Importance of a medical treatment in mesenteric vein thrombosis (MVT)

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Abstract

Mesenteric vein thrombosis (MVT) and particulary superior mesenteric vein thrombosis (SMVT) can induce 5 to 15 percents of mesenteric and intestinal infarctions in a small and large bowels. The thrombotic process can be idiopathic or consecutive to inherited or acquired thrombophilic states. The clinical diagnosis of this event remains difficult and requires always specific imaging investigations to treat as soon as possible. Its evolution and mortality rate are quite different than these observed in arterial mesenteric ischemic accident. Medical treatment with thrombolytic, anticoagulant, antiplatelet and antispasmodic agents, initiated promptly after precocious diagnosis is able not only to prevent surgical procedure but also to reduce significantly the mortality and recurrence rate of this venous thrombotic event.

Key words : Mesenteric vein thrombosis, intestinal infarction, thrombophilia, anticoagulants, thrombolytic drugs, antiplatelet agents.

Intestinal and mesenteric infarctions consecutive to mesenteric vascular occlusion have been reported since the beginning of the 19th century. It remains a rare but dramatic event (1 out of 1.000 surgical abdominal urgencies) with various appearances, multiple causes associated with a bad prognosis and a high mortality rate despite the most sophisticated treatments applied.

Occlusion or subocclusion of the superior and less frequently of the inferior mesenteric arteries has been recognized as responsible for 50 to 75 percents of all the acute mesenteric ischemia and infarctions (1,2,3). It is only after the first two publications of Warren and Eberhard (4), and Donaldson and Stout (5) in 1935 that mesenteric vein thrombosis (MVT) has been accepted as a distinct clinical entity, responsible of mesenteric or bowel ischemia and infarction in 5 to 15 percents of all the cases reported.

The venous thrombosis responsible of mesenteric bowel ischemia or infarction is generally localized in the superior mesenteric vein (SMV) but can also appear in the inferior mesenteric vein (IMV), the splenic, hepatic or portal veins.

MVT is generally observed in pathological processes and in many of them, a causal relationship has often been reported (table 1) (6,7,8). MVT can also appear without any specific underlying pathological processes and then be considered as spontaneous, agnogenic, primary or idiopathic event (Naitove and Weissmann, 1965) (9). However idiopathic MVT appears generally in patients with a familial or personal positive history of thromboembolism (recurrent superficial or deep vein thrombosis or thrombosis in unusual sites). These patients are generally carriers of inherited or acquired hypercoagulable disorders (primary or secondary thrombophilia) (10,11). Primary thrombophilia can be linked to a genetic defect in antithrombotic proteins (Antithrombin III, Protein C, Protein S, Tissue Pathway Factor Inhibitor) synthesis or activity (activated Protein C resistance or Factor V Leiden abnormality) or to a fibrinolytic disorder (hypo or dysplasminogenemia, defect in Tissue Plasminogen Activator or excess in Plasminogen Activation Inhibitor or dyfibrinogenemia) including an important disturbance in the hemostatic equilibrium (table 2). Secondary thrombophilia is more complex and can be consecutive to an abnormal activation of the coagulation cascade associated with an endothelial injury or hemodynamic disorders, an acquired defect in natural antithrombotic proteins (AT III, Proteins C, S), or the presence of an abnormal protein (CPA) like the lupus like anticoagulant (LLA) or antiphospholipid anticoagulant (APA) which can simultaneously activate platelets and plasma coagulation factors and induce endothelial injury.

Secondary thrombophilia is generally related to pathological conditions like liver failure, nephrotic syndrome, myeloproliferative disorders, neoplasm, systemic diseases or to some treatment of physiological states (pregnancy, oestroprogestative contraception...) (table 2). If the final result of arterial or venous thrombosis in the mesenteric vascular system seems to be the same : a mesenteric and intestinal infarction with gangrene, necrosis and perforation, on the contrary the initial symptoms, the clinical evolution and the prognosis are often quite different (12,13). Indeed, if the arterial event is generally acute, brief and easy to diagnose because leading rapidly to bowel gangrene and death, on the contrary the MVT is more insidious and shows a slower and aspecific evolution often exceeding more than 5 days and so making the diagnosis and treatment more difficult (6,7,8,12,13).

