PEPTIC ULCER HAEMORRHAGE IN ESTONIA: EPIDEMIOLOGY, PROGNOSTIC FACTORS, TREATMENT AND OUTCOME

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TARTU 2003

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Minu perele.

Wereoksendamine.
Kui see wiga ilmsiks tuleb, pane kohe lusika täis soola klaasi wee sekka ja
joo ära. Joo peti-piima, see awitab. Wisa wereoksendamise juures on
tarwis arsti abi otsida.
J. M. Jaanus. Rahwa tohter. 1904. Lk. 62.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the publications below, which will be referred to in the following by their Roman numerals:

I   Soplepmann J, Peetsalu A, Peetsalu M, Väli T, Tein A. Endoscopic findings in upper gastrointestinal tract hemorrhage in Tartu University Surgical Clinic: comparison of two periods, 1979–81 and 1989–91. Acta et Commentationes Universitatis Tartuensis 1994; 969: 16–25.

II   Vardja T, Peetsalu M, Soplepmann J, Peetsalu A. Natural history, results of surgery and the costs of treatment of duodenal ulcer disease. Estonian Physician 1995; 2: 113–116 (in Estonian, summary in English).

III Soplepmann J, Udd M, Peetsalu A, Palmu A. Acute upper gastrointestinal haemorrhage in Central Finland province, Finland, and in Tartu County, Estonia. Annales Chirurgiae et Gynaecologiae 1997; 86: 222–228.

IV Soplepmann J, Peetsalu A, Peetsalu M, Tein A, Juhola M. Peptic ulcer haemorrhage in Tartu County, Estonia: epidemiology and mortality risk factors. Scandinavian Journal of Gastroenterology 1997; 32: 1195–1200.

V   Soplepmann J, Peetsalu M, Tein A, Peetsalu A. Long-term results of peptic ulcer haemorrhage. European Journal of Trauma and Emergency Surgery 1999; 22: 177–179.

VI Soplepmann J, Peetsalu M, Väli T, Peetsalu A. Long-term results of surgical treatment of giant duodenal posterior wall ulcers complicated with hemorrhage. Langenbeck`s Archives of Surgery 2003 (submitted for publication).

VII Soplepmann J, Peetsalu M, Sillakivi T, Tein A, Väli T, Peetsalu A. Changes in the treatment of peptic ulcer haemorrhage. Estonian Physician 2002; 81: 468–472 (in Estonian, summary in English).

ABBREVIATIONS

AEV	antrectomy with reconstruction after Herfarth, combined with vagotomy
CI	confidence interval
DPV	duodenal resection with plasty after Helwing, combined with vagotomy
DPWU	duodenal posterior wall ulcer
DU	duodenal ulcer
EIT	endoscopic injection therapy
GU	gastric ulcer
H. pylori	*Helicobacter pylori*
NSAID	non-steroidal anti-inflammatory drug
OGD	oesophagogastroduodenoscopy
PU	peptic ulcer
PUH	peptic ulcer haemorrhage
UGIH	upper gastrointestinal haemorrhage

1. INTRODUCTION

PU is a very common medical condition. Every tenth person suffers from DU or GU at some time during their lives (Johnson, 1994). The key role of *H. pylori* and NSAIDs in PU development has been recognized worldwide. A continuous and dramatic decrease in hospital admissions (Kurata and Corboy, 1988) and elective surgery (Penston *et al.*, 1993; Paimela *et al.*, 1991) for PU during recent decades has been repeatedly reported from different regions. However, emergency admissions and surgery for the complications of PU have not changed much (Kurata and Corboy, 1988; Bloom *et al.*, 1990; Paimela *et al.*, 1991).

Acute haemorrhage is the most common complication of PU. The lifetime prevalence of haemorrhage in PU patients has been estimated to be 15–20% (Vaira *et al.*, 1997). The incidence of PUH has been reported to be between 25–65 per 100,000 population per year (Panos and Walt, 1993; Fraser *et al.*, 1997; van Leerdam and Tytgat, 2002). The incidence rates of PUH are significantly higher in the elderly, and time trends show a continuous increase in the proportion of the elderly (Bloom *et al.*, 1990). The most important risk factor for the development of ulcer bleeding is NSAID use (Kuyvenhoven *et al.*, 1999).

According to the unpublished annual reports of the Bureau of Medical Statistics at the Ministry of Social Affairs of Estonia, PUH has redoubled in incidence during the last 20 years, a phenomenon not observed in the developed world. Changes in the natural course of the disease, more extensive use of ulcerogenic drugs, altering treatment tactics, as well as socio-economic stress may have contributed to the change. The reasons for such a major increase have not been assessed yet. Epidemiological studies that could cast light on the causes of the change have not been performed and thus the present-day epidemiological pattern of PUH in Estonia has been unclear until now.

The prognosis of PUH is determined by a number of patient-, ulcer- and treatment-related factors (Holman *et al.*, 1990; Rockall *et al.*, 1995; Turner *et al.*, 1991), the so-called prognostic factors. Age over 60 years, hypovolaemia, haemoglobin less than 80 g/l, a severe concomitant disease and further bleeding are the main prognostic factors. All these should be considered during the course of treatment to obtain the best possible results. Therefore, the identification and assessment of the clinical relevance of the prognostic factors and, subsequently, their application is an essential aspect of the studies directed to improve the outcome of PUH.

The most important advances in the management of gastrointestinal bleeding were the introduction of blood transfusion, the development of safe surgical treatment, the advent of endoscopic diagnosing and improvements in anaesthesiological support. More recently, endoscopic treatment of bleeding ulcers and of ulcers that have bled has enabled to reduce the frequency of rebleeding and thus to diminish surgical intervention and mortality (Cook *et al.*, 1992; Gralnek *et al.*, 1998; Ohmann *et al.*, 2000).

While the significance of the latter is established, the precise role of surgery, the indications for it and the methods to be used have not yet been clarified in the published literature. Though the overall trend shows a decline in the surgical management of PUH (Williams *et al.*, 1993; Asaki, 2000; Schwesinger *et al.*, 2001), there is still discussion as to whether more aggressive or less aggressive surgical management is called for. Specific problems in choosing the best operative method, depending on the location of the ulcer, are rarely discussed in the literature. Giant ulcers situated in the posterior wall of the duodenum tend to bleed massively and repeatedly and are complicated to be managed operatively.

Overall hospital mortality rate has been reported to vary in a broad range, between 0–14% worldwide (Asaki, 2000; Dertinger *et al.*, 1996). However, it should not exceed 5% nowadays (Zittel *et al.*, 2000). The ways of lowering hospital mortality are widely discussed in the literature currently.

If the patient survives, the further goal is to prevent ulcer relapse and subsequent ulcer complications in long term by applying proper medical therapy or definitive operative treatment. However, researchers have largely neglected the long-term results of PUH.

PU, its complications and gastroduodenal surgery have been studied for more than 70 years at the Clinic of Surgery of Tartu University (Linkberg, 1930; Rulli, 1939; Sarv, 1968; Sibul and Truve, 1968; Petlem and Peetsalu, 1973; Truve *et al.*, 1973; Peetsalu *et al.*, 1990; Vardja *et al.*, 1996; Peetsalu *et al.*, 1998; Sillakivi *et al.*, 2000). The present study, focusing on PUH covers the epidemiology, prognostic factors, short-term and long-term results of the treatment as well as certain aspects of the surgical treatment of PUH patients that have not been studied so far in Estonia.

2. REVIEW OF THE LITERATURE

2.1. Peptic ulcer disease

PU attracts continuously the attention of physicians and researchers worldwide. Some 10% of the population will be affected by PU at some time during their lives (Bernersen *et al.*, 1990). The ratio of DU to GU has been estimated to be between 1:1 to 4:1. The establishment of an ulcer is a multifactorial process, an outcome of imbalance between aggressive (ulcerogenic) and defence mechanisms. Although acid is required for ulcer formation, and suppression of acid aids in healing and prevention of ulcers, acid alone does not generally cause ulcer disease. The two primary risk factors for ulcer disease are *H. pylori* (NIH Consensus Conference, 1994) and NSAID use (Singh and Triadafilopoulos, 1999; Frezza *et al.*, 2001). The natural course of PU is characterised by numerous episodes of spontaneous healing, frequent relapses and occasional complications, e.g. haemorrhage, perforation and obstruction. Haemorrhage is the most common complication of PU. However, less than 1% of PU patients suffer from PUH each year (van Leerdam and Tytgat, 2002)

2.2. Upper gastrointestinal haemorrhage

UGIH is a potentially life-threatening syndrome that may be induced by a number of different disease conditions. The essence of UGIH is release of whole blood into the lumen of the upper gastrointestinal tract.

The incidence of UGIH is estimated at 48 to 150 per 100,000 population per year (Rockall *et al.*, 1995; Cutler and Mendeloff, 1981; Skok, 1998).

Approximately half of UGIH episodes are accounted for by DU and GU (Jensen, 1999; Skok, 1998). Acute gastroduodenal mucosal lesions, esophageal varices, esophagitis and Mallory-Weiss tear are responsible for one-third of the episodes (Sanderson *et al.*, 1990; Wara, 1987; Skok, 1998). Besides, there is a variety of other causes of UGIH including marginal ulcer, Dieulafoy's lesion, benign and malignant tumors, vascular ectasia, angiomas, diverticula, bleeding after surgical or endoscopic procedures, radiation induced gastritis, foreign bodies, haemobilia (Rollhauser and Fleischer, 1997; Skok, 1998; Marek, 2001). These minor causes of bleeding have an incidence of about 10% and no lesions can be detected by endoscopy in up to 10% of the patients (Sanderson *et al.*, 1990).

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2.3. Peptic ulcer haemorrhage

2.3.1. Pathophysiology

Ulcers bleed when the ulcerating process erodes into a blood vessel, either a vein or an artery at the base of the lesion. In most cases the bleeding artery is small ranging from 0.1 to 1.8 mm with a mean of 0.7 mm (Swain *et al.*, 1986). The size of the eroded artery is probably an important determinant of the pattern and outcome of ulcer haemorrhage. A larger artery is evidently related to a poorer outcome. It has been reported that severe bleeding is more common from ulcers located in the posterior wall of the duodenal bulb or high in the lesser curvature of the stomach. These sites are anatomically close to the gastroduodenal and the left gastric arteries (Shafi *et al.*, 1999) which are the largest arteries related to the duodenum and the stomach.

Ulcer bleeding ceases spontaneously in at least 80% of patients without specific intervention (Mondardini *et al.*, 1998). Vasoconstriction and formation of a platelet plug together with a fibrin clot stops bleeding and prevents further haemorrhage (Johnston, 1984; Swain, 1990). Gastric acid and pepsin may disturb the process of a normal coagulation cascade (Patchett *et al.*, 1989; Vreeburg *et al.*, 2001). An arteritis often present in the bleeding vessel can explain why normal mechanisms of clotting do not always prevent rebleeding (Shafi *et al.*, 1999).

2.3.2. Epidemiology

Incidence and patient profile

A continuous decrease in hospital admissions and surgery (Kurata and Corboy, 1988; Penston and Wormsley, 1993; Paimela *et al.*, 1991; Schwesinger *et al.*, 2001) for PU during recent decades has been repeatedly reported from different regions. However, emergency admissions for PU complications lack such a trend (Kurata and Corboy, 1988; Bloom *et al.*, 1990). PUH is estimated to have an incidence of 25–65 per 100,000 population per year (Panos and Walt, 1993; van Leerdam and Tytgat, 2002; Laporte *et al.*, 1991). DU predominates in most series of PUH. In on study the incidence of PUH for men was higher than for women, 59 and 45 per 100,000 per year, respectively. The incidence rate was significantly higher in the elderly, being 6.5 for those <40 years of age and more than 120 for those >60 years of age per 100,000 per year (Ohmann *et al.*, 1992). The admission rates for PUH increase among the elderly (Higham *et al.*, 2002) and the time trends show a continuous increase in the proportion of the elderly (Bloom *et al.*, 1990).

This tendency could be related to the consumption of NSAIDs (McCarthy, 1991). On the other hand, it has been supposed that in the light of new moda-

lities of medical treatment and vanishing elective ulcer surgery, the prophylactic role of the latter has greatly diminished, and subsequently, ulcer complications start appearing at an older age (Paimela *et al.*, 1995).

The absence of signs of PU in a high proportion of patients with PU complications has been reported. In one study bleeding was the first sign of PU in 52% of cases (Holvoet *et al.*, 1991). Asymptomatic ulcers present a major problem, as no preventive measures can be applied against life-threatening ulcer complications. It has been found that in older people ulcer symptoms can be vaguely expressed and NSAID use is often noted in such cases (Katz, 1991).

Death rates of PUH have been estimated to be 1.6–3.9 per 100,000 population (Cutler and Mendeloff, 1981; Paimela *et al.*, 1995).

Predisposing factors

The role of a bacterium, *H. pylori*, in the pathogenesis of PU is widely known. It has been repeatedly demonstrated that eradication of *H. pylori* dramatically alters the natural history of PU by significantly lowering the rate of ulcer recurrence. Recent studies have shown that eradicating this micro-organism in PU patients markedly (18-fold) lowered the rate of PUH (Powell *et al.*, 1994). Besides, eradication of *H. pylori* infection after an episode of PUH results in a significant reduction of both ulcer recurrence and bleeding relapses in long term (Labenz and Börsch, 1994; Graham *et al.*, 1993). This suggests a similarity between the pathogenesis of bleeding ulcer and that of noncomplicated ulcer. However, the prevalence of *H. pylori* in PUH patients, 40–90%, seems to be lower compared with cases of noncomplicated ulcer, 90–100% (Vaira *et al.*, 1997). This fact indicates that factors other than *H. pylori* can result in bleeding PU.

Studies have shown an extremely high prevalence of *H. pylori* infection, 73–87%, among the population of Estonia in three regions; the prevalence is as high as 68–83% even in those born in 1955–1970 (Vorobjova *et al.*, 1994; Maaroos, 1995). Comparable data from the Western countries show significantly lower *H. pylori* infection rates among those born in recent decades, ranging between 10–20% (EUROGAST Study Group, 1993). However, the relationship between *H. pylori* and PUH has not been studied in Estonia yet.

