Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding Applied in Upper Gastrointestinal and Post Partum Bleedings

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**Abstract**

Transcatheter Arterial Embolization (TAE) is a method in which a catheter is inserted into an artery under fluoroscopy guidance. By using material that creates a thrombus, inserted through the catheter, the artery can be occluded and the bleeding stopped.

Endoscopy is the treatment of choice in upper gastrointestinal (GI) bleeding, but 10% to 30% of patients rebleed and needs other treatment options. Post Partum Hemorrhage (PPH) may evolve rapidly and can become life threatening. Obstetrical treatment will manage most cases, but in some cases emergency surgery is needed and in the worst case hysterectomy.

The primary aim of this thesis was to evaluate the clinical usefulness, improve the TAE technique and compare the outcome of TAE with surgery used as “salvage therapy” in patients with upper GI bleeding. Evaluate TAE technique and the long-term effect on the menstrual cycle and fertility in severe PPH.

To evaluate the clinical usefulness 13 patients were treated with TAE after endoscopic treatment failure and 5 were treated for recurrent hemorrhage after emergency surgery.

The clinical outcome and mortality rate of 40 patients treated with TAE was compared with 51 patients treated with surgery of upper GI bleedings.

In 13 patients the ulcer was marked with placement of a metallic clip at endoscopy to be able to locate the exact site of the bleeding ulcer during the TAE procedure.

A retrospective study of 20 patients with severe PPH treated with bilateral TAE of the uterine artery was performed.

TAE was found to be effective and an alternative to emergency surgery for control of massive upper GI bleeding. The 30-day mortality was lower in the TAE group (3%) compared to the surgical group (14%).

By marking the bleeding ulcer at endoscopy using a metallic clip the site of bleeding could be identified on angiography without extravasation of contrast media.

No major impact on fertility or menstruation cycle was found in patients treated with TAE in PPH. TAE in PPH is safe and have no major long-term side effect. By using TAE in PPH hysterectomy can be avoided.

**Keywords**: Post partum hemorrhage, Upper peptic ulcer bleeding, Transcatheter arterial embolization, Endoscopic treatment, Endoscopic marking, Metallic clip

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Dedication

“Patients deserve to be treated better than a side of beef”

The “father” of interventional radiology
Charles Dotter (1920-1985)

To my wife Elisabeth and my children Henrik and Martin
List of Original Papers

This thesis is based on the following original papers, which will be referred to in the text by their roman numerals.

I. Ljungdahl M, Eriksson L-G, Nyman R, Gustavsson S.:
   Arterial embolization in management of massive bleeding from gastric and duodenal ulcers.

II. Eriksson L-G, Sundbom M, Gustavsson S, Nyman R.:
    Endoscopic marking with metallic clip facilitates transcatheter arterial embolization in upper peptic ulcer bleeding.

III. Eriksson L-G, Ljungdahl M, Sundbom M, Nyman R.:
    Transcatheter arterial embolization versus surgery for treatment of upper gastrointestinal bleeding after therapeutic endoscopy failure.
    Manuscript

IV. Eriksson L-G, Lutvica-Mulic A, Jangland L, Nyman R.:
    Massive post partum haemorrhage treated with transcatheter arterial embolization; long-term effects, implication on fertility and technical considerations.
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### Abbreviations

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<tr>
<td>PTA</td>
<td>Percutaneous Transluminal Angioplasty</td>
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<tr>
<td>TAE</td>
<td>Transcatheter Arterial Embolization</td>
</tr>
<tr>
<td>PVA</td>
<td>Polyvinyl alcohol particles</td>
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<tr>
<td>GI</td>
<td>Gastro Intestinal</td>
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<tr>
<td>GDA</td>
<td>Gastro Duodenal Artery</td>
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<td>LGA</td>
<td>Left Gastric Artery</td>
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<td>SMA</td>
<td>Superior Mesenteric Artery</td>
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<tr>
<td>B-II</td>
<td>Billroth II</td>
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<tr>
<td>IR</td>
<td>Interventional Radiology</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>mGY</td>
<td>milli-Gray</td>
</tr>
<tr>
<td>MAST</td>
<td>Medical Anti Shock Trousers</td>
</tr>
<tr>
<td>PPH</td>
<td>Post Partum Hemorrhage</td>
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<td>F</td>
<td>French</td>
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Introduction

Historical background

The first contrast enhanced x-ray image of a vessel was produced January 1896. Just a month after Wilhelm Conrad Roentgen’s discovery of x-rays, OT Lindenthal injected Teichman’s mixture into the veins of an amputated hand (1). However, many decades passed before angiography played a significant role in medicine.

One of the most important historical landmarks in the latest 50 years is Sven-Ivar Seldinger’s access technique. In 1953 Dr. Seldinger (1921-1998) published the description of a percutaneous entry technique in the journal, Acta Radiologica (2). In “Pioneers of angiography” (3) he told how this happened. He had been struggling with the problem of developing a better method of catheterization, when he had “a severe attack of common sense”:

“Now! After an unsuccessful attempt to use this technique, I found myself, disappointed and sad, with three objects in my hand - a needle, a wire and a catheter - and ... in a split second I realized in what sequence I should use them: Needle in, wire in, needle off, catheter on wire, catheter in, catheter advance, wire off.”

The discipline Interventional Radiology (IR) started early in 1960s when the diagnostic x-ray method shifted to a method also to treat. Fluoroscopy and x-ray imaging were used as a diagnostic tool followed by “transcatheter” treatment in varied conditions. One of the first interventional radiologists in this field was Charles Dotter (1920-1985). He altered the course of cardiovascular radiology and is considered the father of IR. He began modifying the Seldinger technique for therapeutic purposes and described percutaneous transluminal angioplasty technique (PTA) 1964 (4). The society of Cardiovascular Radiology was founded in 1974. In addition to diagnostic angiography, members of this society were beginning to expand their interventions. In addition to “Dottering” obstructive lesions, they were beginning to treat gastrointestinal bleeding and pelvic trauma by pharmacologic infusion and embolization (5).