Table I. — **Clinical states in whom MVT can be observed**

— Portal hypertension (cirrhosis, congestive splenomegaly)
— Bowel inflammation disorders (ulcerative colitis, Crohn disease, diverticular disease)
— Intraabdominal infections (abcesses, appendicitis, peritonitis)
— Blunt abdominal trauma, post operative states
— Neoplasms (principally mucus producing) : colonic, pancreatic
— Cardiovascular disorders (heart failure, atrial fibrillation...)
— Myeloproliferative disorders
— Oestrogen therapy (oral contraception, prostate cancer therapy)
— Systemic disorders (DLE, sclerodermia)

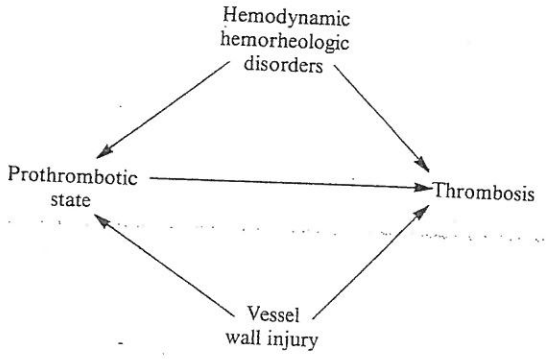
Table II. — **Primary and secondary thrombophilic states**

Primary thrombophilia

Deficiency in ATIII
Prot C
Prot S
HC II
TPFI
APC Resistance (FV Leiden)
Dysfibrinogenemia
Inhibition of fibrinolysis
(Déf in PLG, TPA, FXII, Dysplasminogenemia, Excess of PAI-I)
Hyperhomocystinemia

Secondary trombophilia

Advanced age
Obesity
Immobilization
Post operative state
Trauma
Malignancy
Congestive heart failure
Nephrotic syndrome
Pregnancy
Oral contraceptive use
Oestrogen therapy
Antiphospholid anticoagulant (LLA, ACA)



This event with its vague and subacute evolution can be characterized as follows :

a) *on the clinical aspect* (6,7,8,12,13) *by* :

an intermittent or persistent colickly abdominal pain difficult to localize, out of proportion with the findings of the physical examination, often associated with nausea and vomiting and not improved by antispasmodics or analgesics ;

an abdominal distension with tenderness and persistence of the colic sounds and unfrequently associated with melaena, hematemesis and hematochezia ;

an apparent ascitis which appears only at the beginning of the mesenteric and bowel infarction.

b) *on the biological aspect* (6,7,12,13,17) *by* :

an hemoconcentration and hyperleucocytosis (12.000 to 30.000 WBC/mm^3) with predominance of polymorphonuclear cells (PMN) associated with an increase of alkaline phosfatases and LDH ;

hemostasis disturbances including : platelet hyperactivity with or without thrombocytosis, increased fibrinogen, F. VIII : C, VW F : Ag, V WF : Ri.Cof, factor VII levels, increased release of thrombotic markers like : Betathromboglobulin (BTG), Thromboxane B_2 (TXB_2), Fibrinopeptide A (FPA), Prothrombin fragments 1+2 (F1+2), D-dimers, associated or not with a decrease of some natural inhibitors like : AT III, Proteins C and S.

c) *on the radiological aspect* (6,7,12,13,14) *by* :

for the plain abdominal X-Ray, the barium X-Ray, the contrast enhanced CT Scan and the computerized axial tomography by :

— an aspecific ileus with ascitis
— a dilatation of the small bowel and proximal colon with thickening and irregularity of the wall and separation of the loops with presence of air in the wall and in the portal system ;