NSAIDs are clearly another important factor. Both aspirin and non-aspirin NSAIDs are among the most commonly used medications. It is well known that NSAID use is related to adverse gastrointestinal side effects. These drugs are associated with a high risk of developing GU, but not related to DU formation. However, these drugs can induce bleeding from both locations. Several studies have shown that PUH is closely related to previous NSAID use (Wilcox *et al.*, 1994; Rodriguez and Jick, 1994; Holvoet *et al.*, 1991; Chamberlain, 1993; Shafi *et al.*, 1999; Mellemkjaer *et al.*, 2002). It has been found that these drugs may be more important in causing haemorrhage from GU compared with DU

(Rodriguez and Jick, 1994; Wilcox *et al.*, 1994). Savage *et al.*, 1993, have reported an increased relative risk of 5.1 for haemorrhage and perforation in association with NSAIDs. NSAID use was the strongest independent risk factor for haemorrhage caused by PU (relative risk, 8.4), while the relative risk associated with *H. pylori* infection was 1.5 (Kuyvenhoven *et al.*, 1999). The risk has been found to be higher in case of both *H. pylori* infection and NSAID use, which shows a synergism between the two in causing PUH (Huang *et al.*, 2002). However, the absolute individual risk of the development of PUH in NSAID users has been estimated as low. The risk of developing a serious ulcer complication is in the range of 1.3–2% for a population of NSAID users per year of use (Graham, 1996). The number of cases induced in the whole population becomes important in view of the widespread use of NSAIDs (Langman *et al.*, 1991). Studies show the use of these drugs in 35% to 89% of cases prior to PUH (Holman *et al.*, 1990; Kuyvenhoven *et al.*, 1999; Lanas *et al.*, 1992). Concern has been expressed about the high prevalence of over-the-counter NSAID use in patients with haemorrhage (Wilcox *et al.*, 1994). There is a difference between different NSAIDs in terms of the risk of provoking ulcer haemorrhage. Azapropazone and piroxicam had relative risks higher than 10, while ibuprofen had the lowest risk, 3, in a study by Rodriguez and Jick, 1994. The authors also found that the risk was the highest for the current users, lower for the recent users and the lowest with the past use of these drugs. The risk is also dose-related (Rodríguez *et al.*, 1994), though low-dose aspirin too is associated with ulcer bleeding (Stack *et al.*, 2002; Loke *et al.*, 2003). Irregular use of NSAIDs, compared with non-use, is related to a significantly higher, 5.5-fold, risk of PUH than the 1.9-fold risk in daily users (Imhof *et al.*, 1997). No risk reduction has been found to be associated with the use of oral enteric-coated, oral slow-release or rectal formulations of the drugs (Mellemkjaer *et al.*, 2002). NSAID consumption is increasing, especially in the elderly (Glise, 1990; Leivonen and Kivilaakso, 1991), while women use these drugs more often than men (McCarthy, 1991; Savage *et al.*, 1993). The elderly are more prone to take them due to cardiovascular disease and disorders of the locomotor system. Daily users of NSAIDs who bleed are suggested to have fewer PU symptoms prior to the onset of bleeding compared with nonusers who bleed (Klein *et al.*, 1993). NSAID users infected with *H. pylori* have an almost redoubled risk of bleeding PU in comparison with uninfected NSAID users (Hawkey, 2000). It has been found that bleeding DU patients with neither *H. pylori* infection nor NSAID use are extremely rare (only 2%), which suggests that the pathogenesis of bleeding DU is similar to that of non-complicated DU disease (Gisbert *et al.*, 2001).

Although it was reported recently that the use of NSAIDs was lower in Estonia than in developed countries (Kiivet *et al.*, 1992), the use of these drugs has not been studied in Estonian PUH patients.

The previous history of PU or PUH is strongly associated with the risk of haemorrhage (Laporte *et al.*, 1991; Weil *et al.*, 2000). The proportion of patients

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bleeding from PU tends to increase with the length of individual ulcer history. Within 10 years of the diagnosis approximately 15% of ulcers have bled, while after 20 years the proportion affected is 20–40% (Dobrilla *et al.*, 1993). If a PU patient has already suffered from ulcer haemorrhage, the risk of a second bleeding is 15% within three years and it might be as high as 50% in ten years (Penston and Wormsley, 1992).

Besides, oral anticoagulants and corticosteroids, heart failure, diabetes, current smoking (Weil *et al.*, 2000), immoderate alcohol consumption (Andersen *et al.*, 2000) and blood group 0 (Kuyvenhoven *et al.*, 1999) have been found to enhance the risk of PUH. The incidence of UGIH is stated to be higher in socioeconomically deprived areas (Dallal and Palmer, 2001).

2.4. Diagnosis

PUH patients usually present with melaena and/or haematemesis. Bleeding may vary in intensity from a minor episode to a severe exsanguinating haemorrhage.

The primary goal of diagnosing is to assess whether bleeding is directly life-threatening and to establish the source of bleeding. Several approaches can be used to determine the cause of bleeding: endoscopy (OGD), barium x-ray studies, selective angiography, and radionuclide scanning. OGD has been the "golden standard" of diagnosing UGIH since the first Consensus Development Conference on Gastrointestinal Endoscopy and Its Role in Upper Gastrointestinal Bleeding held in 1980. It was stated there that OGD is the most sensitive and specific method to identify the causative lesions and their location in most UGIH patients (Pitcher, 1990). The diagnostic yield of OGD is up to 99% in UGIH patients (Dertinger *et al.*, 1996). The complication rate of OGD is low, 2.8%, including hypoxia, hypotension, arrhythmias, bleeding and perforation (Marek, 2001). Today, every patient with UGIH should undergo OGD. According to current consensus opinion, OGD should be performed within the first 24 hours but not necessarily as an emergency procedure. Prospective controlled trials have shown that urgent diagnostic endoscopy does not influence mortality (Panos and Walt, 1993). However, early OGD is of benefit in high-risk patients who should be subjected to endoscopy after stabilizing their condition (Spiegel *et al.*, 2001).

In 1974 Forrest et al. first described the status of ulcer at endoscopy in patients with PUH. They divided the lesions into those actively bleeding, lesions with an evidence of recent bleeding, and lesions without an evidence of bleeding (Forrest, 1974). The Forrest classification of the type of ulcer haemorrhage at endoscopy has been modified to meet the needs and widely accepted due to its prognostic relevance, ability to predict rebleeding (Kohler and Riemann, 1991; van Leerdam *et al.*, 2000).

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2.5. Prognostic factors for mortality

Various factors have been suggested as predictive for the adverse outcome of PUH. Both clinical and endoscopic prognostic factors have been suggested to predict the outcome.

2.5.1. Clinical factors

There are several clinical prognostic factors that have been suggested to be predictive for an adverse outcome of haemorrhage. These can be grouped into factors indicating large initial bleeding and those not associated with the amount of initial bleeding.

Among the factors reflecting large initial bleeding, red haematemesis, anaemia with haemoglobin less than 80–100 g/l and haemodynamic shock carry a high risk of mortality (Clason *et al.*, 1986; Holman *et al.*, 1990; Katschinski *et al.*, 1994; Dallal and Palmer, 2001). Other factors are patient-related and not indicative of a large bleeding. Most authors agree that age over 60 years (Clason *et al.*, 1986; Peterson, 1990) and severe concomitant disease (Turner *et al.*, 1991; Rockall *et al.*, 1995) enhance the risk to patient life.

Further, distinction between ceased bleeding, continued bleeding and re-bleeding is of vital importance in terms of outcome. Continued bleeding and rebleeding are closely associated with patient mortality (Turner *et al.*, 1991; Katschinski *et al.*, 1994) and rebleeding is the most important prognostic factor (Katschinski *et al.*, 1994) increasing mortality 10-fold (Dallal and Palmer, 2001).

Mortality was twofold higher in patients taking NSAIDs according to one study. Other studies have failed to demonstrate a significant difference in outcome between NSAID users and non-users (Peterson, 1990). However, recent NSAID use has been found to predispose bleeding ulcer patients to in-hospital recurrent bleeding (Godil *et al.*, 2000).

The above mentioned clinical factors can be very helpful in grading patients into low- and high-risk groups. The prognostic importance of these factors is even more powerful when combined with endoscopic risk factors.

2.5.2. Endoscopic factors

Endoscopic factors predictive of rebleeding and hence of a poorer outcome include ulcer size ≥2 cm (Hsu *et al.*, 1996) and ulcer location within proximity to large arteries — high gastric minor curvature ulcer (Brullet *et al.*, 1996) and DPWU (Swain *et al.*, 1986).

A major contribution to the prediction of further haemorrhage has been achieved with the definition of the features of the ulcer seen at endoscopy. The appearance of an ulcer at endoscopy, according to the Forrest classification, is closely related to prognosis (Table. 1).

Table 1. Forrest classification, endoscopic features, prevalence, rebleeding rate and mortality (Kolkmann and Meuwissen, 1996; Johnston, 1990; Shafi *et al.*, 1999)*

Forrest type	Endoscopic feature	Prevalence (%)	Rebleeding (%)	Mortality (%)
Ia	Spurting bleeding	18	85–100	11
Ib	Oozing bleeding		40–55	
IIa	Visible vessel	17	18–51	11
IIb	Adherent clot	17	18–24	7
IIc	Pigmented spot	20	10	3
III	Clean ulcer base	42	0–5	2

* In case the patients were not provided endoscopic therapy

Scoring systems have been developed to predict the risk of death combining clinical and endoscopic prognostic factors. These systems might be useful in developing treatment protocols. High-risk patients would benefit from a more intensive therapy and low-risk patients could be discharged early or treated on an outpatient basis (Rockall *et al.*, 1996).

2.6. Treatment

Management of PUH should be carried out in hospital. In selected low-risk cases out-patient treatment has been recommended (Rockall *et al.*, 1996).

The primary goals of therapeutic modalities for treating PUH are resuscitation, control of active bleeding, prevention of rebleeding and, ultimately, prevention of ulcer recurrence and subsequent bleeding in long term.

Bleeding from PU will stop spontaneously in about 80–85% of patients (Mondardini *et al.*, 1998; Zittel *et al.*, 2000).

Current management of patients with PUH requires a multidisciplinary approach with a skilled endoscopist, experienced surgeon, gastroenterologist and nurses. In many cases the support of anaesthesiologists and of an intensive care unit are needed. Twenty-four-hour blood transfusion and laboratory service is essential.

2.6.1. Resuscitation

Crucial to the safe management of patients with PUH is continuous monitoring of the patient's clinical condition and prompt fluid transfusion aimed at normalization of the circulatory status. Although prospective randomized studies are lacking (Duggan, 2001), blood transfusion to maintain haemoglobin between 70 to 90 g/l seems sufficient (Jiranek and Kozarek, 1996). Excess transfusion may reduce the physiological hypercoagulable state of PUH patients, probably as a result of the citrate contained in stored blood (Henriksson and Svensson, 1991). A state of shock may require more aggressive transfusion.

2.6.2. Medical therapy

After initial haemostasis has been achieved, a potent and maintained acid inhibition may generate optimal conditions for clotting and thus prevent rebleeding (Lanas *et al.*, 1995; Vreeburg *et al.*, 2001). However, randomized controlled trials performed with H_2 blockers using various doses, or with Omeprazole have shown a reduction in rebleeding rates and surgery but not in mortality (Kolkmann and Meuwissen, 1996; Selby *et al.*, 2000; Zed *et al.*, 2001). The vasoconstrictors Vasopressin and Somatostatin as well as the antifibrinolytic drug Tranexamic acid have been found to produce no benefit in terms of stopping bleeding or preventing recurrence (Villanueva and Balanzo, 1997; Kubba *et al.*, 2001). Therefore, available pharmacological therapy alone cannot be recommended as a treatment of choice for an acute bleeding episode of PU. However, two randomized trials demonstrate that as compared with a placebo or cimetidine, an intravenous proton pump inhibitor can significantly reduce rebleeding from PU after successful endoscopic haemostasis (Cash, 2002). Besides, it is reasonable to promote the beginning of ulcer healing from the start (Zittel *et al.*, 2000; Kubba *et al.*, 2001).

There is increasing evidence that eradication of *H. pylori* can actually "cure" PU (Rauws and Tytgat, 1990; Laine *et al.*, 1998) and thereby avoid possible subsequent PUH (Macri *et al.*, 1998). Prospective randomised studies show that eradication of *H. pylori* infection after an episode of PUH result in a significant reduction of both ulcer recurrence and bleeding relapse compared to conventional antisecretory treatment (Graham *et al.*, 1993; Jaspersen *et al.*, 1995). This evidence suggests that the only definitive medical therapy for prevention of recurrent PUH in long term is eradication of *H. pylori*.

2.6.3. Endoscopic therapy

In recent years it has become possible besides observing bleeding ulcers visually, to attempt cessation of bleeding or to prevent possible rebleeding by intervention at the time of endoscopy.

Endoscopic hemostatic therapy should be used only in patients who have persistent bleeding or a high risk of recurrent bleeding (Bown, 1991). In the case of a clean ulcer base (Forrest III) endoscopic therapy is not indicated.

Randomized controlled trials in patients with PUH and a nonbleeding visible vessel have found endoscopic therapy superior to traditional medical and surgical treatment in terms of lowering rebleeding rates and reducing the need for blood transfusion and emergency operations (Gralnek et al., 1998). A meta-analysis of clinical trials showed that endoscopic therapy also reduces hospital mortality (Cook et al., 1992). Various methods of endoscopic therapy: injection, thermocoagulation and Nd:YAG laser therapy have shown similar results in randomized controlled trials in terms of initial haemostasis, rebleeding, surgery, transfusion, and mortality (Lee and Leung, 1997). Yet for economic and practical reasons, injection therapy seems to be superior (Qvist et al., 1994; Lee and Leung, 1997). Applying endoscopic pure ethanol injection therapy in a total of 1603 cases, Asaki and colleagues from five other institutions report excellent results. They achieved successful initial haemostasis in 99.2% of PUH patients. The rebleeding rate was 9.3% and most of these cases were retreated using endoscopic therapy. Only 1.9% of the patients needed emergency operation (Asaki, 2000). Systematic second-look endoscopy with retreatment significantly reduces the risk of recurrent bleeding, but it does not substantially reduce the risk of salvage surgery or mortality (Marmo et al., 2003). With respect to the cost, endoscopic therapy is considerably less expensive than emergency surgery for patients with PUH, while patients prefer it to surgery as an initial or subsequent treatment for the emergency control of bleeding (Jensen, 1999).