Another important landmark in IR history was the invention of the PTA balloon 1974 by A Gruntzig. He developed a new balloon catheter, manufactured the device on his kitchen table and used it first on February 12, 1974 in a patient with intermittent claudication due to subtotal stenosis of the superficial femoral artery (6, 7).

J Rosch reported the first case of transcatheter arterial embolization (TAE) for acute upper gastrointestinal bleeding in 1972. He performed a selective catheterization of gastroepiploic artery in a patient with a prepyloric bleeding ulcer and injected epinephrine combined with autogenous blood clot as embolic agent (8).

BJ Brown et al reported the first case of embolization for post partum bleeding in 1979. Three separate surgical procedures failed to reveal the source of bleeding and standard surgical techniques, including bilateral ligation of the hypogastric arteries were unsuccessful in producing hemostasis. Angiography successfully identified the specific bleeding vessel, and transcatheter embolization with gelatin sponge fragments stopped the hemorrhage (9).
Transcatheter Arterial Embolization (TAE)

A guidewire and a catheter are inserted into an artery under fluoroscopy guidance. Contrast media is injected into the artery during recording images. The blood flow and the shape of the vessel wall can be evaluated and sources of internal bleeding can be detected. By using material that creates a thrombus (embolic agent), applied through the catheter into the bleeding site, the vessel will be occluded and the bleeding stopped.

The angiographic sign of ongoing bleeding are contrast media extravasation (fig. 1). It has been shown experimentally that a bleeding rate as low as 0.5 mL/min can be demonstrated angiographically (10). Other useful signs in locating the bleeding site are a “pseudoaneurysm” like lesion in the artery (fig. 2). However, frequently intermittent bleeding brings about difficulties to choose the exact area/site for embolization, when no bleeding signs are identified at angiography. In order to overcome this problem the bleeding can be provoked by injecting vasodilators and/or anticoagulants selectively into the suspected bleeding vessel.

There is a large number of embolic agents i.e. metallic coils, gelatin sponge, polyvinyl alcohol particles (PVA), microspheres, glue, alcohol etc. to chose between.

Large embolic agents such as coils and gelatin sponge pledges are mostly preferable for large vessels. Especially in organs with a rich collateral supply (such as stomach, duodenum and uterus) can proximal vessel be occluded without risk of tissue infarction.

Liquid agents such as alcohol or glue will in most cases embolize the most distal vascular supply and result in ischemia and/or infarcted tissue. Some materials such as gelatin sponge are biodegradable and should be used when recanalization of the embolized vessel are desirable.

Gelatin sponge is a water-insoluble hemostatic material prepared from purified skin gelatin, intended for application to bleeding surfaces. It is used as a biodegradable, intravascular embolic agent. Gelatin sponge promotes hemostasis by development of and providing structural support to thrombus. Pledgets cut from a sheet of gelatin sponge are large and will result in a proximal artery occlusion. An additional technique is to create gelatin sponge slurry by mixing gelatin sponge and contrast media between two syringes via a stopcock. Gelatin sponge has the potential to induce a short-term occlusion with minimum tissue reaction and is absorbed completely, with little tissue reaction. This absorption is dependent on several factors, including the amount used, degree of saturation with blood or other fluids, and the site of use. Studies have revealed that the resorption time for gelatin sponge used intravascular occurs within 7-21 day after embolization (11).

Metallic coils were made by cutting pieces of a guide wire. They are now available in different shapes and sizes. Thrombogenic synthetic fiber bundles are attached to the metallic pieces providing structural and chemical support to thrombus causing a permanent occlusion of the vessel. A coil with size 0.018-inch (0.46 mm) in diameter is called “microcoil” and a coil with size 0.035-inch (0.89 mm) in diameter is called “macrocoil” (fig. 3).
Introduction

Figure 1.
Celiac artery injection (black arrow) shows the GDA with extravasation of contrast media (white arrow).

Figure 2.
Celiac artery injection (black arrow) shows the GDA with pseudoaneurysm like lesion (white arrow).

Figure 3.
Microcoils in different shapes with trombogenic synthetic fibers.
Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding

Anatomy

Knowing the anatomy of the vascular supply of a specific bleeding organ is a prerequisite for a successful treatment using TAE and to avoid severe complications. A rich collateral network characterizes the arterial supply to the upper GI organs as well as the uterus.

Arterial supply of duodenum reaches the duodenum on its posterior aspects to spread afterwards along its anterior aspect (12) (fig. 4). Both branches from the gastroduodenal artery (GDA) and superior mesenteric artery (SMA) and occasionally branches arising from the proper hepatic artery i.e. supraduodenal artery (13) supply the duodenum. A rich arterial communication exists between the GDA and SMA via the pancreatic arcade arteries and inferior pancreatico duodenal artery (14) (fig. 5).

The left gastric artery (LGA) arises from the celiac artery it supplies the lower third of the esophagus and the upper part of the stomach. The left gastroepiploic artery arises from the splenic artery it supplies the stomach along the upper part of the greater curvature. The right gastroepiploic artery arises from the gastroduodenal branch of the hepatic artery it supplies the lower part of the greater curvature.

