after surgery as were seen within the first four years of surgery, with most cases (60%) occurring 10-30 years after splenectomy [7]. In addition to this worrying notion, another important message arising from recent evidences is that almost two thirds of cases occurred in patients under 50 years of age, many of whom without additional risk factors for severe sepsis [11].

An increased risk of vascular complications involving both the venous and the arterial vessels may result from splenectomy. Possible vascular complications arising

in splenectomized patients include *in-situ* thrombosis, thromboembolism, vascular smooth muscle impairment, vasospasm, or atherosclerosis. Potential underlying mechanisms for an increased risk of thromboembolism after splenectomy are related to the loss of the spleen's filtering activities allowing particulate matter and damaged cells to persist in the circulation, leading to changes in the endothelium that result in hypercoagulability [12]. Other changes that have been reported to occur after splenectomy that might potentially contribute to thrombosis risk include increased platelet and leukocyte counts, hemoglobin, cholesterol, and C-reactive protein levels. Data from the Danish National Patient Registry [13] on thromboembolism risk in the first 90 days after splenectomy indicated that the overall adjusted odds ratio for venous thromboembolism in splenectomized patients was 32.6 *versus* the general population and 3.2 *versus* appendectomy patients in the first 90 days after surgery, falling to 7.1 and 2.8, respectively, at 91-365 days, and 3.4 and 3.2, respectively, after one year. The presence of an underlying intravascular hemolysis, very often associated with hematological indications for splenectomy such as thalassemia, increases the risk of thromboembolic events and pulmonary arterial hypertension. More relevant for patients who underwent splenectomy in course of distal pancreatectomy is the possibility of secondary portal vein thrombosis. Some prospective studies revealed that its incidence ranges from 5% to 37%, all cases occurring within two months from operation [11]. This is probably the result of local surgical factors rather than to the absence of the spleen [5].

Attempts of Prophylactic Strategy For Splenectomized Patients

The above-considered recent understanding of the role of the spleen, as well as the continuing evidence of data documenting the long- and short-term adverse events associated with splenectomy, underlines the opportunity of a prophylactic strategy for splenectomized patients. This seems reasonable also for splenectomized patients in course of pancreatic surgery.

Strategies to prevent serious infections and reduce the risk of overwhelming postsplenectomy infection include: a) patient education, b) vaccination and c) antibiotic prophylaxis. On this concern, translation into the clinical practice of international recommendations and guidelines may prove quite difficult because of inclusion in most studies of patients with malignant and non-malignant disorders, or different age groups or geographic settings [14, 15].

Education of splenectomized patients is important as the vast majority of them are thought to be unaware of their increased susceptibility to severe sepsis. Proper information to patients and relatives reduces infectious complications, i.e. notification to their physicians of any acute febrile illness, information on the risk of parasitic infections in tropical countries, need of additional antibiotic prophylaxis in case of surgical/dental procedures.

Vaccines used in patients at risk of overwhelming postsplenectomy infection are the multivalent pneumococcal polysaccharide vaccine, the epta-valent diphtheria vaccine, the protein-conjugate pneumococcal vaccine, the *Haemphilus influenzae type b* conjugate vaccine, and the meningococcal vaccine. Although there are many indications for the utilization of these vaccines [15], this prophylactic strategy is not commonly adopted in clinical practice also in patients splenectomized for hematological disorders [7, 8]. The protein-conjugate pneumococcal vaccine is able to induce the production of opsonizing anticapsular antibodies and it is recommended for children older than five years and adults who are scheduled for splenectomy (booster dose at least two weeks before surgery). The serological response variably declines and monitoring of antibody titres at intervals of 6-12 months might be helpful for the assessment of whether revaccination is needed. Current guidelines also recommend immunization against *Haemophylus influenzae type b* and *Neisseria meningitidis*, for adults and children [14, 15]. For both these vaccines a single dose seems sufficient in adults even if the effective antibody response should be yearly assessed [11].

The use of antibiotics for the prevention of overwhelming postsplenectomy infection is not evidence based and there is no agreement on how long these drugs should be taken [16]. Moreover, antibiotic prophylaxis might reduce but not abolish the risk of overwhelming postsplenectomy infection [7]. In adults, guidelines recommend prophylaxis with 250-500 mg per day of amoxicillin or 500 mg per day of phenoxymethylpenicillin (possible alternatives with co-trimoxazole or erythromycin), although these options are becoming less effective because of the increasing development of resistant pneumococcal strains [17]. Although there is no consensus on the duration of treatment, the British guidelines propose life-long treatment with regards to the persistent risk of sepsis, particularly in patients with concomitant hematological diseases or an impaired immune system, or in patients who fail to gain adequate antibodies level after vaccination [15].

Strategies for preventing vascular complications in splenectomized patients in the perioperative period are essentially based upon pharmacological thromboprophylaxis schedules which are similar to that utilized for many other surgical conditions [18]. Prevention of late vascular events is based on the same principles adopted in the general population at risk, i.e. reducing modifiable thrombotic risk factors together with long-term aspirin administration.

A practical scheme of a prophylactic strategy for pancreatectomized patients with associated splenectomy is proposed in Table 1.

Table 1. Proposal of a prophylactic strategy for pancreatectomized patients with associated splenectomy.

Two weeks before elective splenectomy:

a) baseline titration of antibodies against pneumococci strains
b) immunization against pneumococcal, *Haemophilus influenzae type b* and meningococcal infections; booster dose of multivalent pneumococcal vaccine plus a single dose of conjugate meningococcal vaccine plus a single dose of conjugated *Haemophylus influenzae type b* vaccine

Two months after splenectomy:

- second dose of anti-pneumococcal vaccine

Six-twelve months after splenectomy:

- titration of antibodies against pneumococci strains (and eventual revaccination)

Yearly:

- annual vaccination against viral influenza

After splenectomy for six months:

- antibiotic prophylaxis: 250-500 mg per day of amoxicillin or 500 mg per day of phenoxy-methylpenicillin (possible alternatives with co-trimoxazole or erythromycin); afterwards, antibiotic prophylaxis is required after tooth extraction/dental procedures or surgery in general

Lifelong:

- aspirin (possible alternatives: anti-platelet aggregation drugs)

Conclusions

Immunological, infectious and thromboembolic complications represent the main adverse effects of post-splenectomy condition. Spleen-preserving distal pancreatectomy is become increasingly common in elective surgery; as a consequence, less splenectomy interventions will be probably performed in the near future. In the meanwhile, considering the morbidity and mortality associated with the absence of the spleen, preventive measures against overwhelming postsplenectomy infection and vascular complications should be adopted. Prophylaxis against encapsulated bacteria is an unavoidable and valuable option, as well as anti-platelet aggregation drugs. Patients, relatives and general practitioners need to be aware of the long-term risk of overwhelming postsplenectomy infection and of the advisability of a correct antibiotic treatment.

Conflicts of interests The authors have no potential conflict of interests

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