However, there exist limitations to endoscopic therapy. In some cases the technique is initially ineffective, in others rebleeding occurs even after haemostasis has been achieved. The most common reason for the failure of endoscopic haemostasis is inadequate access to the lesion due to massive bleeding or extensive scarring. Presence of shock on admission as well as arterial bleeding at endoscopy (Ishikawa et al., 1994), DPWU (Thomopoulos et al., 2001), large ulcer (Church and Palmer, 2003), visible vessel larger than 2 mm in diameter and concomitant disease (Nishiaki et al., 2000) make an unsuccessful outcome more likely. Hypotension and ulcer size larger than 2 cm have been found to be predictive of the failure of endoscopic retreatment (Lau et al., 1999). In such patients surgery could be a better option than endoscopic retreatment (van Lanschot et al., 2002).

The ineffectiveness of three attempts of endoscopic therapy should be considered an indication for surgery (Ishikawa et al., 1994).

2.6.4. Surgical treatment

Despite the availability of more specific and effective medical treatment, some patients with PUH require surgical treatment (Donahue, 2000). The annual incidence of operations performed due to PUH has been reported to be between 2.8 to 10 per 100,000 population (Mäkelä *et al.*, 1992; Gustavsson *et al.*, 1988). While elective ulcer surgery has decreased dramatically all over the world (Paimela *et al.*, 1987; Fallahzedah, 1993; Schwesinger *et al.*, 2001), there is yet no uniform understanding of the role of surgery in treating PUH in the published literature. It is still discussed whether more aggressive or less aggressive surgical management is called for (Imhof *et al.*, 2003). Centres with both aggressive surgical policy and conservative approach have reported excellent results. Bender et al., not relying on endoscopic therapy, operated on 66 of 159 patients (42%) according to a strict protocol with no mortality but 17% complication rate (Bender *et al.*, 1994).

Indications

Most authors find endoscopic therapy as the method of choice for controlling active bleeding as well as for reducing the risk of rebleeding and hence the need for operative management (Sacks *et al.*, 1990; Cook *et al.*, 1992). Time trends of operations for PUH are on decline (Williams *et al.*, 1993; Asaki, 2000; Schwesinger *et al.*, 2001). Therefore, it is justified to state that it will be increasingly difficult to train surgeons to perform emergency surgery for bleeding ulcers and to maintain these skills, because fewer and fewer such operations are being performed (Jensen, 1999).

Surgery is needed in about 5–10% of PUH cases nowadays (Qvist *et al.*, 1994; Zittel *et al.*, 2000). Emergency surgery is indicated in cases of (1) severe haemorrhage unresponsive to initial resuscitative measures; (2) failure of endoscopic and medical therapy to control persistent or recurrent bleeding and (3) a coexisting second indication for operation, such as perforation, obstruction or suspected malignancy (Stabile and Stamos, 2000). In the past decades, some centres advocated early elective surgery in patients with a high risk of rebleeding (Mueller *et al.*, 1994). This approach reduced mortality to below 10%, while it was previously 25% in these patients (Zittel *et al.*, 2000). However, the need for early elective surgery is disappearing due to the fact that repeated endoscopic treatment in the case of rebleeding has been found to be highly effective reducing the need for surgical treatment without increasing the risk of death (Asaki, 2000; Lau *et al.*, 1999).

Methods

The type of emergency surgery to be undertaken is controversial. The type and severity of the pathology, the condition of the patient, the subjective bias and surgical experience of the operator influence the choice of operation. In recent years more and more surgeons prefer nondefinitive methods like oversewing or ulcer excision alone (Ohmann, 2000), referring to them as easier and safer (Zittel *et al.*, 2000) and relying upon subsequent medical therapy (Röher *et al.*, 1996; Gilliam et al., 2003). Others advocate definitive approach, vagotomy and pyloroplasty or partial gastrectomy, whenever the patient`s condition and surgical expertise enable to perform them (Herrington and Davidson, 1987; Stabile and Stamos, 2000). A randomized study compared nondefinitive surgery and definitive surgery showing no significant difference in mortality. However, 10% of nondefinitively operated patients died of fatal rebleeding, while none of the definitively operated patients did (Poxon *et al.*, 1991). Nondefinitive operations resulted in a significantly higher rebleeding rate, 23% versus 3% for definitive operations, and mortality, 23% versus 14% (no significant difference), respectively (Kubba *et al.*, 1996). Rebleeding rates can be lowered if oversewing of the ulcer is combined with the ligation of the gastroduodenal and right gastro-epiploic arteries (Millat *et al.*, 1993). Postgastrectomy and postvagotomy syndromes have been pointed out as a drawback of definitive operations (Zitell *et al.*, 2000; Johnson and Chir, 2000).

Common operations for DU haemorrhage include:
1. Truncal vagotomy / proximal gastric vagotomy and pyloroplasty with excision of the ulcer / oversewing of the ulcer;
2. Truncal vagotomy and antrectomy with excision of the ulcer;
3. Proximal gastric vagotomy with excision of the ulcer / oversewing of the ulcer.

Common operations for bleeding GU include:
1. Oversewing / excision of the ulcer
2. Wedge resection of the stomach
3. Distal gastrectomy
4. Truncal vagotomy with pyloroplasty and excision / oversewing of the GU
5. Truncal vagotomy and antrectomy with excision of the prepyloric ulcer
(Stabile and Stamos, 2000; Donahue, 2000)

Laparoscopic suturing of actively bleeding DU via duodenotomy has been successively performed in a series of six patients (Martin *et al.*, 1998).

2.6.5. Giant duodenal posterior wall ulcers

Bleeding DPWU represent a specific problem and are dealt with separately in many studies. Being close to the anatomical position of the largest artery, which is related to the duodenum, gastroduodenal artery, they are often the source of

severe bleeding (Swain 1990). Deep and large DU with a diameter of >2 cm, known as giant ulcer (Collen *et al.*, 1994; Simeone *et al.*, 1999), is more likely to erode into the large artery. Both giant ulcer (Hunt and McIntyre, 1990; Hsu *et al.*, 1996) and DPWU (Swain *et al.*, 1986) are factors predictive of rebleeding and hence of a poorer outcome. It has been found that a posterior location of DU is a poor prognostic factor not only because these ulcers have a strong tendency to bleed but also because these ulcers are associated with aged and high-risk patients (Millat *et al.*, 2000).

One of the factors adversely affecting the results of endoscopic therapy is a posterior location of DU. DPWU makes an unsuccessful outcome more likely due to rebleeding (Kolkmann and Meuwissen, 1996) and a higher need for emergency surgery compared with anteriorly located ulcer (Thomopoulos *et al.*, 2001). Mortality rate has been found to be higher for DPWU, 4%, than for anterior wall ulcers, 0.9% (Branicki *et al.*, 1990). Therefore, patients with bleeding DPWU are regarded as high-risk patients. Early elective operation after primary endoscopic treatment and stabilizing of the patients is advocated in this situation (Mönig *et al.*, 2002).

The choice of the operation method is complicated in the case of bleeding DPWU often penetrating into the pancreas and scarring the duodenum circumferentially to lead to stenosis (Chang *et al.*, 1998). In these cases oversewing of the ulcer base combined with vagotomy (Gostout *et al.*, 1992), or gastric resection according to Billroth II (Hunt and McIntyre, 1990; Wu *et al.*, 2002) is often performed. However, oversewing of the bleeding duodenal poterior wall ulcer may result in excess mortality due to the high rate of recurrent bleeding (17–23%) in these ulcers (Hunt and McIntyre, 1990; Kubba *et al.*, 1996). Weinberg`s procedure, which combines vagotomy and the oversewing of the vessel with the ligation of the gastroduodenal and gastroepiploic arteries, has revealed an effect superior to that of vagotomy and oversewing alone in terms of rebleeding (Millat *et al.*, 1993). Billroth II gastric resections, on the other hand, may cause duodenal stump leak as major morbidity with a rate of up to 22% (Millat *et al.*, 1993). Trying to avoid this, complex methods with management of the duodenal stump in the case of DPWU have been introduced, including omentoplasty and duodenostomy (Wu *et al.*, 2002). Complicated handling of bleeding penetrating DPWU has led some surgeons to perform extreme, even anecdotal, operations: oversewing of the bleeding ulcer base together with Billroth II resection with Nissen duodenojejunostomy, Tomoda valve construction and Braun enteroenterostomy (Meissner, 1994). Technically relatively simple ulcer exteriorising operations — DPV, described by Helwing (Figure 1, publ. VI), and AEV, described by Herfarth (Figure 2, publ. VI) — enable to have a good control of bleeding and simultaneously to solve the problem of stenosis (Helwing and Heymann, 1978; Herfarth *et al.*, 1977). The possible hazards of rebleeding, typical of oversewing, as well as duodenal leakage and pancreatitis, often present in Billroth II resection, are avoided with the use of these methods. A similar approach of leaving the ulcer base out of the

lumen, i.e. exteriorizing the ulcer in the case of giant DPWU, has been recommended also elsewhere (Herrington and Davidson, 1987).

2.7. Short-term outcome

In the late 80-ies and early 90-ies, it was often stated that mortality rates of 10% for UGIH and PUH had remained on the same level for decades despite the advances in diagnosing, resuscitation, surgery and medical therapy (Gilbert, 1990; Holman et al., 1990; Henriksson and Svensson, 1991). This phenomenon was related to the growing proportion of the elderly among haemorrhage patients (Gilbert, 1990). Yet already then had some units achieved mortality rates as low as 3–4% (Gostout et al., 1992; Sanderson et al., 1990).

While the mortality of PUH should not exceed 5% nowadays (Zittel et al., 2000), overall mortality in some centres could be as high as 14% with a mortality of 56% for operatively treated and 10% for conservatively treated patients (Dertinger et al., 1996).

2.8. Long-term results

When a patient is discharged from hospital it is essential that the next goal is to prevent further ulcer relapse and subsequent recurrence of ulcer bleeding in long term, thus increasing survival. While short-term results of PUH have been extensively dealt with in the literature, the long-term outcome of the patients, in contrast, has been insufficiently studied. To prevent recurrent bleeding in long term, various models of treatment have been discussed: maintenance therapy with acid blockers, H. pylori eradication, and definitive ulcer surgery.

In a follow-up study 530 PUH patients were treated conservatively with H2-blockers until ulcer healing, while they did not receive either maintenance therapy or H. pylori eradication thereafter. Over a median follow-up of 36 months as many as 169 (32%) of them developed another ulcer complication: bleeding (166 cases) and perforation (3 cases). DU with a previous history of bleeding was the main risk factor for late recurrent haemorrhage (Ng et al., 1996). The authors conclude that in such patients, if H. pylori is negative, maintenance H2-blocker therapy or definitive acid-reducing surgery should be seriously considered to reduce complications in long term. In H. pylori positive patients eradication is indicated.

Maintenance therapy with H2-blockers significantly reduced recurrent haemorrhage from DU during 1-year follow-up (Jensen et al., 1994).

Labenz and Börsch compared the natural course of PU and the course after H. pylori eradication. They found that the 1-year ulcer relapse rate decreased from 65% to 2%, and the 2-year relapse rate decreased from 87% to 5% after

H. pylori treatment. Moreover, the 2-year rate of ulcer complications decreased from 34% to 0.4% after eradication (Labenz and Börsch, 1996). Thus *H. pylori* eradication can actually cure PU and prevent ulcer bleeding and rebleeding.

Mueller et al. analysed the results of 48 months follow-up in definitively operated and in conservatively treated (H2-blockers on demand at home) patients. The cumulative 5-year PU rebleeding rate was 6% for surgically treated versus 13% for conservatively treated patients. The difference was not statistically significant (Mueller *et al.*, 1994).

The long-term prognosis for patients who present with PUH is poor, however, most deaths are a consequence of a comorbid disease but not of recurrent ulcer bleeding. Hudson et al. compared previous PUH patients, aged over 60 years, to matched controls in terms of mortality and causes of death during a mean follow-up of 34 months. The 29% mortality rate for the patients was significantly higher than the 12% rate for the controls. The increased mortality was predominantly due to a variety of smoking related diseases rather than recurrent PU complications. Only 1.2% of previous PUH patients died of ulcer bleeding. Unfortunately, the rate of rebleeding was not studied in this series. It is worth mentioning that in as many as 1% of the PUH patients gastric cancer, which was not diagnosed during initial admission, was found during follow-up (Hudson *et al.*, 1995).

In another study of 121 PUH patients, 25% died mainly of cardiovascular and pulmonary disease during a median follow-up of 36 months. While 9% of the patients suffered another PUH episode during the period under study, no deaths could be attributed to PU complications (Kubba *et al.*, 1997).

Rorbaek-Madsen *et al.* found that the cumulative survival rate of GU bleeding patients in an 8-year study was significantly reduced in comparison with the expected survival rate of a matched background population. Excess mortality was not related to ulcer disease, but was mainly due to cardiovascular disorders and non-gastric malignancy (Rorbaek-Madsen *et al.*, 1994).

A comparative study of long-term survival of a general population cohort and PUH patients showed that PUH patients carry a twofold higher risk of death. Nine percent of the deaths in PUH patients and 3% of the deaths in general population were caused by UGIH in long term (Ruigomez *et al.*, 2000).

3. AIMS OF THE STUDY

The aims of the present study were:

1. To characterize the epidemiological pattern of PU related UGIH in Tartu county covering incidence, patient population structure, predisposing factors, H. pylori infection rate, location of the ulcer and mortality (publs. I–IV).

2. To determine the prognostic factors for short-term adverse outcome of PUH (publ. IV).

3. To assess changes in the treatment tactics of PUH in recent years. To evaluate the role of endoscopic therapy and surgical treatment in PUH patients and their impact on short-term outcome (publ. VII).

4. To assess long-term results in conservatively treated and operatively managed PUH patients (publ. V).

5. To establish in terms of long-term outcome the operative methods of Helwing and Herfarth, proposed for bleeding giant posterior wall ulcers of the duodenum (publ. VI).