The arterial supply to the uterus (fig. 6) originates mainly from the uterine artery, arising from internal iliac artery, and also some from the ovarian artery, arising from aorta at the level of the first lumbar vertebra (fig. 7) (15, 16). The uterine artery and the ovarian artery form anastomoses in the area of the adnexa structures (fig. 8). The uterine artery is hypertrophied with high flow in the peripartum period (fig. 9). Rarely the uterine arteries are doubled (fig. 10).
Figure 4.
Arterial supply of stomach and duodenum.
Figure 5.
SMA injection (black arrow) in a patient with occluded celiac trunk demonstrates the arterial communication between SMA and GDA via pancreatic arcade arteries and inferior pancreatico duodenal artery (white arrow).
Arterial supply of uterus: Schematic anatomical picture demonstrates blood supply to the uterus.

Figure 6.
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Figure 7.
Left ovarian artery injection (arrow) with typical tortuous appearance. Arising from aorta at the level of the first lumbar vertebra.

Figure 8.
Left ovarian artery with anastomoses (arrow) to the uterine circulation.

Figure 9.
The uterine artery is hypertrophied (arrow) with high flow in the peripartum period.

Figure 10.
A patient with doubled uterine artery on left side, demonstrating an uterine artery with cranial branch post embolization (white arrow) and a caudal branch still supplying uterus (black arrow).
Introduction

Shock caused by hemorrhage (hypovolemic shock)

Hemorrhage is the most common cause of hypovolemic shock. Hemorrhage decreases the mean systemic filling pressure and as a consequence decreases venous return, cardiac output falls below normal and shock ensues.

Approximately 10% (350-550 mL) of total blood volume can be removed with no significant effect on arterial pressure or cardiac output. Greater blood loss usually diminishes the cardiac output and blood pressure falls (17). Both cardiac output and blood pressure will fall to zero when about 35-45% (1500-2500 mL) of the total blood volume has been removed. The decrease in blood pressure initiates a sympathetic reflex that stimulates the vasoconstrictor system throughout the body resulting in constriction of the arterioles in most parts of the body and thereby greatly increasing the total peripheral resistance (18). The veins and venous reservoirs constrict, thereby helping to maintain adequate venous return despite diminished blood volume. Furthermore, heart rate will increase markedly.

Clinical background

Upper peptic ulcer bleeding is usually presented with hematemesis with bright red blood or brown clumps of partially digested blood similar to coffee grounds and bloody or black faeces combined with low blood pressure, dizziness and fainting.

The incidence of peptic ulcer disease is decreasing mainly due to introduction of H2-receptor antagonists, proton-pump inhibitors and antibiotic treatment of Helicobacter pylori (19-23). However, hospitalization and mortality due to peptic ulcer bleeding are still high among the elderly (fig. 11) (24-27). The prognosis for massive bleeding is mainly determined by patient risk factors, related to advanced age and associated medical illness (28). In the last two decades endoscopy has become the cornerstone of diagnosis and treatment leading to substantial decrease in numbers of operations performed for peptic ulcer bleeding (29-32). The vast majority approximately 70-80% of bleeding peptic ulcer ceases spontaneously without any intervention (33, 34). Endoscopy treatment can usually achieve primary hemostasis in the majority of the remaining patients. However, 10% to 30% of patients rebleed following endoscopic therapy (35, 36). If endoscopy treatment of the bleeding ulcer fails emergency surgery may be needed. However, mortality rate after emergency surgery for gastroduodenal bleeding is high and varies approximately between 15% and 48% and occur as a result of complications in elderly patients with significant comorbidities (37-41). Important factors to reduce mortality and morbidity are to stop the bleeding as soon as possible and to minimize the risk of rebleeding (42).

TAE has been introduced and many authors recommend TAE as salvage therapy when endoscopic treatment fails (40, 43-45). However, comparative studies are nearly non-existent. Only one earlier study has compared the clinical outcome of TAE with emergency surgery (46).

Figure 11.
The maternal blood volume shortly before delivery is approximately 30% above the normal. The cause of the increased blood volume is mainly hormonal, causing increased fluid retention by the kidneys. The bone marrow becomes increasingly active and produces an excess of red blood cells combined with the excess fluid volume. Therefore, at the time of birth of the baby, the mother has approximately 1 to 2 liters of extra blood volume in her circulation system, allowing the mother to be able to bleed significant with a considerably safety factor.

Severe Post Partum Hemorrhage (PPH) may evolve very rapidly and unexpected and can become life threatening within a few minutes. Obstetrical mechanical and medical treatment will manage most cases but in some cases emergency surgery is needed and in the worst case can result in hysterectomy. Hysterectomy is a major psychological trauma to a young woman and a high-risk operation following a massive bleeding.

Although maternal mortality rates have declined greatly in the developed countries, post PPH remains a leading cause of maternal mortality elsewhere. According to World Health Organization PPH is considered to be responsible for 25% of maternal death worldwide (47). The mortality rate per million maternities in United Kingdom has more than doubled since the previous triennium 1997-1999 (48) and severe PPH remains a common medical emergency problem even in western countries.

PPH is defined as an estimated blood loss of more than 500 mL with vaginal delivery (49) and more than 1000 mL for cesarean section (50). However, This definition is of limited practical use as accurate quantification of blood loss is seldom possible, because of difficulties in evaluation of blood loss with visual observation only. It have been suggested that PPH should be diagnosed with any amount of blood loss that threatens the hemodynamic stability of the woman. Combs et al defined PPH by a post partum hematocrit drop of 10% or by need for transfusion (49). PPH is classified as early within the first 24 hours and late after 1 day to 6 weeks after delivery (51). The main cause of PPH is uterine atony and retained placental tissue. Other causes are placental abnormalities such as placenta accreta, praevia and abruption, lacerations of the perineum, vagina or cervix, vessel malformations, ruptured uterus and coagulations defects.

Extensive blood loss due to PPH can lead to hypovolemic shock, severe coagulation disorder and serious morbidities such as renal and hepatic failure, adult respiratory distress syndrome and rarely pituitary gland necrosis (52). It is estimated that excessive bleeding complicates 5–15% of delivery (50).