2. for the angiographic and ultrasonic investigations by :
— the absence of mesenteric venous flow (more frequently in the SMV than in the IMV) with thrombus extended sometimes to the portal system, associated to peritoneal fluid and thickening of the intestinal wall and "valvulae conniventes" in the jejunoileal segment ;
— a reflux of contrast medium in the aorta ;
— a spasm of the superior mesenteric artery (SMA) with minimal opacification of the distal arcades but absence of thrombus in the SMA.

d) *on the physical examination at surgery or autopsy* (6,7,8,12,13) :
the mesenteric venous thrombosis (MVT) can be localized in the SMV or in the IMV alone or extended to the portal system The most incriminated SMVT is generally associated with proximal colon and middle portion of small bowel ischemia and infarction, while the IMVT will more usually affects the distal colon.

The involved bowel segment appears purple red and dark blue, its wall and the adjacent mesentery are thickened and infiltrated with blood. Arteries are free of thrombus, but veins are thrombosed.

The transition zone between normal and infarcted segments is not well defined like in arterial thrombosis.

Serosanguineous peritoneal fluid is also constantly present and perforation and necrosis of the ischemic bowel are sometimes observed.

Without treatment the mortality rate of MVT is very high (80 to 100%). This percentage can only be reduced by an early diagnosis and therapy. Therefore it is necessary to confirm each clinical suspicion of MVT, as early as possible with modern imaging technics like : ultrasonography, computerized axial tomography, magnetic resonnance and angiography in order to reduce the delay between diagnosis and treatment and so to improve the survival rate and reduce the frequency of recurrence (6,7,13).

Most ot the treatments applied during the last 60 years have only reduced the mortality from 95% to 35% (table III). It is only when thrombolysis or anticoagulant therapy can promptly be initiated that the mortality can significantly be reduced to 12% (table III). Three factors seem to play also an important role in the survival rate of the patients with MVT, they are : the advanced age of the patients, the presence and nature of associated diseases and the timing of surgical procedure in patients with mesenteric and intestinal infarction (7).

Table III. — **Mortality rate of MVT with bowel infarction**

— Without surgical treatment	95%
— With surgical treatment	65%
— With surgical treatment without anticoagulant therapy	95%
— With surgical treatment and anticoagulant therapy	35%
— With precocious anticoagulant therapy or thrombolysis without surgery	12%

The choice of treatment of MVT is dependent on the presence or absence of associated intestinal and mesenteric infarction (3,6,7,8,12,13,15,16).

In the absence of mesenteric or intestinal infarction, when the diagnosis of MVT is promptly established, thrombolytic therapy with Urokinase (UK) at a dose of 4.000 UI/min or Recombinant plasminogen activator (RTPA) at a dose of 0,1 mg/min will be administrated directly into the occluded vessel through a transjugular or percutaneous catheter until complete repermeabilisation (16). Afterwards, this treatment will be relayed by an anticoagulant therapy with first IV heparin during 5 to 10 days and after AVK (hydroxycoumarin) during 3 to 6 months in order to avoid or reduce the frequency of recurrence (table IV). Antiplatelet agents (prostaglandin inhibitors, platelet membrane receptors inhibitors, direct or indirect calcium antagonists or stimulants or substitutes of PGI_2 and NO (table V) and drugs required to treat associated diseases, can be combined with the anticoagulant therapy especially in patients with primary and secondary thrombophilia (17).

When MVT is complicated by intestinal and mesenteric infarction, laparotomy with venous thrombectomy combined with mesenteric and intestinal resection are required and followed by a prolonged anticoagulant therapy similar to these used in the treatment of MVT without intestinal infarction (table VI). Thrombectomy

Table IV. — **Treatment of MVT without mesenteric and bowel infarction**

1. Thrombolysis in the occluded mesenteric vein through transjugular or percutaneous catheter with
   - UK : 4 000 UI/min
   - RTPA : 0.10 mg/min