4. PATIENTS AND METHODS

The thesis is based on seven separately designed studies covering different aspects of PUH. These were carried out from 1992 to 2001 at the Clinic of Surgery of Tartu University Clinics. The main characteristics of the studies are presented in Table 2.

Table 2. The characteristics of the seven studies constituting the thesis.

Study type	Study site	Study period	No of patients (male/female)	Goals of the study	Publication (publication No)
1. Retrospective	TUC*	1979–1981 1989–1991	206 (148/58) 401 (274/127)	Epidemiology of UGIH and PUH	Acta et Commentationes Universitatis Tartuensis (I)
2. Retrospective	TUC	1979–1993	635	Incidence changes of PUH	Eesti Arst (II)
3. Prospective	TUC	1992–1994	263 (159/104)	Epidemiology of UGIH and PUH	Ann Chir Gynaecol (III)
4. Prospective	TUC	1992–1993	144 (94/50)	1. Epidemiology of PUH 2. Prognostic factors for PUH	Scand J Gastroenterol (IV)
5. Prospective	TUC	1992–1997	163 (112/51)	Long-term results of operated and conservatively treated PUH patients	European Journal of Trauma and Emergency Surgery (V)
6. Prospective	TUC	1984–2001	16 (13/3)	Long-term results of ulcer exteriorising operations	Am J Surg (VI)
7. Prospective/ retrospective	TUC	1992–1993 1999–2000	212 (148/64) 177 (135/42)	Role of EIT and surgery in PUH	Eesti Arst (VII)

* Tartu University Clinics

4.1. Patients

Altogether data of 1270 patients were collected and studied. The study groups are partly overlapping because a patient could enter different studies at a time (Table 2.).

In a retrospective pilot study (publ. I) the data of endoscopic findings for all UGIH patients treated at the Clinic of Surgery of Tartu University Clinics during 1979–81 and 1989–91 were included. A total of 206 patients passed endoscopy during 1979–81 and 401 during 1989–91. The sources of haemorrhage and the patients` characteristics for the two periods were compared.

In a retrospective study (publ. II) with a defined area (Tartu county) data from all case histories of patients with PU complications, either haemorrhage or perforation, were included in an epidemiological analysis for a 15-year period (1979–93). The evaluation of incidence was based on the population data obtained from the Statistics Bureau of Tartu County.

The third study (publ. III) was a prospective defined-area unselected epidemiological study comparing UGIH epidemiology in a province of Central Finland and in Tartu county. The data of 298 consecutive patients from Central Finland and 263 from Tartu county were collected during a two-year period (1.8.1992–31.7.1994).

The data of 144 PUH patients, ≥15 years of age, were assessed in a prospective unselected defined-area (Tartu county) study (publ. IV) over two years (1.1.1992–31.12.1993) in order to assess the epidemiology and the mortality risk factors of PUH.

The fifth study (publ. V) was designed as a prospective non-randomised study of the long-term results of PUH. Included were all 163 patients who had suffered from PUH during 2.5 years (1.1.1992–30.6.1994) and had survived hospital treatment. Of the patients 61 had been operated (all definitive operations) and 102 had been treated conservatively, with a 4–6 week H_2-blocker therapy course, and received intermittent H_2-blocker treatment on demand thereafter. In a mean time of 17 months (12–31 months) 47 operatively treated and 86 conservatively treated patients passed a follow-up examination with endoscopy, the results of which were graded according to a modified Visick scale.

During 1984–93, sixteen patients with giant, penetrating posterior wall duodenal ulcers with haemorrhage were operated according to the methods, described by Herfarth and Helwing, at the Clinic of Surgery of Tartu University Clinics (publ. VI). Of the patients 4 died due to the reasons not related to PUH and two were lost for follow-up. Ten patients passed long-term follow-up examination with endoscopy during the years 2000–2001. The results of the assessment of quality of life were graded according to a modified Visick scale.

In the seventh study (publ. VII) the prospective data of 212 PUH patients, treated at the Clinic of Surgery of Tartu University Clinics in 1992–1993, and

the retrospective data of 177 PUH patients treated in 1999–2000, were gathered. The periods were compared in terms of patient structure characteristics, treatment tactics and treatment results.

4.2. Methods

4.2.1. Data

The data for the first study (publ. I) were obtained from endoscopy record cards. The primary data for the analysis of the case histories for the second study (publ. II) were obtained from the computerised database of Tartu University Clinics.

For the third (publ. III) and fourth (publ. IV) studies, the data were gathered prospectively. Clinical data, the results of laboratory analyses, as well as the findings of endoscopy, operation and autopsy were obtained from case histories.

For the fifth (publ. V) study the data were collected prospectively.

For the sixth study (publ. VI) the primary data of the operated patients were obtained from the computerised database of Tartu University Clinics. Then case histories were studied for the identification of patients operated according to the methods of Herfarth and Helwing.

Data on mortality and causes of death for the follow-up periods in the fifth and sixth studies (publs. V, VI) were obtained from the Registry Office of the Tartu County Government.

For the seventh study (publ. VII) the data for the comparison of the two periods, 1992–1993 and 1999–2000, were obtained from case histories.

4.2.2. Patient questionnaire

All patients participating in the prospective studies were questioned according to a standard questionnaire (publs. III, IV), which consisted of items about previous PUH and/or UGIH, history and symptoms of PU, other major diseases, smoking habits, alcohol consumption and NSAID use.

4.2.3. Area of study

The epidemiological studies reflect the situation in a defined area, the town of Tartu and Tartu county, further referred to as Tartu county.

4.2.4. Incidence

Incidence rates were calculated as new cases per 100,000 population per year (publs. II, III, IV).

4.2.5. Endoscopic diagnosing and follow-up examination

In all patients the source of bleeding had been diagnosed by means of OGD (except for one case of X-ray diagnosis in study III). In the fourth study (publ. IV) two biopsy specimens were obtained during OGD both from the gastric antrum and corpus for evaluation of *H. pylori* infection. In the long-term follow-up studies (publs. V, VI) examination of the patients, including endoscopic examination, was performed in outpatient conditions. The presence or absence of ulcer recurrence was determined.

4.2.6. Definitions: ulcer location, operations and mortality

The ulcers were classified in accordance with location into DU, pyloric ulcer, prepyloric ulcer and GU in the fourth study (publ. IV). In the other epidemiological studies the ulcers were classified into GU and DU, while DU comprised duodenal bulb ulcers, pyloric and prepyloric ulcers.

Nondefinitive operations include ulcer suturation or excision. Definitive operations include partial gastrectomies and/or operations with vagotomy.

Mortality was estimated as death rate in patients during hospital treatment.

4.2.7. Endoscopic therapy

In the seventh study (publ. VII) the role of the endoscopic treatment of PUH was assessed. EIT was the method of choice in endoscopic treatment. Injection therapy with absolute alcohol, epinephrine (1:10,000) or their combination was used.

4.2.8. *H. pylori* infection

In the fourth study (publ. IV) *H. pylori* infection rate was estimated. In 120 PUH cases two gastric mucosal biopsy samples were taken from the antrum and two from the corpus, stained according to Giemsa and investigated microscopically for the presence of *H. pylori* infection.

4.2.9. Visick scale

The quality of life in the long-term follow-up studies (publs. V, VI) was graded according to a modified Visick scale (Vardja T, 1996). The Visick scale estimates were the following: Visick I — excellent: no symptoms; Visick II — good: mild, no disturbing symptoms interfering with normal life or work; Visick III — satisfactory: mild or moderate symptoms causing a certain degree of discomfort or disability; Visick IV — poor: severe symptoms or recurrent ulcer on endoscopy.

4.2.10. Operation methods

The fifth study (publ. V) discusses the long-term results in patients operated for PUH. In all cases definitive operations with ulcer removal, either partial gastrectomies or operations with vagotomy, were performed.

Two ulcer exteriorising operation methods for giant DPWU penetrating into the pancreas, complicated with haemorrhage, are described and assessed for long-term outcome in the sixth study (publ. VI).

Duodenal resection with plasty after Helwing

DPV is presented in Figure 1, publ. VI. Kocher maneuver is performed to mobilize the duodenum. The front wall of the duodenum is opened by two semicircular incisions. In case of bleeding the ulcer base is oversewn. The duodenum is resected so that the penetrating base of the ulcer remains in the pancreas. The posterior wall is sutured in a one-row manner, shifting the gastric end over the ulcer base. The sutures pass through all layers of the posterior wall of the gastric end to the distal edge of the giant ulcer and the posterior wall of the duodenal end. Thus the ulcer base is left out of the duodenal lumen, i.e. is exteriorised. The front wall is sutured in an ordinary two-row manner. Further, vagotomy is performed.

Antrectomy with reconstruction after Herfarth

AEV is presented in Figure 2, publ. VI. Kocher maneuver is performed to mobilize the duodenum. After dissecting the lower part of the stomach, antrectomy is performed. Current bleeding is stopped by oversewing the vessel. The stump of the stomach is closed leaving an opening for the anastomosis on the side of the larger curvature. Then the back wall is sutured in one row, all layers of the stomach to the distal edge of the ulcer together with the duodenal wall. This exteriorises (leaves out of the lumen) the ulcer base. The gastric stump and the front wall of the anastomosis is sutured in an ordinary two-layer manner. Truncal vagotomy is performed additionally.

4.2.11. Statistical methods

The data were analysed by StatView® Student for the Macintosh. The medians with 95% confidence intervals (CI) were calculated for age. The absolute numbers were compared with chi-square test. Continuity correction was applied to approximate the chi-square test where necessary. The level of significance was set at 0.05 throughout the study.

5. RESULTS

The results are divided into five main sections. Epidemiology of UGIH and PUH in Tartu county is discussed in the first section (publs. I–IV). The second section deals with the prognostic factors of PUH (publ. IV). In the third part the role of endoscopic therapy and surgical treatment in PUH patients is assessed (publ. VII). Long-term results in conservatively and surgically treated PUH patients are evaluated in the fourth part (publ. V). The fifth section presents two surgical methods, DPV after Helwing and AEV after Herfarth, for management of bleeding giant DPWU penetrating into the pancreas. The long-term results in the patients operated with the use of these mehods are reported (publ. VI).
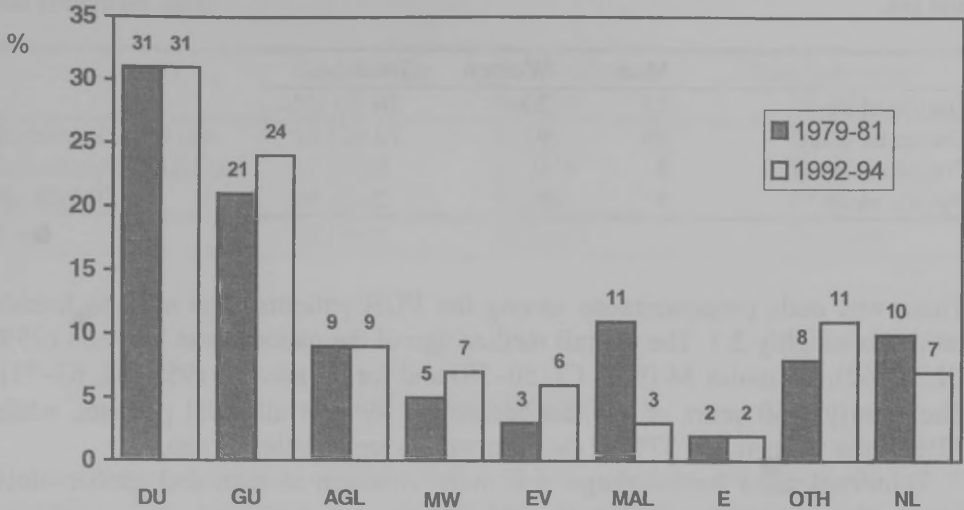
5.1. Epidemiology

5.1.1. Upper gastrointestinal haemorrhage

The overall incidence of UGIH was 98.6 per 100,000 adults (≥15 years of age) per year in 1992–1994 in Tartu county. The incidence by age groups is shown in Table 2, publ. III. The total male to female ratio was between 2.5:1 (1979–1981) to 1.5:1 (1992–1994) during the periods studied. The mean age of the patients was 58.8 years. The proportion of the patients ≥60 years of age was 49% (129/263), while it was 35% for men (56/159) and 70% for women (73/104).

Of the patients 47% (108/231) had taken NSAIDs prior to bleeding. The elderly had taken these drugs significantly more often than the young and the women more often than the men (Table 3, publ. III).

The cause related distribution of UGIH in 1979–81 and in 1992–94 is depicted in Figure 1. PU was responsible for more than half of all UGIH cases. In 1979–81 its share was 52% and in 1992–94 it was 55%. Acute gastric mucosal lesions, Mallory-Weiss tear, oesophageal varices, malignancies and oesophagitis accounted approximately for 30% of UGIH cases. The share of malignancies decreased from 11% to 3%. No other significant change took place during the 15 study years. The diagnostic yield of endoscopy for UGIH was more than 90% in all studies.

The mortality rate of UGIH was 10% (26/263).

Abbreviation	Meaning	Abbreviation	Meaning
DU — duodenal ulcer		MAL — malignancies	
GU — gastric ulcer		E — oesophagitis	
AGL — acute gastric mucosal lesions		OTH — other	
MW — Mallory-Weiss tear		NL — no lesion revealed	
EV — oesophageal varices			

Figure 1. Causes of upper gastrointestinal haemorrhage.

5.1.2. Peptic ulcer haemorrhage

The time trends of the overall incidence of PUH are depicted in Figure, publ. II. The incidence was between 18 and 28 (mean 23) per 100,000 population per year for the years 1979–1990. For 1991–93 there occurred a sharp increase in PUH incidence which was between 33 to 48 (mean 40).

During 1992–94 there were no cases of PUH in male patients aged <20 and in female patients aged <30 years. The older age groups had a considerably higher relative risk of developing PUH than the younger ones. The incidence rate was 12 for those aged 20–29 and more than 10-fold higher, over 135, for those ≥70 years of age. For men the relative risk was more than two times higher than for women (Table I, publ. IV).

As to the sources of PUH, gastric ulcer had the highest overall incidence, 26, followed by duodenal ulcer, 22 per 100,000 per year. Duodenal ulcer had a higher incidence for men followed by gastric ulcer, while it was vice versa for women. The incidence of PUH according to the location of ulcer is shown in Table 3.