TAE has been developed as an alternative to surgery and has been shown to preserve fertility and reduce morbidity (53-56). However, the long-term effect is not well known. A few authors have reported data regarding the long-term effect on the menstrual cycle and the possibility of preserved fertility (57-60).

Bleeding caused by uterine atony is often presented without contrastmedia extravasation (fig. 12) or identified as a diffuse irregular contrast enhancement with tortuous vessels at angiography (fig. 13). Pseudoaneurysm is presented as a rounded well-shaped contrast-enhanced structure in the uterine wall or the cavity of the uterus (fig. 14). On color Doppler images pseudoaneurysm are presented as a rounded anechoic structure with posterior acoustic enhancement and showing swirling blood flow (fig. 15).
Introduction

Figure 12.
Patient with massive PPH due to uterine atony after vaginal delivery. Left uterine artery angiogram demonstrates no contrast medium extravasation.

Figure 13.
Patient with massive PPH due to uterine atony after cesarean section. Bleeding identified as a diffuse irregular contrast enhancement, due to contrast media extravasation into the uterine cavity (arrow).

Figure 14.
Patient with massive PPH after cesarean section. Right uterine artery angiogram demonstrates a pseudoaneurysm in the uterine wall (arrow).

Figure 15.
Color doppler image with pseudoaneurysm (arrow).
Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding
Study aims

Aims of the thesis

Evaluate the clinical usefulness, improve the TAE technique and compare the outcome of TAE with surgery used as “salvage therapy” in patients with upper GI bleeding.
Evaluate TAE technique and the long-term effect on the menstrual cycle and fertility in severe PPH.

Specific aims of individual studies:

1. Assess the therapeutic usefulness in patients managed with TAE in non-variceal upper GI-bleeding.
   (Study I)

2. Develop a method to mark the bleeding site in upper peptic ulcer bleeding with a metallic clip during endoscopy used as a guide in TAE in order to enhance the possibility that the correct area is embolized.
   (Study II)

3. Compare the clinical outcome in patients treated with either TAE or surgery in severe upper GI-bleeding after failed endoscopic treatment.
   (Study III)

4. To evaluate early and late complications in patients with severe PPH managed with TAE and its influence on menstrual cycle and fertility and to improve the embolization technique.
   (Study IV)
Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding
Material and Methods

Material and methods

Study I
A study of 18 patients between October 1998 to September 2001 (eleven women and seven men, mean age 78 years, range 53 to 94 years). With massive peptic ulcer bleeding treated with TAE. Thirteen patients were treated with TAE after endoscopic treatment failure and 5 patients were treated for recurrent hemorrhage after emergency surgery. All patients were selected to TAE because they were considered poor surgical candidates caused by concurrent diseases and hemodynamic instability. Data recorded were; patient demographics, concurrent diseases, endoscopic diagnosis, surgical report, hemoglobin concentration, and blood pressure, transfusion requirement, angiographic treatment, complications, need for operation and in-hospital mortality.

All angiographic procedures were performed with standard percutaneous transfemoral catheterization. The celiac trunk and SMA were selectively examined. Ongoing bleeding was defined as extravasation of contrast media or a pseudo-aneurysm like lesion. Embolization was performed as close as possible and on both sides of the bleeding site. If no bleeding site were identified a “blind” embolization of the entire GDA or LGA was performed depending of the result of the endoscopic examination. In all patients metallic coils were used as embolic agent.

Study II
A study of 13 patients between September 2003 and February 2005 (five women and eight men, mean age of 75 years, range 30-93 years) with massive upper peptic ulcer bleeding. The bleeding site was identified with endoscopy and treatment performed to stop the bleeding. The ulcer was then marked with placement of a metallic clip at its edge. The purpose was to locate the exact site of the bleeding ulcer at angiography in order to facilitate the TAE procedure. Only ulcers considered by the endoscopist to present a high risk of recurrent bleeding or hemostasis considered less feasible were marked.

Angiography with TAE was performed if the patient continued to experience bleeding or had a recurrence of bleeding. Guided by the placed metallic clip the catheterization was performed as selectively as possible and the branches closest to the clip were embolized. A transfemoral approach was used in all cases. Both the celiac trunk and SMA were selectively examined. Three patients had definite hemostasis after endoscopy and were not treated with embolization; instead they were examined with plain upper radiography every 24 hours until the clip was found to be dislocated at a maximum of 5 days. Benefit from clip marking was considered when there was no sign of contrast media extravasation before embolization and if the clip made it possible to identify and efficiently embolize the vessel close to the clip.
Study III

From January 1998 to December 2005 a total of 658 patients were diagnosed with upper GI bleeding due to gastric or duodenal ulcer, combined gastric ulcer and duodenal ulcer, stomal ulcer or Dieulafoy’s lesion. In 567 (86%) patients who underwent emergency endoscopy, the bleeding had ceased either spontaneously or was successfully stopped by endoscopic treatment (one or two attempts). Ninety-one (14%) patients rebleed or continued to bleed after initial emergency endoscopy treatment and were managed with either surgery or TAE. These 91 patients were included in the study. Forty patients (18 included in paper I) were treated with TAE and 51 patients were treated with surgery.

A retrospective analysis with a review of the medical records was performed. The following variables were recorded: demographic variables, endoscopic diagnoses, comorbidities, the lowest hemoglobin levels, total transfusion requirements, hospitalization lengths, post procedure complications, and mortality rates. Relative survival rate was calculated. Survival probability was calculated with Kaplan Meier technique.

The patients were mainly referred to TAE when they were considered as poor surgical candidates because of their high comorbidities. Since 2002, there has been a complete on call system for interventional radiologists in our institution. Embolization of GDA was performed in 33 patients, embolization of LGA in 5 patients and both GDA and LGA in 2 patients.