   Until repermeabilization
2. Anticoagulant therapy
   a) Heparin (IV) : 500-1000 UI/kg/24 h during 5 to 10 days followed by
   b) AVK (Sintrom® or Marcoumar®) at adjusted dose giving a INR between 2.5-3.5 during 3 to 6 months
3. Antiplatelet agents
4. Treatment of associated disease in non idiopathic MVT

Table V. — **Antiplatelet agents**

A. **Prostaglandin inhibitors**
   1. *Cyclooxygenase inhibitors*
      — Aspirin®
      — NSAI
   2. *TXA2 inhibitors*
      — Piracetam (Nootropil®)
      — Ridogrel, Nafagrel

B. **Platelet membrane receptors inhibitors**
   1. *Non glycoprotein receptors inhibitors*
      — Buflomedil (Loftyl®)
      — Pentoxifylline (Torental®)
      — Naftidrofuryl (Praxilene®)
      — Ketanserin (Sufrexal®)
      — Heparin
      — Dextrans
   2. *Glycoprotein receptor inhibitors*
      — Ticlopidine (Ticlid®)
      — Clopidogrel

C. **Calcium antagonists**
   1. *Direct*
      — Verapamil (Isoptine®), Nifedipine (Adalat®)
      — Diltiazem (Tildiem®), Felodipine (Plendil®)
      — Isradipine (Lomir®), Flunarizine (Sibelium®)
      — Nimodipine (Nimotop®)
   2. *Indirect*
      — Dipyridamole (Persantine®)
      — Pentoxyfylline (Torental®)
      — Imidazo-quinazolinone (Anagrelid®)

D. **Stimulants or substitutes of PGI2 and NO**
      — Persantine®, Torental®, Loftyl®
      — Corvaton®, Iloprost®, Ciprostene®

alone is rarely successfull because it removes only thrombi localized in large venous trunks and not the obstruction in small veins in the vicinity of the ischemic bowel (3,6,7,12,15). Large resection of involved ischemic intestinal segment (small of large bowel) with end to end anastomosis is to combine with thrombectomy in the majority of the cases. This surgical procedure is to be followed immediately by a prolonged anticoagulation therapy often combined with antiplatelet agents in order to avoid all thrombotic recurrence. The recur-

Table VI. — **Treatment of MVT with mesenteric and bowel infarction**

1. *General resuscitation measures*
   - — Fluid replacement
   - — Correction of electrolyte imbalance
   - — Correction of hypertension and acidosis
   - — Optimizing of cardiac and renal status
   - — Broad spectrum antibiotics administration in cases of peritonitis, gangrene or perforation
2. *Early surgical procedures including :*
   - — Large resection of involved bowel
   - — Thrombectomy and venous revascularization
3. *Anticoagulant therapy*
   - — Heparin (IV) 500-1000 UI/kg/24 h during 5 to 10 days
   - — AVK (Sintrom® or Marcoumar®) dose giving a INR between 2.5-3.5 during 3 to 6 months
4. *Antiplatelet agents and antispasmodic drugs*

rence appears generally at the site of anastomosis and can be reduced from 30% to 14% with anticoagulants. In some cases, the persistance of a mesenteric arterial spasm associated to the venous thrombosis can be also incriminated in the pathogeny of the recurrence and requires the administration of antispasmodic drugs like papaverine, prostacycline or NO inducers (7,8,12).

When gangrene, peritonitis or perforation are present with the mesenteric and intestinal infarction, general resuscitation measures, antibiotherapy and a "second look laparotomy" will be considered (table V) (3,12,15).

In patients will primary or secondary thrombophilla especially linked to a defect in AT III, Protein C, S or a Resistance to activated Protein C, oral anticoagulant therapy will be absolutely prolonged indefinitely and for the women oral contraception and pregnancy withdrawn.

In conclusion, it appears that a medical treatment alone, promptly applied after the specific imaging confirmation of a clinical MVT suspicion, can not only prevent the appearance of mesenteric and intestinal infarction, but also the recurrence and the extension of the thrombotic process.

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