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Table 3. Incidence per 100,000 per year of peptic ulcer haemorrhage by ulcer location and sex.

	Men	Women	Total
Gastric ulcer	33	20	26
Duodenal ulcer	39	9	22
Prepyloric ulcer	5	6	6
Pyloric ulcer	4	0	2

There was male preponderance among the PUH patients. The male to female ratio was roughly 2:1. The overall median age of the patients was 59 years (95% CI, 56–62), for males 54 (95% CI, 50–58) and for females 67 (95% CI, 63–71). The elderly, ≥60 years of age, accounted for 49% of all PUH patients, while 72% of the women and 37% of the men were over 60 years of age.

Duodenal ulcer haemorrhage was more common in men and gastric ulcer haemorrhage in women (Table III, publ. IV).

In as many as 27% of the PUH patients, ulcer was asymptomatic prior to haemorrhage. There was no difference between the sexes, age groups or the causes of bleeding in terms of the rate of asymptomatic ulcers.

Active bleeding (Forrest I) was present in 10% of the PUH patients at endoscopy. In 55% stigmata of recent bleeding (Forrest II) and in 35% an ulcer without stigmata of bleeding (Forrest III) were found.

Of the PUH patients 8% died in the prospective defined-area study during 1992–1993. The overall mortality rate in Tartu county was 3.7 per 100,000 inhabitants. Patients aged ≥65 years accounted for 75% of the deaths.

5.1.3. Predisposing factors

Of the patients 18% (25/140) had suffered from previous PUH and 45% (63/140) had an established PU diagnosis prior to haemorrhage.

H. pylori infection was common in PUH patients, 89% (107/120) of the PUH patients were infected. It was present in 100% (14/14) of the prepyloric ulcer patients, in 93% (43/46) of the DU patients and in 81% (43/53) of the GU patients. The differences were not significant.

Nearly half of the PUH patients, 45% (62/137), had used NSAIDs at least 48 hours before the onset of bleeding. Half of them had been on regular NSAID treatment for more than one week, the others had used these drugs episodically. NSAID use by patients with different ulcer locations is presented in Table 4. NSAID use together with alcohol consumption and smoking habits by sex and age is shown in Table II, publ. IV.

Table 4. NSAID use by patients with haemorrhage from gastric ulcer, duodenal ulcer and prepyloric ulcer

	Gastric ulcer No (%)	Duodenal ulcer No (%)	Prepyloric ulcer No (%)
Regular NSAID use	16 (26)	7 (14)	6 (43)
Episodical NSAID use	17 (27)	11 (21)	2 (14)
No NSAID use	29 (47)	34 (65)	6 (43)
Total	62 (100)	52 (100)	14 (100)

5.2. Prognostic factors

Sixteen factors related to PUH patients were analysed for enhancing the risk of mortality. The prognosis was the poorest in patients suffering from major cardiac disease as a concomitant disease, in patients with rebleeding during treatment and in patients admitted with systolic blood pressure less than 100 mmHg. Mortality was 30% or higher for these patients. Age ≥ 65 years and haemoglobin level lower than 80 g/l on admission were both significantly related to the adverse prognosis. The other factors did not have a significant impact on mortality, however, the haematemesis versus no haematemesis and ongoing bleeding during OGD (Forrest I) were close to significant (Table IV, publ. IV).

5.3. Treatment and short-term outcome

The data of all PUH patients treated during 1992–1993 (period I) and 1999–2000 (period II) were evaluated in terms of changes in patient profile, treatment tactics and the results of short-term outcome. No significant change had taken place in the patient population. Neither sex or age distribution, ulcer location nor the type of haemorrhage (Forrest) had changed during the seven-year period (Table 5).

However, EIT was markedly more often used in period II. EIT was used in 32% (45/139) of all Forrest I and II patients in period I and in 70% (89/127) in period II. Patients with ongoing bleeding at endoscopy received EIT in 54% of the cases and patients with stigmata of recent bleeding in 28% of the cases in period I, while the respective rates were 83% and 66% in period II.

Surgical treatment decreased from 40% (85/212) to 6% (11/177) during the seven-year period (p=0.0001). Mortality rate was 7% (14/2121) in period I and 2% (4/177) in period II (p=0.042).

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Table 5. Characteristics of peptic ulcer haemorrhage patients during 1992–1993 (period I) and 1999–2000 (period II).

	Period I No of patients (%)	Period II No of patients (%)	p
Number of patients	212	177	NS**
Men	148 (70)	135 (76)	NS
Women	64 (30)	42 (24)	
Mean age	56	57	
Men	53	54	
Women	66	68	
Patients aged ≥65	71 (34)	72 (41)	NS
Men	34 (23)	46 (34)	0.038
Women	37 (58)	26 (62)	NS
Ulcer location			
DU	113 (53)	103 (58)	NS
GU	97 (46)	68 (38)	NS
MU*	2 (1)	6 (3)	NS
Ulcer location in men			
DU	89 (60)	86 (64)	NS
GU	57 (39)	44 (33)	NS
MU	2 (1)	5 (4)	NS
Ulcer location in women			
DU	24 (38)	17 (41)	NS
GU	40 (63)	24 (57)	NS
MU	0	1 (2)	NS
Type of haemorrhage			
Forrest I	24 (12)	30 (17)	NS
Forrest II	115 (56)	97 (55)	NS
Forrest III	67 (33)	50 (28)	NS
No information	6 (–)	0	

* MU — marginal ulcer

** NS — difference statistically not significant

5.4. Long-term results in conservatively and operatively treated peptic ulcer haemorrhage patients

Eleven percent of both the conservatively treated patients (11/102) and operatively treated patients (7/61) died during two years after hospital treatment for PUH. No death was related to PU complications. The causes of death are listed in Table 6.

Table 6. Causes of death after hospital treatment for PUH during two-year follow-up.

Cause of death	Nr
Cardiovascular disease	9
Malignancy	5
Cerebrovascular disease	2
Liver failure	1
Accident	1

The treatment had provided excellent (no complaints) and good (minor complaints) results in 79% (37/47) of the operatively treated and in 40% (34/86) of the conservatively treated PUH patients. Poor results (recurrent ulcer and/or severe complaints) had been obtained in 13% (6/47) of the operated and in 49% (42/86) of the conservatively treated patients, while 6% (3/47) and 16% (14/86), respectively, had suffered another PUH episode during the follow-up period (Table 7).

Table 7. Long-term results in operatively and conservatively treated PUH patients.

Long term results	Operative treatment		Conservative treatment		Chi square
	N	%	N	%	p
Visick I	22	47	17	20	0.0021
Visick II	15	32	17	20	0.1756
Visick III	4	9	10	12	0.7915
Visick IV	6	13	42	49	0.0001
— Bleeding recurrence	3	6	14	16	0.1731
— No bleeding recurrence	3	6	28	33	0.0014

5.5. Long-term results in patients treated surgically for giant duodenal posterior wall ulcers complicated with haemorrhage

Sixteen patients were operated due to bleeding giant DPWU using DPV after Helwing (Figure 1, publ. VI) and AEV after Herfarth (Figure 2, publ. VI), during 1984–93. Of the patients 10 had presented with stenosis of the pyloroduodenal region.

Follow-up was performed in 2000 and 2001. Two patients were lost for follow-up and 4 had died during the years that had passed from the operation. Analysis of the death certificates of the latter revealed that they died due to reasons not related to their operation or PU.

Of the ten patients assessed for long-term results 7–16 years (mean 11 years) after operation, nine completed a questionnaire of subjective health quality according to Visick and passed endoscopy. One patient agreed with a telephone interview only. The results of the investigation show that long-term results were excellent or good in 90% (9/10) of the cases according to the Visick scale. In one patient the long-term result was assessed as satisfactory. Endoscopy revealed no cases of ulcer recurrence. The anastomoses after DPV and AEV were sufficiently wide in all cases.

6. DISCUSSION

6.1. Epidemiology

6.1.1. Upper gastrointestinal haemorrhage

The overall incidence of UGIH was 98.6 per 100,000 adults per year during the period of 1992–1994 in Tartu county. The incidence rate seems to be medium, considering the range of incidence rates from 48 to 150 as reported from elsewhere (Rockall *et al.*, 1995; Skok, 1998; Cutler and Mendeloff, 1981). The incidence showed a substantial increase with age. The incidence of UGIH for men in comparison with women was more than twofold in all age groups except in those ≥ 70 years of age. A similar pattern has been reported in a study from the United Kingdom (Rockall *et al.*, 1995). The preponderance of male over female UGIH patients is a world-wide phenomenon.

Several studies report ageing trends in UGIH patients during recent decades (Gilbert, 1990). Indeed, the proportion of the elderly was high in Tartu county. Half of the patients were ≥60 years of age there. However, there was a pronounced discrepancy between the sexes, 35% of the men and 70% of the women were aged ≥60. The overall proportion of the elderly has been reported to be close to that, 47% (Skok, 1998), in some regions and even higher, 63% in others (Figure 2, publ. III). According to demographic data, persons ≥60 years of age account for 18% in Tartu county.

The incidence rates of UGIH were notably lower for younger women than for men but showed a more pronounced increase with age and almost equalized in the older age groups. This indicates that there exist also factors other than *H. pylori* contributing to age and sex related discrepancies. One of these is the circumstance that certain causes of haemorrhage are observed mostly in younger men (Mallory — Weiss tear which is mostly related to alcohol abuse), whereas others are more likely to occur in older women (GU). It has also been found that elderly women consume more NSAIDs than men (Savage *et al.*, 1993), which places them at a higher risk of NSAID related lesions, particularly of GU. NSAID use prior to haemorrhage was frequent. Nearly half of the patients had received NSAIDs, while the elderly and the women had used them significantly more often than younger patients and men. The same observation has been made elsewhere as well (Savage *et al.*, 1993).

OGD is the main diagnostic tool in UGIH. In more than 90% of cases the source of haemorrhage can be established at endoscopy. In our study the main cause of UGIH was PU accounting for more than half of the total number of cases, followed by acute gastric mucosal lesions, Mallory-Weiss tear and oesophageal varices. The distribution of the causes of UGIH was close to that reported from some other centres (Wara, 1987; Henriksson and Svensson, 1991; Skok, 1998) and had not changed significantly in Tartu county during the 15

years under study. However, lately there have been reports of a relative decrease in incidence of PU as the cause of UGIH. The current frequency of PUH may be as low as 25–29% followed by portal hypertension as the cause of UGIH with a frequency of 19%. Such a decrease in PUH may reflect changes in the incidence of *H. pylori* infection as well as the use of novel NSAIDs (Marek, 2001).

The mortality rate of UGIH was 9.9% in Tartu. Mortality rates are mostly reported to be around 10% (Clason *et al.*, 1986; Katschinski *et al.*, 1994; Skok, 1998). Several specialized units have achieved rates as low as 3.7–4.8% (Sanderson *et al.*, 1990; Holman *et al.*, 1990).

6.1.2. Peptic ulcer haemorrhage

Our data from Tartu county from 1979 to 1993 showed a sharp, nearly 2-fold increase in the incidence of PUH since 1991. Unpublished data from the same area show continuing increase in PUH incidence up to 55 per 100,000 per year in 1998. Furthermore, according to the unpublished data of the Bureau of Medical Statistics at the Ministry of Social Affairs of Estonia the incidence rate of PUH in Estonia has a tendency to increase. The incidence of PUH was 40 cases per year per 100,000 population in 1993, rose up to 56 in 1999 and reached a peak with 77 cases in 2001. The incidence rates were on a medium level more than 10 years ago and achieved high levels at the beginning of the 90-ies in comparison with to the range of 25–58 per 100,000 per year as estimated by other researchers (Panos and Walt, 1993; Cutler and Mendeloff, 1981). By now the incidence rate of PUH in Estonia seems to have exceeded the highest levels ever reported. It should be emphasized that the other important PU complication, ulcer perforation, has the same dramatic increasing pattern of the incidence rate (Sillakivi *et al.*, 2002).

Our opinion is that such an increase could be of multi-factorial origin. Sharp changes in social and economic conditions, low use of anti-ulcer drugs, declining elective ulcer surgery, smoking habits, increasing alcohol abuse, increasing NSAID use and high *H. pylori* infection rate among the Estonian population may have produced the dramatic increase in PU complications, particularly PUH.

The role of rapidly changing social and economic conditions cannot be underestimated. After the regaining of independence in 1991 dramatic changes have taken place in Estonia with a major decline in economy and an increase in unemployment from 0.6% in 1990 to 10% in 1996 (Statistical Yearbook of Estonia 1999).

Low use of antiulcer drugs in the first half of the 90-ies in Estonia has been reported recently. The use of these drugs was at least 4 times lower among the

Estonian population compared with the inhabitants of Stockholm county in terms of defined daily doses per 100,000 population (Kiivet *et al.*, 1998).

Prevalence of smoking is high in Estonia. In a stratified random sample of 2086 adults, 30–59 years of age, 58% of the men and 26% of the women smoked (Pärna *et al.*, 2002).

The role of the high prevalence of *H. pylori* infection in Estonia is discussed below in the section "Predisposing factors".

Haemorrhage has been found to disproportionately affect the elderly (Bloom *et al.*, 1990). Indeed, the incidence rate of PUH rose significantly with age in our study, being 10-fold higher for patients aged ≥70 (over 135 per 100,000 per year) compared with those aged 20–39 (11.5 per 100,000 per year). The incidence was higher for men in all age groups. The same age and sex related differences have been noted in a German study (Ohman *et al.*, 1992) and in a US study (Cutler and Mendeloff, 1981). In women growth in incidence rate with age was steady, while in men there appeared a sharp 6-fold increase in the rate in the age group 40–49 in comparison with younger patients in Tartu county (Table I, publ. IV). In the German study the incidence rate showed more uniform growth. Compared with our study, the overall incidence rate was twice lower for patients aged <50, equalized for those aged 50–79 and was twice higher for those aged ≥80. The US study shows a very high incidence (242 per 100,000 per year) in patients over 65 years of age in comparison with the corresponding rate in Tartu county.