In the surgical group emergency surgery with a BII-resection was performed in 29, duodenotomy or gastrotomy and over-sewing of the bleeding ulcer/artery in 14, re-resection after previous B-II resection in 6 and other types in 2 patients (explorative laparotomy and small intestine resection).

Study IV

A retrospective study of 20 patients (mean age 30 years, range 23-40 years) with severe PPH treated with bilateral TAE of the uterine artery. The patients were treated between 1993 and 2004. Seven patients had vaginal delivery (1 after vacuum exeresis due to miscarriage) and 13 had cesarean section delivery.

If the obstetrical treatment failed with continuous bleeding the patient was referred to angiography and TAE. To determine the long-term side effects and implications on menses and fertility the patients were asked to answer a questionnaire regarding their post embolization history. Pregnancies since the embolization, attempting to get pregnant, infertility, miscarriages, number of pregnancies, term or preterm, delivery method, menses, pain history, bladder problems and incontinence were asked for. Clinical, biochemical and hematological data were collected from the medical records. Gelatin sponge and coils were used as embolic agent.

The radiation dose was measured in 6 patients and the radiation dose to the ovaries was calculated.
Material and Methods

Embolization technique in upper GI bleeding

A transfemoral approach was used in all cases by placing a 5F (1.67 mm) introducer into the common femoral artery. The celiac trunk and SMA were selectively examined using a 4F (1.35 mm) catheter (SHK, Cordis, Miami Lakes FL, USA; Cobra, Terumo, Tokyo, Japan). The GDA or LGA was then selectively catheterized using a 3F (1.00 mm) Microcatheter system (Tracker, Boston scientific, Natick MA, USA). Iodine contrast media (Omnipaque 200 mgI/mL, Amersham GE Healthcare AS, Norway) were injected by hand 5-10 mL/injection.

Depending of the endoscopic findings, extravasation of contrast media at angiography or the position of a marking metallic clip (a technique to mark the bleeding site at endoscopy used in our institution since 2003 (66)), a selective catheterization of the bleeding branch was performed. When no contrast media extravasation was seen or when no marking clip were placed a “blind” embolization of entire GDA or LGA was performed, depending of the endoscopic findings. Both sides of the bleeding site were embolized in order to prevent “back door” bleeding. The endpoint was complete occlusion of the target vessel or occlusion of the vessels as near as possible to the extravasation or marking clip. No embolic agents other than coils was used in this study, 0.035-inch (0.89 mm) stainless steel macrocoils (William Cook, Europe, Denmark) or 0.018-inch (0.46 mm) platinum microcoils (Boston scientific, Natick MA, USA). The procedures were performed in local anesthesia in all patients.

Embolization technique in PPH

A catheter was placed into abdominal aorta at the level of the renal arteries. Approximately 20 mL Iodine contrast media (10-15 mL/s) (Omnipaque 200 mgI/mL) were injected. Images of the pelvic region were obtained in order to identify the type of lesion, the position of the uterine arteries and possibly supply from ovarian arteries. Both uterine arteries were selectively catheterized from a unilateral transfemoral approach (Cobra catheter, Terumo Tokyo, Japan) and 5-10 mL contrast media were injected by hand to confirm correct position. A piece of gelatin sponge intended for local hemostasis in surgery (Gelfoam®, Pharmacia & Upjohn, Kalamazoo, Mich, USA) was scraped with a scalpel. Approximately 1-3 square centimeters of gelatin sponge was suspended in a solution mixed with 50% saline and 50% contrast media (Omnipaque 200 mgI/mL) to create a slurry by mixing between two syringes via a three-way stopcock. It was then injected into both uterine arteries regardless if contrast media extravasation was seen or not until circulatory arrest was obtained. If selective catheterization was impossible (i.e. due to spasm) the embolization material were injected at the level of the anterior division of the internal iliac artery. If there was a clear vessel tear micro- or macrocoils were used as embolic agent unilaterally to obtain hemostasis in addition to the gelatin sponge mix.
Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding
**Results**

**Study I**

Superselective catheterization and embolization were feasible in all patients. In 9 of 13 patients, treated primarily with TAE, extravasation of contrast media at angiography indicated continuing bleeding. Immediate hemostasis was achieved in 8 of these patients. One patient continued to bleed after embolization and required an emergency operation. One patient needed a reemobilization after 3 days for recurrent bleeding. In 4 patients there were no signs of bleeding at the time of angiography and the main artery (GDA) was embolized (“blind embolization”) because of the findings at endoscopy. In one patient with a Dieulafoy's lesion sclerotherapy and embolization failed to stop the bleeding. This patient had an emergency operation and the lesion was over-sewn but the patient died 18 days postoperatively.

Five patients were treated for recurrent bleeding after surgery. Four of the 5 patients showed signs of continuing bleeding at the time of angiography. Hemostasis was obtained in all 5 after embolization one needed a reemobilization for recurrent bleeding after 25 days. All patients in this group recovered satisfactorily.

**Study II**

Ten of 13 patients underwent angiography. In 8 patients hemostasis was obtained after embolization. Two patients underwent emergency surgery, 1 with occluded celiac trunk making catheterization impossible, and 1 with multiple large duodenal ulcers not possible to treat with TAE. In 1 patient reembolization was necessary to obtain final hemostasis.

The clip stayed in place in 11 patients and was dislocated in 2 patients at the time of x-ray. The result of the embolization procedure benefited from the clip marking in 6 patients. The clip made it easier to identify the suspected bleeding vessel without sign of contrast extravasation. The bleeding vessel was the supraduodenal artery with no connection to GDA in 2 cases and the pancreatic inferior artery with connection with superior mesenteric artery in 1 case. It was possible to reduce the “coiled distance” in 3 cases with suspected bleeding site directly from GDA. In these cases a short distance of GDA were embolized as close as possibly and on both sides of the clip. In 1 case with clear contrast media extravasation there was no benefit from the clip. The extravasation in this case was observed close to the clip. In the 8th case the clip had dislocated at the time of TAE.

There were no complications observed and no patient developed signs of ischemia leading to perforation or problems with gastric emptying.
Transcatheter Arterial Embolization in the Management of Life Threatening Bleeding

Study III

The most common causes of bleeding were duodenal ulcers, 83% in patients referred to TAE and 63% in patients referred to surgery. Patients who underwent TAE were older (76 years, SD 10) and had slightly more comorbidities than the patients who underwent surgery (71 years, SD 13). Hospitalization time was slightly longer in the surgical group (13 days, range 2-67) compared to the TAE group, (10 days range 3-43). The lowest hemoglobin level (median 72 g/L) was equal in both groups. The group treated with TAE required transfusions of median 17 units of packed red cells (range 3-50) compared to 19 (range 0-90) units in the surgical group.

Primary hemostasis was achieved in 30 of 40 (75%) who underwent TAE and 42 of 51 patients (82%) who underwent surgery. Five of 10 patients who rebled or continued to bleed after TAE were treated with a second TAE procedure and hemostasis was achieved in all 5 patients. The remaining 5 patients underwent emergency surgery. Hemostasis was achieved in 4 patients (3 bleeding ulcers were over-sewn and 1 BII-resection). The 5th patient underwent exploration and no ongoing bleeding was identified at the time of surgery. No complications related to the embolization procedure, such as groin hematoma or bowel ischemia leading to perforation or problems with gastric emptying, were observed.

Eight of 9 patients who rebleed or continued to bleed after surgery was treated with TAE and hemostasis were achieved in all 8 patients. One patient was successfully reoperated and the bleeding vessel was over-sewn. Two additional patients in the surgical group, needed a second surgical procedure due leakage with abscess formation after BII-resection.

Thirty-day mortality rate in patients treated with TAE was 1 of 40 (3%) compared to 7 of 51 (14%) in patients treated by surgery (p<0.07). None of these patients who died had a second procedure of either TAE or surgery. The cause of death in the patient who died within 30-days after TAE (age 79 years) was multi organ system failure. All 7 patients who died after surgery were elderly with a mean age of 80 years (range 71-89 years). The causes of death were multiorgan failure in 4 patients, myocardial infarction in 1, respiratory failure in 1 and sepsis with shock in 1 patient.

The Kaplan-Meier estimate shows that the initial differences in mortality rate between the 2 groups were equalized after 1 year. The relative survival curve demonstrates that both groups have similar mortality rate and somewhat higher than that of an aged matched control group. Around 50% of the patients in both groups were alive 5 years after the actual episode of peptic ulcer bleeding.
Results

Study IV

Hemostasis using TAE was obtained in all 20 patients. In 18 cases selective embolization of the uterine arteries was performed, in 2 cases the anterior division of internal iliac was embolized due to spasm of the uterine artery. No bleeding supplied from the ovarian arteries was identified.

Seven patients had vaginal delivery and no sign of contrast media extravasation was observed in this group. Absorbable gelatin sponges were used in all 7 cases as the primary embolic agent and no metallic coils were used. Two patients rebled and were reembolized using gelatin sponge as embolic agent. Two patients needed curettage to obtain hemostasis in addition to embolization due to retained placental parts.

Thirteen patients had cesarean section delivery. Gelatin sponge were used in all 13 cases as the primary embolic agent, in 2 of these cases coils were added due to massive contrast media extravasation. In this group with obstetric hemorrhage after cesarean section reembolization was necessary in 5 patients. Four had clear signs of contrast media extravasation, primarily only embolized with gelatin sponge. They were all successfully reembolized with coils unilaterally One case had no signs of extravasation of contrast and was successfully reembolized using only gelatin sponge. All the 20 patients who were contacted answered the questionnaire. The only short-term complication registered was a temporary low-grade fever reaction in 7 patients. The average follow-up time was 8.2 years (follow-up range 1.0-12.1 years). The number of registered long-term complications was 6. Endometrial infection in 1 patient 3 weeks after embolization. Two patients had complained of transient pelvic pain, 2 with transient numbness in legs and 1 patient with reduced tactile sensitivity in right thigh. Normal menses resumed in all patients.

Four patients had a total of 5 full-term and 2 preterm (gestation week 34 and 35) pregnancies. All delivered healthy infants by cesarean section with no recurrence of PPH. One of these patients had 3 full-term infants and also 1 miscarriage (gestation week 9). They all had a follow-up time longer than 4 years. One patient had six unsuccessful in vitro fertilization attempts. There was no desire and no attempts to get pregnant in the group with follow up time between 1.6-2.6 years.

The mean radiation dose to the ovaries was 586 mGy (range 204-729 mGy).
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Discussion

The results in this thesis demonstrate that TAE is a minimal invasive, safe and effective method to treat different life threatening bleedings and should be the method of choice instead of surgery. The method was here applied in upper GI and PPH, but the method has also been found applicable in many other areas. TAE can be used in many situations such as trauma, lower GI, nasal and postoperative hemorrhages (61-63).