In our study GU haemorrhage had the highest overall incidence, followed by DU and prepyloric ulcer. However, DU incidence was higher in men, while GU prevailed in women and the incidence of DU was low, close to that of pre-pyloric ulcer. Several studies have found that GU is a more frequent cause of PUH than DU (Wilcox *et al.*, 1994; Ohmann *et al.*, 1992), whereas others report the contrary (Rockall *et al.*, 1995).

The distribution of PUH patients (Figure 1, publ IV) reveals a predominance of younger men and elderly women: 37% of the men and 72% of the women were aged ≥60. Several studies demonstrate a high proportion of the elderly among PUH patients. In studies from the United Kingdom 81% (Holman *et al.*, 1990) and 74% (Rockall *et al.*, 1995) of the patients were aged ≥60, in an Australian study their share was 69% (Turner *et al.*, 1991). In Tartu county the proportion of patients aged ≥60, 49%, was lower compared with that in the above mentioned studies. This difference can be partly explained by the lower proportion of the elderly in the whole population of Estonia. The other possible contributing factor is the high *H. pylori* infection rate among the inhabitants of Estonia.

Mortality rates of PUH vary widely, from 3% (Gostout *et al.*, 1992) to 16.9% (Clason *et al.*, 1986). Though not close to the lowest rates, the 8.3% mortality in Tartu county is comparable to rates observed in most centres. Some authors have reported lower mortality rate, relating it to specialized unit

management, strict protocol (Sanderson *et al.*, 1990), aggressive approach (Bender *et al.*, 1994) and restrictive blood transfusion policy (Henriksson and Svensson, 1991).

6.1.3. Predisposing factors

The role of *H. pylori* in PU development has been recently established. It has been shown that eradication of this bacterium reduces both ulcer recurrence and bleeding relapses in long term (Labenz and Börsch, 1994; Graham *et al.*, 1993). It is suggested that *H. pylori* infection rate depends on the socioeconomic level. According to the United Nations "Human Development Report 1994", Estonia ranked behind developed countries with respect to the level of socioeconomic development. This could be the reason why *H. pylori* infection is more common in Estonia than in the Western countries, affecting 73–87% of the population in 3 regions studied (Maaroos, 1995). Even younger people from cohorts born in 1955–70 had an infection rate as high as 68–83% (Maaroos, 1995; Vorobjova *et al.*, 1994) and schoolchildren aged 9–15 had an infection rate of 56% (Vorobjova *et al.*, 2000). Comparable data from the Western countries show significantly lower *H. pylori* infection rates among those born in recent decades, ranging between 10–20% (EUROGAST Study Group, 1993). The high *H. pylori* infection rate might result in the high prevalence of PU disease, account for the subsequent high incidence rate of PUH and be the reason for the higher PUH incidence among the younger population found in our study.

H. pylori infection was frequently (89%) observed in the gastric mucosa of PUH patients. Its presence was slightly higher in prepyloric and DU patients than in GU patients.

The recently reported somewhat lower NSAID consumption among the population of Estonia compared with that of developed countries (Kiivet *et al.*, 1992) may have an impact on age distribution as these drugs are more often used by the elderly. This could explain the lower incidence rate of PUH among the elderly compared with that in other countries (Cutler and Mendeloff, 1981; Ohmann *et al.*, 1992).

NSAID use has been established to carry enhanced risk for PU genesis as well as for PUH development. Studies show the use of these drugs in 35% to 89% of cases (Holman *et al.*, 1990; Lanas *et al.*, 1992). According to our study, 45% of the patients had used NSAIDs before the onset of bleeding. Regular NSAID treatment prior to PUH was significantly more often observed in the elderly. In women the use of these drugs was considerably more frequent than in men.

NSAIDs seem to be more related to prepyloric ulcers and GU than to DU (Holvoet *et al.*, 1991; Glise, 1990). Our study confirms this finding: the proportion of regular NSAID users among the patients with prepyloric ulcer

(43%) was slightly higher than among the GU patients (26%) and significantly higher than among the DU patients (14%).

In one-fourth of the patients from Tartu county haemorrhage developed from asymptomatic ulcers. Asymptomatic ulcers present a major problem, as no preventive measures can be applied against life-threatening ulcer complications. It has been found that in older people ulcer symptoms can be vaguely expressed and NSAID use is often present in such cases (Katz, 1991). The presence of ulcer symptoms was not related to NSAID use in a previous study (Holvoet *et al.*, 1991). According to our study ulcer symptoms before bleeding were related neither to age, sex, diagnosis nor NSAID use.

Of the other possible predisposing factors for ulcer haemorrhage, smoking was significantly more frequent in men than in women in our study. 60% of the men and 15% of the women were smokers. The figures are close to those reported for the Estonian population (Pärna *et al.*, 2002).

6.2. Prognostic factors

In our patients mortality was associated with higher age, shock, haemoglobin level <80 g/l, major cardiac disease and recurrent bleeding. These risk factors coincide with those established by other researchers (Holman *et al.*, 1990; Rockall *et al.*, 1995; Turner *et al.*, 1991; Zittel *et al.*, 2000).

6.3. Treatment and short-term outcome

Medical therapy and surgery have limitations in treating PUH. Since its advent, endoscopic therapy of PUH has shown high effectiveness and has therefore spread rapidly. Furthermore, randomized controlled trials showed the benefits of endoscopic therapy in terms of lowering rebleeding, surgery, transfusion, and mortality (Lee and Leung, 1997). By now endoscopic therapy is the first choice and surgery is considered a selective therapeutic option, only to be applied if endoscopic haemostasis fails (Lanschot *et al.*, 2002). With respect to the cost, endoscopic therapy has been found to be considerably less expensive than emergency surgery for patients with PUH and patients prefer it, as initial or subsequent treatment for the emergency control of bleeding, to surgery (Jensen, 1999).

Our study focused on changes in treatment at the Clinic of Surgery of Tartu University Clinics during the last years. The two periods, 1992–1993 and 1999–2000, that were compared did not differ either in the structure of the patient population, ulcer location or the type of haemorrhage according to Forrest.

However, treatment tactics changed considerably during the 7 years under consideration. While EIT was used in 22% of the patients in period I, it was applied in more than half of the patients in period II. In period II, EIT was more often used both in the actively bleeding patients (Forrest I) and in those who showed endoscopic signs of recent bleeding (Forrest II).

In about 80–85% of PUH cases bleeding stops spontaneously (Zittel *et al.*, 2000). However, studies have shown that approximately half of patients with PUH suffer from recurrent bleeding without endoscopic treatment. In the case of Forrest I type haemorrhage, 88% of patients either bleed unceasingly or develop a new episode of bleeding. In Forrest II patients bleeding recurs in 43% of cases. In Forrest III type rebleeding occurs very seldom, in 3% of patients (Jensen, 1990). Therefore endoscopic therapy should be used in patients with ongoing bleeding or in those with high risk of recurrent bleeding (a visible vessel or a clot in the ulcer base). Endoscopic therapy is not indicated if the ulcer base is clean.

EIT is considered technically simple, effective and safe (Asaki 2000). The possible complications include perforation and onset of uncontrollable bleeding, which are relatively rare, with an incidence of 0.9% (Pitcher, 1990). No complications occurred in our patients.

Based on the meta-analysis of the studies performed in the 80-ies, Sacks found that endoscopic therapy reduces significantly the rate of rebleeding, the need for emergency surgery and mortality (Sacks *et al.*, 1990). Bleeding recurs in up to 20% of PUH patients after endoscopic therapy (Kolkman *et al.*, 1996). In these cases repeated endoscopic treatment is indicated due to its high, 75% efficiency (Lau *et al.*, 1999). Surgical hemostasis should be used only in case endoscopic and medical therapies fail (Swain, 1995). It has been found that surgery is needed in only 5–6% of PUH patients (Ohmann *et al.*, 2000). Asaki and colleagues from six Japanese centres got even better results employing EIT with absolute alcohol in 1603 patients with PUH. Only 149 developed recurrent bleeding, which was stopped by repeated EIT in most cases. In 31 cases (2%) emergency surgery was needed to stop bleeding. Ten of the 1603 patients enrolled died (Asaki, 2000).

Our material shows a significant decline in surgery, from 40% to 6%, during the seven-year study period, the diminished need for so-called early elective surgery being largely responsible for it. Early elective surgery was, until quite recently, used in PUH patients at high rebleeding risk, who had not been subjected to endoscopic therapy. The operation was performed in an elective setting shortly after the condition of the patient was stabilised.

The mortality of the studied PUH patients decreased from 7% to 2% during the period considered. Our opinion is that the significant fall in the need for surgical therapy and the decrease in mortality are related to the more extensive use of EIT in the late part of the studied period. Some authors claim that mortality from PUH is around 10% and that it has not declined during recent decades (Iambrenghi *et al.*, 1995). However, in many departments a lower than

5% mortality of PUH patients was achieved even at the end of 80-ies (Holman *et al.*, 1990). Although there exist centres reporting death rates of 14% (Dertinger *et al.*, 1996), the standpoint that they should not exceed 5% nowardays (Zittel *et al.*, 2000) seems to be justified.

The more extensive use of endoscopic therapy as the treatment of first choice has enabled to diminish the need for surgical treatment as well as the mortality of PUH patients at the Clinic of Surgery of Tartu University Clinics.

6.4. Long-term results in conservatively and operatively treated peptic ulcer haemorrhage patients

The surgeon dealing with PUH is faced with multiple tasks among which stabilising the patient's condition and reducing the risk of recurrent bleeding in an attempt to diminish mortality are the initial ones. The further goal is to prevent ulcer relapse and subsequent ulcer complications in long term by applying medical therapy or definitive operative treatment. However, long-term results of PUH have been rarely assessed in the literature.

In our case control study further ulcer haemorrhage occurred in 16% of the conservatively treated and in 6% of the operatively treated patients during the two-year follow-up period. However, the difference was not statistically significant. Intermittent therapy with H_2 blockers after conservative hospital treatment resulted in nearly 50% of recurrence of ulcer bleeding, ulcer relapse or severe symptoms and 40% of excellent and good results. In a similar study 13% of the patients on intermittent H_2 blocker therapy rebled during a mean follow-up of 48 months (Mueller *et al.*, 1994). The latter study reports the 6% late complication rate of PU in definitively operated patients. In a Hong Kong study (Ng *et al.*, 1996) the risk of a further ulcer complication, both haemorrhage and perforation, has been found to be as high as 32% over a median follow-up period of 36 months. The patients were treated with H_2 blockers until ulcer healing and received no maintenance therapy thereafter.

These unsatisfactory results indicate that intermittent therapy after PUH fails to control PU and further haemorrhage in long term, and should not be advocated for patients. Ranitidine administered in a maintenance regimen has revealed the capacity to reduce both DU relapse and further ulcer bleeding (Jensen *et al.*, 1994). However, lifelong maintenance therapy for all ulcer haemorrhage patients is expensive. The recent advent of drugs for *H. pylori* eradication has expanded the possibilities of treating PU. The first long-term results of the use of these drugs after complications appear to be promising (Jaspersen *et al.*, 1995; Labenz *et al.*, 1996). Some authors claim that definitive ulcer surgery should be avoided in PUH patients (Röher *et al.*, 1996) and that the mere undersewing of the bleeding vessel and its branches should be per-

formed (Kolkman *et al.*, 1996). We are of the opinion that when operative treatment is indicated, definitive procedures with ulcer removal should not be abandoned, as they provide an instant and complete control of the bleeding site as well as yield good long-term results. In our study excellent and good long-term outcome was achieved in 80% of the patients. Surgical treatment with vagotomy has been found to be superior to therapy with H_2 blockers also in terms of abdominal complaints and dyspepsia in patients with PU. It produces a level of complaints almost identical to that seen in the community population (Lindsetmo *et al.*, 1998). Definitive operative treatment is also a safe procedure. No hospital deaths resulted from early elective operation in our patients. The two patients who died had undergone emergency operation.

Patients surviving an episode of PUH carry a two-fold higher risk of death compared with the general population in long term (Ruigomez *et al.*, 2000). However, although the long-term prognosis for patients discharged from hospital after treatment due to PUH is poor, most deaths cannot be attributed to recurrent ulcer bleeding (Kubba *et al.*, 1997; Hudson *et al.*, 1995). In our study altogether 18 patients died within two years after hospital treatment due to reasons unrelated to PUH. Deaths resulted mainly from cardiovascular disease (9/18) and malignancies of various locations (5/18). Among the latter cases one patient had been diagnosed with praepyloric ulcer during hospital treatment but died of gastric cancer. Obviously, cancer diagnosis had been previously missed.

6.5. Long-term results in patients treated surgically for giant duodenal posterior wall ulcers complicated with haemorrhage

Giant DPWU penetrating into the pancreas are often the cause of severe hemorrhage, primarily owing to the erosion of a. gastroduodenalis (Swain, 1990). In such cases the choice of the operative method is complicated, particularly when ulcer hemorrhage is accompanied with stenosis of the pyloro-duodenal zone.

The results of our investigation demonstrate that in these cases, excellent or good long-term results without ulcer recurrence can be obtained in 90% of cases with the application of DPV or AEV. An earlier study of 15 patients by Helwing and Heymann yielded good results in all cases 8–24 months after operation (Helwing and Heymann, 1978). Our results confirm good outcome for the first time for a much longer period, on average 11 years after operation.

In our opinion, the important determinant accounting for the achievement of such good long-term results with the use of Helwing`s method is the focus on the salvaging resection of the pyloroduodenal region together with form and function preserving plasty after Holle`s concept (Holle and Hart, 1967; Holle,

1977). Holle's pyloroplasty, though not widely used, showed good long-term results in our earlier study (Vardja *et al.*, 1996) and has also been recommended recently by other researchers (Donahue, 2000). According to Holle's concept, DPWU is excised. This is feasible in the case of relatively small ulcers. However, in the case of giant ulcers penetrating into the pancreas, there arise technical problems. DPV, which uses the exteriorizing of the ulcer base, enables to skip possible hazards and is technically simpler compared with ulcer excision. At the same time, stenosis from scarring around the ulcer, which, according to our present study is frequent, can be simultaneously excised.

Our data show that DPV in the case of a bleeding giant DPWU can prevent several postoperative complications that may develop with the use of other widely used operative techniques.