Endoscopic therapy is the method of choice in patients with upper GI bleeding. Study I indicated that TAE was effective and an alternative to emergency surgery for control of massive upper GI bleeding, especially in elderly patients with concurrent diseases and when endoscopic treatment fails. The outcome of an acute GI bleeding in these patients is dependent on a minimal invasive therapy with a low risk of rebleeding. In study III there was a clear trend to lower 30-day mortality in the TEA group despite that the TAE group was older and had slightly more comorbidities than the surgical group. The mortality rate in both groups was somewhat higher than that of an aged matched control group. However, almost half of the patients were alive after 5 years, which demonstrate that most patients in this high age group return to a normal life after this life saving treatment. With TAE none of the patients demonstrated any complications in short or long term that could be related to the TAE procedure. Also by using TAE, unnecessary surgical resection of the upper GI tract can be avoided. Another advantage of TAE was that most of the patients suffering from recurrent bleeding after initial treatment with surgery or TAE could be effectively treated with TAE and thus avoiding a second surgical procedure. In the long term both TAE and surgery seem to be effective as there was no signs of late rebleeding (>30 days) in any of the groups. These results is also supported by the findings in the study of Ripoll et al (46) who also compared the outcome of TAE and surgery in the treatment of upper peptic ulcer bleeding after failed therapeutic endoscopy. They retrospectively reviewed a group of 70 patients, 31 managed with TAE and 39 with surgery. No differences were found in the incidence of recurrent bleeding, need for additional surgery or death, despite that the TAE patients were older and had more comorbidities.

The accepted procedure in TAE for peptic ulcer bleeding is selective embolization of at least one vessel, chosen by findings of contrast media extravasation, aneurysm formation at angiography or endoscopic findings before angiography. The LGA is chosen as the target vessel for gastric bleeding and the GDA and its branches are chosen for duodenal bleeding. Contrast media extravasation is the only direct angiographic criteria to diagnose active bleeding or define the bleeding site. Upper peptic ulcer bleeding is considered to be of arterial origin and is intermittent in nature (64, 65). Complex arterial anatomy particular in the bulb and duodenal region in combination with frequently intermittent bleeding bring about difficulties to choose the exact area/site for embolization. In this situation the entire GDA or LGA is recommended to be “blindly” embolized in cases with endoscopic detected duodenal or gastric bleeding (66-68).

The marking technique (study II) with a metallic clip can be used to identify the exact position of the bleeding ulcer even if there is no contrast media extravasation. This technique enhances the possibility to choose the right target vessel and to embolize the actually bleeding artery that will most likely reduce the risk of rebleeding. This is especially important when the bleeding artery arises separately from proper hepatic artery i.e. supra-duodenal artery with no connection to GDA and when the artery is in connection with SMA (69). In these cases a “blind” embolization of entire GDA will not be sufficient.

TAE in patients with PPH is safe and have no major long-term side effect as shown in study IV. No negative effect on menstrual cycle was demonstrated. Four patients had a total of seven pregnancies with normal conception delay, and all delivered healthy infants by cesarean section with no recurrence of PPH.

No large prospective studies concerning PPH embolization are reported in the medical literature. However, in three case series, a total of 38 patients with persistent PPH were embolized with a success rate of 90–95% (56, 70, 71). Successful pregnancies
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have also been reported in other studies in women who had undergone embolization for PPH (57-60). There has been a case report of amenorrhoea following embolization for PPH, secondary to necrosis of the uterine wall and obliteration of the cavity (72).

Cesarean section delivery was high represented in this study. Thirteen of 20 patients had cesarean section and 6 of these had a clear contrast media extravasation indicating a laceration of the uterine artery. Four of these, who were primarily embolized with only gelatin sponge rebled and the pseudoaneurysm like lesions on the angiograms indicated that the cause might have been the surgical trauma. In order to achieve hemostasis they had to be reembolized with coils proximal to the bleeding site. The other 2 patients with clear contrast media extravasation were primarily embolized with coils near the bleeding site, in addition to gelatin sponge bilaterally, to obtain hemostasis. The combination of surgical trauma together with atony of the uterus might be the explanation for the development of the massive bleeding in these cases. It also demonstrates that gelatin sponge alone as embolic agent might not be sufficient. The hemostasis was only temporary and when the blood pressure and volume raised the gelatin sponge might have been “washed out” causing the bleeding to start again, demonstrating the necessity of use coils in these situations. It is also important to embolize the contra lateral side with gelatin sponge to prevent collateral “feeding” of the bleeding site and to embolize until complete circulatory arrest is obtained on both sides in order to minimize the risk of re-bleeding. Extravasation of contrast media seems less common after vaginal delivery and the bleeding is more diffuse and embolization with only gelatin sponge was found to be sufficient in these cases.

The critical condition of the patients with ongoing massive PPH often makes the anesthesiologists and the obstetrician reluctant to move the patient outside of the intensive care unit or operating room. However, the risks of transfer have to be weighed against the benefits of embolization in the equipped angiography suite, as the success of the procedure relies on the quality of the fluoroscopy and x-ray images. In order to make the transportation to the angiosuite safer and to gain time medical anti shock trousers (MAST) can be used (73). After insertion of urine catheter the MAST can be applied. The MAST stops the bleeding below renal arteries. In most cases inflation to 25-35 mmHg (millimeter of mercury) is sufficient. The pressure can be maintained for 4-8 hours. The use of MAST gain time and will enable for the interventionalist and the staff to arrive and prepare to treat the patient. The anesthesiologist can concentrate on replacement of blood loss and coagulation disorder and to stabilize patient before transfer. The leg compartments of the MAST can remain inflated during the embolization procedure and allow access to the femoral artery. The advantages of uterine embolization over surgical intervention include the benefit of preserving fertility, the ability to verify the success of procedure with angiography and embolization of collateral vessels and other sources of bleeding such as ovarian arteries, vaginal, cervical branches and rarely inferior epigastric artery (described in study IV).

The radiation doses to the ovaries in study IV exceeded greatly those used in most routine diagnostic studies (74, 75). Despite the relatively high radiation dose there were no reports of radiation induced skin reactions or children borne with damages or malformations. It is still very important to take every measure to keep the radiation dose as low as possibly to the ovaries. However, to stop the life threatening bleeding in a safe way is the most important task in this situation.