Some authors have recommended, in DPWU hemorrhage, the oversewing of the bleeding vessel, with or without pyloroplasty, combined with vagotomy (Mills, 1991; Gostout *et al.*, 1992; Mönig *et al.*, 2002). However, a significant drawback of oversewing is occurrence of early recurrent hemorrhage in up to 17–23% of operated patients (Hunt and McIntyre, 1990; Kubba *et al.*, 1996), with high mortality (Kubba *et al.*, 1996; Kuttila *et al.*, 1991).

Bumm and Siewert recommend to combine the oversewing of the bleeding vessel in the ulcer base, through duodenotomy, with the extraluminal ligation of a. gastroduodenalis, a. gastroepiploica dextra and a. pancreatoduodenalis (Bumm and Sievert, 1998). Although postoperative mortality in this case has been reported as 3–6%, long-term results obtained with this method are not available. Besides, one should also take into account that the mere ligation of the bleeding vessel, or the oversewing of the ulcer does not eliminate stenosis due to giant ulcer.

As an alternative, Billroth II gastric resection is performed in giant DU (Hunt and McIntyre, 1990). However, we consider that Billroth II gastric resection is less appropriate than Billroth I type resection because of the possibility of duodenal leakage following the atypical closure of the duodenal stump, as well as a significantly more frequent occurrence of postgastrectomy syndromes. Therefore, AEV with Billroth I reconstruction after Herfarth should be recommended, where the base of the giant penetrating ulcer is not excised but exteriorized (Herfarth *et al.*, 1977), together with truncal vagotomy. Herrington and Davidson have also suggested a similar method (Herrington and Davidson, 1987). Our earlier study of long-term outcome on average 8 years after operation shows that truncal vagotomy with antrectomy in DU patients yields excellent and good results without ulcer recurrence in 98% of cases (Vardja *et al.*, 1996).

Recent studies have shown that *H. pylori* eradication results in low recurrent bleeding in cases of conservatively treated PUH (Graham *et al.*, 1993; Labenz and Börch, 1994). These findings have encouraged some authors to question performance of operations with vagotomy in DU hemorrhage (Ohmann *et al.*, 2000; Zittel *et al.*, 2000). Would it be right to resort to minimal surgery i.e. to

attack only the bleeding vessel without vagotomy and to rely on *H. pylori* eradication? However, as Millat *et al.* have pointed out, the prevalence of *H. pylori* in bleeding PU is not well defined and has been assessed to be lower than in uncomplicated ulcers (Millat *et al.*, 2000). The success of *H. pylori* treatment has been reported to be 55–80% (Maaroos *et al.*, 2001; Vaira *et al.*, 1997). Besides, development of giant DU has been associated with the use of NSAIDs (Collen *et al.*, 1994), representing one of the main risk factors for PUH (Santander *et al.*, 1996). Moreover, NSAID induced ulcer hemorrhage can develop without *H. pylori* infection. Therefore, we agree with the viewpoint of Stabile and Stamos that until now no data support the efficacy of an operation for bleeding DU that does not include vagotomy (Stabile and Stamos, 2000). Our good long-term results from recent and present studies also serve as an argument for the use of vagotomy.

Surgical expertise in PU is on the way of disappearance, because elective surgery is rarely needed (Johnson and Chir, 2000) and conservative treatment is prevailing in ulcer hemorrhage. If surgical treatment of bleeding giant DPWU, penetrating into the pancreas, is indicated, we recommend the use of DPV after Helwing or AEV after Herfarth, combined with vagotomy, which yielded good long-term results in the present study.

7. CONCLUSIONS

1. Peptic ulcer haemorrhage is the most common cause of upper gastro-intestinal haemorrhage, being responsible for more than half of haemorrhage cases in Tartu county, Estonia. Women with peptic ulcer haemorrhage are older, have consumed NSAIDs in most cases (64%) and suffer mostly from gastric ulcer haemorrhage, while men are younger, have consumed less NSAIDs (36%) and are mostly prone to duodenal ulcer bleeding.

   A considerable, nearly 2-fold rise in peptic ulcer haemorrhage has taken place in Tartu county since 1991. The incidence of peptic ulcer haemorrhage is high in Tartu county, Estonia, in comparison with that in developed countries owing to the higher incidence rate among the younger population. The incidence rate is lower in the elderly compared with reports from developed countries.

   The prevalence of *H. pylori* infection was 89% in peptic ulcer haemorrhage patients.

2. The main prognostic factors for an adverse outcome of peptic ulcer haemorrhage included major concomitant cardiac disease, rebleeding during treatment, systolic blood pressure less than 100 mmHg on admission, age ≥65 years and haemoglobin lower than 80 g/l on admission.

3. The more extensive use of endoscopic injection therapy in peptic ulcer patients has enabled to diminish the need for surgical treatment as well as the mortality.

4. Intermittent H_2 blocker therapy after an episode of peptic ulcer haemorrhage should be avoided due to unsatisfactory long-term outcome in terms of ulcer recurrence and further ulcer haemorrhage.

   Good long-term results can be achieved in the majority of peptic ulcer haemorrhage patients by employing definitive operative procedures directed to the pathogenesis of peptic ulcer disease.

5. In the surgical treatment of bleeding giant duodenal posterior wall ulcers, penetrating into the pancreas, the use of duodenal resection with plasty after Helwing, or antrectomy after Herfarth, both combined with vagotomy, yield good long-term results.

8. REFERENCES

Andersen IB, Jorgensen T, Bonnevie O, Gronbaek M, Sorensen TI. Smoking and alcohol intake as risk factors for bleeding and perforated peptic ulcers: a population-based cohort. Epidemiology 2000; 11: 434–439.

Asaki S. Efficacy of endoscopic pure ethanol injection method for gastrointestinal ulcer bleeding. World J Surg 2000; 24: 294–298.

Bardhan KD, Cust G, Hinchliffe RFC, Williamson FM, Lyon C, Bose K. Changing pattern of admissions and operations for duodenal ulcer. Br J Surg 1989; 76: 230–236.

Bender JS, Bouwman DL, Weaver DW. Bleeding gastroduodenal ulcers: Improved outcome from a unified surgical approach. Am Surg 1994; 60: 313–315.

Bernersen B, Johnsen R, Straume B, Burhol PG, Jenssen TG, Stakkevold PA. Towards a true prevalence of peptic ulcer: the Sørreisa gastrointestinal disorder study. Gut 1990; 31: 989–992.

Bloom BS, Fendrick AM, Ramsey SD. Changes in peptic ulcer and gastritis/duodenitis in Great Britain, 1970–1985. J Clin Gastroenterol 1990; 12: 100–108.

Bown S. Bleeding peptic ulcers. Veni, vidi, vici per via naturalis. BMJ 1991; 302: 1417–1418.

Branicki FJ, Boey J, Fok PJ, Pritchett CJ, Fan S-T, Lai ECS, Mok FPT, Wong W-S, Lam SK, Hui W-M, Ng MMT, Lok ASF, Lam DKH, Tang APK, Wong J. Bleeding duodenal ulcer. A prospective evaluation of risk factors for rebleeding and death. Ann Surg 1990; 211: 411–418.

Brullet E, Campo R, Calvet X, Coroleu D, Rivero E, Simo Deu J. Factors related to the failure of endoscopic injection therapy for bleeding gastric ulcer. Gut 1996; 39: 155–158.

Bumm R, Sievert JR. Chirurgisches Vorgehen beim Ulcus ventriculi und Ulcus duodeni. Chirurg 1998; 69: 588–596.

Cash BD. Evidence-based medicine as it applies to acid supression in the hospitalized patient. Crit Care Med 2002; 30: 373–378.

Chamberlain CE. Acute hemorrhagic gastritis. Gastroenterol Clin North Am 1993; 22: 843–873.

Chang T-M, Chen T-H, Shih C-M, Gueng M-K, Tsou S-S. Partial or complete circular duodenectomy with highly selective vagotomy for severe obstructing duodenal ulcer disease: an initial experience. Arch Surg 1998; 133: 998–1001.

Church NI, Palmer KR. Ulcers and nonvariceal bleeding. Endoscopy 2003; 35: 22–26.

Clason AE, Macleod DAD, Elton RA. Clinical factors in the prediction of further haemorrhage or mortality in acute upper gastrointestinal haemorrhage. Br J Surg 1986; 73: 985–987.

Collen MJ, Santoro MJ, Chen YK. Giant duodenal ulcer. Evaluation of basal acid output, nonsteroidal antiinflammatory drug use, and ulcer complications. Dig Dis Sci 1994; 39: 1113–1116.

Cook DJ, Guyatt GH, Salena BJ, Laine L. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Gastroenterology 1992; 102: 139–148.

Cutler JA, Mendeloff AI. Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. Dig Dis Sci 1981; 26 (July Suppl): 90–96.

Dallal HJ, Palmer KR. Upper gastrointestinal haemorrhage. BMJ 2001; 323: 1115–1117.

Dertinger SH, Vestner H, Müller K, Merz M, Hahn EG, Altendorf-Hofman A, Ell C. Prospective Untersuchung zu Diagnostik, Therapie und Verlauf der akuten gastrointestinalen Blutung bei 397 Patienten. Wien Klin Wochenschr 1996; 108/22: 717–721.

Dobrilla G, Zancanella L, Amplatz S. The need for long-term treatment of peptic ulcer. Aliment Pharmacol Ther 1993; 7: 3–15.

Donahue PE. Parietal cell vagotomy versus vagotomy-antrectomy: ulcer surgery in the modern era. World J Surg 2000; 24: 264–269.

Duggan JM. Review article: transfusion in gastrointestinal haemorrhage — if, when and how much? Aliment Pharmacol Ther 2001; 15: 1109–1113.

EUROGAST Study Group. Epidemiology of, and risk factors for, Helicobacter pylori infection among 3194 asymptomatic subjects in 17 populations. Gut 1993; 34: 1672–1676.

Fallahzadeh H. Elective procedure for peptic ulcer: A disappearing operation. Am Surg 1993; 59: 20–22.

Forrest JAH, Finlayson NDC, Shearman DJC. Endoscopy in gastrointestinal bleeding. Lancet 1974; 2: 394–397.

Fraser A, Masson J, Buckner L, McKnight G, Bramley P, Smith WC, Mowat NAG. Long-term survival, symptoms and drug use after peptic ulcer haemorrhage. Gut 1997; 40 (Suppl 1): 8.

Frezza M, Gorji N, Melato M. The histopathology of non-steroidal anti-inflammatory drug induced gastroduodenal damage: correlation with Helicobacter pylori, ulcers and haemorrhagic events. J Clin Pathol 2001; 54: 521–525.

Gilbert DA. Epidemiology of upper gastrointestinal bleeding. Gastrointest Endosc 1990; 36 (Suppl 5): 8–13.

Gilliam AD, Speake WJ, Lobo DN, Beckingham IJ. Current practice of emergency vagotomy and *Helicobacter pylori* eradication for complicated peptic ulcer in the United Kingdom. Br J Surg 2003; 90: 88–90.

Gisbert JP, Gonzalez L, de Pedro A, Valbuena M, Prieto B, Llorca I, Briz R, Khorrami S, Garcia-Gravalos R, Pajares JM. Helicobacter pylori and bleeding duodenal ulcer: Prevalence of the infection and role of non-steroidal anti-inflammatory drugs. Scand J Gastroenterol 2001; 36: 717–724.

Glise H. Epidemiology in peptic ulcer disease. Scand J Gastroenterol 1990; 25 (Suppl 175): 13–18.

Godil A, DeGuzman L, Schilling RC 3rd, Khan SA, Chen YK. Recent nonsteroidal anti-inflammatory drug use increases the risk of early recurrence of bleeding in patients presenting with bleeding ulcer. Gastrointest Endosc 2000; 51: 146–151.

Goligher JC, Hill GL, Kenny TE, Nutter E. Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5–8 years. Br J Surg 1978; 65: 145–151.

Gostout CJ, Wang KK, Ahlquist DA, Clain JE, Hughes RW, Larson MV, Petersen BT, Schroeder KW, Tremaine WJ, Viggiano TR, Balm RK. Acute gastrointestinal bleeding. Experience of a specialized management team. J Clin Gastroenterol 1992; 14: 260–267.

Graham DY, Hepps KS, Ramirez FC, Lew GM, Saeed ZA. Treatment of Helicobacter pylori reduces the rate of rebleeding in peptic ulcer disease. Scand J Gastroenterol 1993; 28: 939–942.

Graham DY. Nonsteroidal anti-inflammatory drugs, Helicobacter pylori, and ulcers: Where we stand. Am J Gastroenterol 1996; 91: 2080–2086.

Gralnek IM, Jensen DM, Kovacs TOG, Jutabha R, Jensen ME, Cheng S, Gorbein J, Freeman ML, Machicado GA, Smith J, Sue M. Clinical and enonomic outcomes of individuals with severe peptic ulcer hemorrhage and nonbleeding visible vessel: An analysis of two prospective clinical trials. Am J Gastroenterol 1998; 93: 2047–2056.

Gustavsson S, Kelly KA, Melton LJ, Zinsmeister AR. Trends in peptic ulcer surgery: a population-based study in Rochester, Minnesota, 1956–1985. Gastroenterology 1988; 94: 688–694.

Hawkey CJ. Risk of ulcer bleeding in patients infected with Helicobacter pylori taking non-steroidal anti-inflammatory drugs. Gut 2000; 46: 310–311.

Helwing E, Heymann H. Postpylorishe Resection des komplizierten Ulcus der Duodenalhinterwand im Rahmen form- und funktionsgerechter Magenchirurgie. Technik und erste Ergebnisse. Chirurg 1978; 49: 29–32.

Henriksson AE, Svensson J-O. Upper gastrointestinal bleeding with special reference to blood transfusion. Eur J Surg 1991; 157: 193–196.

Herfarth C, Merkle P, Mattes P. Billroth I-Resektion beim großen penetrierenden Duodenalhiterwand-Ulcus. Chirurg 1977; 48: 123–124.

Herrington JL Jr., Davidson J. Bleeding gastroduodenal ulcers: Choice of operations. World J Surg 1987; 11: 304–314.

Higham J, Kang JY, Majeed A. Recent trends in admissions and mortality due to peptic ulcer ulcer in England: increasing frequency of haemorrhage among older subjects. Gut 2002; 50: 460–464.

Holle FK. The physiopathologic background and standard technique of selective proximal vagotomy and pyloroplasty. Surg Gynecol Obstet 1977; 145: 853–859.