In order to achieve effective results with TAE, it is important with a close multidisciplinary collaboration. Concerns have been raised that failed attempts at radiological intervention may affect the final outcome by delaying definite surgical therapy (29). Therefore, it is crucial to have an on call system for interventional radiologist so the TAE procedure can be done quick and effectively at any time during the day and night without unnecessary delay. It is also important to have an equipped angiosuite at or close to the operation ward, giving the option to perform endoscopy, angiography and TAE or to convert to open surgery, if needed. This setting also allows the anesthesiologist to have a complete intensive care monitoring of the critical ill patient during the procedures. If these requirements are fulfilled, TAE can be accepted as an alternative to surgery.
Conclusion

The use of TAE is a safe and effective method to control severe upper GI-bleeding as well as severe PPH with small risk of complications. TAE in upper GI-bleeding has a lower 30-day mortality rate compared to surgery. Marking the bleeding ulcer with a metallic clip can enhance the safety and effectiveness of TAE. TAE in PPH does not seem to have any major negative effect on menstrual cycle or fertility. The results in this thesis strongly argue for increased use of TAE in upper GI bleeding after therapeutic endoscopy failure and in PPH after conservative obstetrical treatment failure as an alternative to surgery.
**Summary in Swedish**

Detta arbete handlar om kateterburen terapi vid svåra livshotande blödningar. Två typer av blödningar ingår i detta arbete: 1: blödande magsår och 2: svåra förlossningsblödningar.


Förstahandsmetod för diagnostik och behandling av blödande magsår är endoskopi (gastroskopi). De allra flesta blödande magsår slutar att blöda spontant eller efter endoskopisk behandling (ca 70-80%). Dock reblöder 10-30% efter endoskopisk behandling och då krävs antingen operation eller kateterburen embolisering. Det är ofta äldre patienter med andra samtidiga sjukdomar som drabbas av blödande magsår. För dessa patienter är akut operation påfrestande med hög dödlighet som följd.


Avsikten med denna avhandling var att studera resultaten och att förbättra teknik och logistik vid kateterburen behandling vid dessa två tillstånd. Jämföra det kliniska utfallet och dödligheten hos patienter behandlade för blödande magsår antingen med kirurgi eller embolisering. Utveckla en metod att märka ett blödande magsår vid endoskopi med ett ”metalleclips” i syfte att underlätta emboliseringen vid kärlröntgen. Resultatet visade att man med detta clips kan välja rätt ”målkärl” med större precision än vid ”blind” embolisering.

**Studie I** avsåg att beskriva tekniken, det kliniska utfallet samt den terapeutiska nytan med embolisering använd vid blödande magsår. Arton patienter behandlades, 13 efter misslyckad endoskopisk behandling och 5 med fortsatt blödning efter operation för blödande magsår. Det gick att utföra embolisering på alla patienter. Det gick att stoppa blödningen med embolisering hos 17 av 18 patienter, 2 krävde 2 emboliseringstillfällen, en krävde akut operation efter misslyckad embolisering. Resultatet indikerade att emboliseringsmetoden är en effektiv metod som alternativ till kirurgi.

**Studie 2** avsåg att utveckla en teknik att märka ett blödande magsår vid gastroskopi för att underlätta katetraseringen av rätt kärl vid kateterburen embolisering. Det är vanligt att man vid kärlröntgen på en patient med blödande magsår inte ser någon pågående blödning just vid bildtagningstillfället. Man kan då med ledning av gastroskopifyndet utföra en ”blind” embolisering av ett kärl som man tror ligger i närheten av det blödande magsåret. Om man märker såret med ett ”metalleclips” som kläms fast i kanten av det blödande magsåret vid gastroskopi kan man se dess position vid röntgen och utföra emboliseringen med ledning av detta clips. Resultatet visade att man med detta clips kan välja rätt ”målkärl” med större precision än vid ”blind” embolisering.
**Studie 3** avsåg att jämföra det kliniska utfallet samt jämföra dödligheten hos patienter som antingen är behandlade med kirurgi eller med kateterburen embolisering för blödande magsår. Under en åttaårs period diagnostiserades 658 patienter med blödande magsår och 567 (86%) av dessa slutade blöda spontant eller efter endoskopisk behandling. Nittioen patienter (14%) slutade ej att blöda efter endoskopisk behandling och av dessa behandlades 40 med kateterburen embolisering och 51 med kirurgi. Vid jämförelse av dessa två grupper visade resultatet att i gruppen som behandlades med kirurgi var 30-dagars dödligheten 14% (7 patienter) mot bara 3% (1 patient) i gruppen som behandlades med embolisering trots att de i emboliseringsgruppen var äldre (76 år median mot 71) och något sjukare. Detta indikerade att emboliseringsstekniken var lika effektiv men mer skonsam mot patienten än kirurgi.

**Studie 4** var en retrospektiv studie av 20 patienter som genomgått embolisering pga. svår förlossningsblödning och som avsåg att utvärdera förekomsten av tidiga och sena komplikationer samt påverkan på menstruationscykeln och fertiliteten. Medeluppföljningstiden var 8,2 år (varierade mellan 1,0 - 12,1 år). Resultatet visade att inga tidiga eller sena betydelsefulla komplikationer förekom. Vare sig menstruationscykeln eller fertiliteten påverkades negativt i den undersökta gruppen emboliserade kvinnor. Vid embolisering p.g.a förlossningsblödning efter kejsarsnitt kunde blödningarorsaken i åtminstone 6 fall härledas till det kirurgiska traumatet. Emboliseringsstekniken var effektiv, säker och skonsam både vad gäller behandling av blödande magsår och behandling av svår förlossningsblödning och bör föredras som 1:a metod före kirurgi. Genom att märka det blödande magsåret med metalclips kan effektiviteten förbättras med minskad risk för reblödning.
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