Holle F, Hart W. Neue Wege der Chirurgie das Gastroduodenalulkus. Medizinische Klinik 1967; 62: 441–450.

Holman RAE, Davis M, Gough KR, Gartell P, Britton DC, Smith RB. Value of a centralised approach in the management of haematemesis and melaena: experience in a district general hospital. Gut 1990; 31: 504–508.

Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E, Hautekeete ML. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. Gut 1991; 32: 730–734.

Hsu P-I, Lai K-H, Lin X-Z, Yang Y-F, Lin M, Shin J-S, Lo G-H, Huang R-L, Chang C-F, Lin C-K, Ger L-P. When to discharge patients with bleeding peptic ulcers: a prospective study of residual risk of rebleeding. Gastrointest Endosc 1996; 44: 382–387.

Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic ulcer disease: a meta-analysis. Lancet 2002; 359: 14–22.

Hudson N, Faulkner G, Smith SJ, Langman MJS, Hawkey CJ, Logan RFA. Late mortality in eldrly patients surviving acute peptic ulcer bleeding Gut 1995; 37: 177–181.

Hunt PS., McIntyre RLE. Choice of emergency operative procedure for bleeding duo-denal ulcer. Br J Surg 1990; 77: 1004–1006.

Imhof M, Ohmann C, Hartwig A, Thon K-P, Hengels K-J, Röher H-D, DÜSUK Study Group. Which peptic ulcers bleed? Results of a case-control study. Scand J Gastroenterol 1997; 32: 131–138.

Imhof M, Ohmann C, Röher HD, Glutig H. Endoscopic versus operative treatment in high-risk ulcer bleeding patients – results of a randomised study. Langenbeck`s Arch Surg 2003; 387: 327–336.

Ishikawa M, Kikutsuji T, Miyauchi T, Sakakihara Y. Limitations of endoscopic haemostasis by ethanol injection and surgical management for bleeding peptic ulcer. J Gastroenterol Hepatol 1994; 9: 64–68.

Jaspersen D, Koerner T, Schorr W, Brennenstuhl M, Raschka C, Hammar C-H. Helicobacter pylori eradication reduces the rate of rebleeding in ulcer hemorrhage. Gastrointest Endosc 1995; 41: 5–7.

Jensen DM. Heat probe for hemostasis of bleeding peptic ulcers: techniques and results of randomized controlled trials. Gastrointest Endosc 1990; 36: 42–49.

Jensen DM. Management of severe ulcer bleeding. N Engl J Med 1999; 340: 799–801.

Jensen DM, Cheng S, Kovacs TOG, Randall G, Jensen ME, Reedy T, Frankl H, Machicado G, Smith J, Silpa M, Van Deventer G. A controlled study of Ranitidine for the prevention of recurrent hemorrhage from duodenal ulcer. N Engl J Med 1994; 330: 382–386.

Jiranek GC, Kozarek RA. A cost-effective approach to the patient with peptic ulcer bleeding. Surg Clin North Am 1996; 76: 83–103.

Johnson AG. Management of peptic ulcer. Br J Surg 1994; 81: 161–163.

Johnson AG, Chir M. Proximal gastric vagotomy: Does it have a place in the future management of peptic ulcer. World J Surg 2000; 24: 259–263.

Johnston JH. The sentinel clot and invisible vessel: pathologic anatomy of bleeding peptic ulcer. Gastrointest Endosc 1984; 30: 313–5.

Johnston JH. Endoscopic risk factors for bleeding peptic ulcer. Gastrointest Endosc1990; 5: 16–20.

Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Langman M. Prognostic factors in upper gastrointestinal bleeding. Dig Dis Sci 1994; 39: 706–712.

Katz J. The course of peptic ulcer disease. Med Clin North Am 1991; 75: 831–840.

Kiivet RA, Bergman U, Sjöqvist F. The use of drugs in Estonia compared to the Nordic countries. Eur J Clin Pharmacol 1992; 42: 511–515.

Kiivet RA, Bergman U, Sjöstedt S, Sjöqvist F. Ulcer surgery in Estonia, a consequence of drug delay? Lancet 1998; 351: 146.

Klein WA, Krevsky B, Klepper L, Ljubich P, Niewiarowski TJ, Rothstein KD, Dabezies MA, Fisher RS. Nonsteroidal antiinflammatory drugs and upper gastro-intestinal hemorrhage in an urban hospital. Dig Dis Sci 1993; 38: 2049–2055.

Kohler B, Riemann JF. The endoscopic doppler: its value in evaluating gastroduodenal ulcers after hemorrhage and as an instrument of control of endoscopic injection therapy. Scand J Gastroenterol 1991; 26: 471–476.

Kolkmann JJ, Meuwissen SGM. A review on treatment of bleeding peptic ulcer: a collaborative task of gastroenterologist and surgeon. Scand J Gastroenterol 1996; 31 (Suppl 218): 16–25.

Kubba AK., Choudari C., Rajgopal C., Palmer KR. The outcome of urgent surgery for major peptic ulcer haemorrhage following failed endoscopic therapy. Eur J Gastro-enterol Hepatol 1996; 8: 1175–1178.

Kubba AK, Choudari C, Rajgopal C, Ghosh S, Palmer KR. Reduced long-term survival following major peptic ulcer haemorrhage. Br J Surg 1997; 84: 265–268.

Kubba AK, Selby NM, Hawkey CJ. Update in the pharmacological management of peptic ulcer haemorrhage. Scand J Gastroenterol 2001; 4: 337–342.

Kurata JH, Corboy ED. Current peptic ulcer time trends. J Clin Gastroenterol 1988; 10: 259–268.

Kuttila K, Havia T, Pekkala E, Ali-Melkkilä T. Surgery of acute peptic ulcer haemorrhage. Ann Chir Gynaecol 1991; 80: 26–29.

Kuyvenhoven JP, Veenendaal RA, Vandenbroucke JP. Peptic ulcer bleeding: interaction between non-steroidal anti-inflammatory drugs, Helicobacter pylori infection, and the ABO blood group system. Scand J Gastroenterol 1999; 34: 1082–1086.

Labenz J, Börsch G. Role of Helicobacter pylori eradication in the prevention of peptic ulcer bleeding relapse. Digestion 1994; 55: 19–23.

Labenz J, Tillenburg B, Peitz U, Börsch G. Long-term consequences of H. pylori eradication: Clinical aspects. Scand J Gastroenterol 1996; 31 (Suppl 215): 111–115.

Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. Am J Gastroenterol 1998; 93: 1409–1415.

Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology 1992; 103: 862–869.

Lanas A, Artal A, Blas JM, Arroyo MT, Lopez-Zaborras J, Sainz R. Effect of parenteral Omeprazole and Ranitidine on gastric pH and the outcome of bleeding peptic ulcer. J Clin Gastroenterol 1995; 21: 103–106.

Langman MJS. Epidemiologic evidence on the association between peptic ulceration and anti-inflammatory drug use. Gastroenterology 1989; 96: 640–6.

Langman MJS, Brooks P, Hawkey CJ, Silverstein F, Yeomans N. Working party report to the world congresses of gastroenterology, Sydney 1990. Non-steroidal anti-inflammatory drug associated ulcer: Epidemiology, causation and treatment. J Gastroenterol Hepatol 1991; 6: 442–449.

Laporte J-R, Carné X, Vidal X, Moreno V, Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. Lancet 1991; 337: 85–89.

Lau JYW, Sung JJY, Lam YH, Chan ACW, Ng EKW, Lee DWH, Chan FKL, Suen RCY, Chung SCS. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999; 340: 751–756.

Lee JG, Leung JW. Therapeutic modalities for treatment of peptic ulcer bleeding. Gastroenterologist 1997; 5: 26–40.

Leivonen M, Kivilaakso E. Peptic ulcer bleeding today: Risk factors and characteristics of the disease. Scand J Gastroenterol 1991; 26: 1013–1019.

Linkberg A. Ulcus ventriculi röntgenoloogilisest diagnoosimisest ja kirurgilisest ravist. Eesti Arst 1930; 9: 253–260.

Loke, YK, Bell A, Derry, S. Aspirin for the prevention of cardiovascular disease: calculating benefit and harm in the individual patient. Br J Clin Pharmacol 2003; 55: 202.

Maaroos H-I. Helicobacter pylori infection in Estonian population: Is it a health problem? Ann Med 1995; 27: 613–616.

Maaroos H-I, Keevallik R, Kolk H, Kull I, Labotkin K, Suurmaa K, Tammur R. Helicobacter pylori infektsiooniga seotud peptilise haavandi ravi uus kontseptsioon. Eesti Arst 2001;80:68–74.

Macri G, Milani S, Surrenti E, Passaleva MT, Salvadori G. Surrenti C. Eradication of Helicobacter pylori reduces the rate of duodenal ulcer rebleeding: a long-term follow-up study. Am J Gastroenterol 1998; 93: 925–927.

Marek TA. Gastrointestinal bleeding. Endoscopy 2001; 33: 920–929.

Marmo R, Rotondano G, Bianco MA, Piscopo R, Prisco A, Cipolletta L. Outcome of endoscopic treatment for peptic ulcer bleeding: is a second look necessary? A meta-analysis. Gastrointest Endosc 2003; 57: 62–67.

Martin I, O`Rourke N, Bailey I, Branicki F, Nathanson L, Fielding G. Laparoscopic underrunning of bleeding duodenal ulceration: a minimalist approach to therapy. Aust NZ J Surg 1998; 68: 213–215.

McCarthy DM. Acid peptic disease in the elderly. Clin Geriatr Med 1991; 7: 231–254.

Meissner K. Billroth II resection with modified Nissen duodenojejunostomy for duodenal ulcer hemorrhage associated with duodenal stricture. Hepato-Gastroenterol 1994; 41: 526–528.

Mellemkjaer L, Blot WJ, Sorensen HT, Thomassen L, McLaughlin JK, Nielsen GL, Olsen JH. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol 2002; 53: 173–181.

Millat B, Hay J-M, Valleur P, Fingerhut A, Fagniez P-L, and the French Associations for Surgical Research. Emergency surgical treatment for bleeding duodenal ulcer: oversewing plus vagotomy versus gastric resection, a controlled randomized trial. World J. Surg. 1993; 17: 568–574.

Millat B, Fingerhut A, Borie F. Surgical treatment of complicated duodenal ulcers: controlled trials. World J Surg 2000; 24: 299–306.

Mills PR. Upper gastrointestinal hemorrhage. Curr Opin Gastroenterol 1991; 7: 920–924.

Mondardini A, Barletti C, Rocca G, Garripoli A, Sambataro A, Perotto C, Repici A, Ferrari A. Non-variceal upper gastrointestinal bleeding and Forrest`s classification: diagnostic agreement between endoscopists from the same area. Endoscopy 1998; 30: 508–512.

Mueller X, Rothenbuehler J-M, Amery A, Meyer B, Harder F. Outcome of peptic ulcer hemorrhage treated according to a defined approach. World J Surg 1994; 18: 406–410.

Mueller X, Rothenbuehler JM, Amery A, Harder F. Early definitive operation for bleeding peptic ulcer. J R Coll Surg Edinb 1994; 39: 235–238.

Mäkelä J, Laitinen S, Kairaluoma MI. Complications of peptic ulcer disease before and after introduction of H2-receptor antagonists. Hepato-Gastroenterol 1992; 39: 144–148.

Mönig SP, Lübke T, Baldus SE, Schäfer H, Hölscher AH. Early elective surgery for bleeding ulcer in the posterior duodenal bulb. Own results and review of the literature. Hepato-Gastroenterol 2002; 49: 416–418.

Ng EKW, Chung SCS, Lau JTF, Sung JJY, Leung JWC, Raimes SA, Chan ACW, Li AKC. Risk of further ulcer complications after an episode of peptic ulcer bleeding. Br J Surg 1996; 83: 840–844.

NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. JAMA 1994; 272: 65–69.

Nishiaki M, Tada M, Yanai H, Tokiyama H, Nakamura H, Okita K. Endoscopic hemostasis for bleeding peptic ulcer using a hemostatic clip or pure ethanol injection. Hepato-Gastroenterol 2000; 47: 1042–1044.

Ohmann C, Thon K, Hengels K-J, Imhof M, DÜSUK Study Group. Incidence and pattern of peptic ulcer bleeding in a defined geographical area. Scand J Gastroenterol 1992; 27: 571–581.

Ohmann C, Imhof M, Röher H-D. Trends in peptic ulcer bleeding and surgical treatment. World J Surg 2000; 24: 284–293.

Paimela H, Tuompo PK, Peräkylä T, Saario I, Höckerstedt K, Kivilaakso E. Peptic ulcer surgery during the H_2-receptor antagonist era: a population-based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987. Br J Surg 1991; 78: 28–31.

PaimelaH, Joutsi T, Kiviluoto T, Kivilaakso E. Recent trends in mortality from peptic ulcer disease in Finland. Dig Dis Sci 1995; 40: 631–635.

Panos MZ, Walt RP. Current management of bleeding peptic ulcer. Drugs 1993; 46: 269–280.

Patchett SE, Enright H, Afdhal N, O`Connell W, O`Donoghue DP. Clot lysis by gastric juice: an *in vitro* study. Gut 1989; 30: 1704–1707.

Peetsalu A, Tamm A, Härkönen M, Varis K, Sipponen P, Karonen S-L, Väli T, Villako K. The effect of vagotomy and antrectomy on serum pepsinogens I and II. Scand J Gastroenterol 1990; 25: 455–461.

Peetsalu M, Maaroos H-I, Peetsalu A. Completeness of vagotomy, Helicobacter pylori colonization and recurrent ulcer 9 and 14 years after operation in duodenal ulcer patients. Eur J Gastroenterol Hepatol 1998; 10: 305–311.

Peetsalu M, Sillakivi T, Väli T, Tein A. Endoscopic diagnoses and treatment of peptic ulcer hemorrhage at the Clinic of Surgery of Tartu University Clinics. Acta Medica Lituanica 2001; Suppl 7: 109.

Penston JG, Crombie IK, Waugh NR, Wormsley KG. Trends in morbidity and mortality from peptic ulcer disease: Tayside versus Scotland. Aliment Pharmacol Ther 1993; 7: 429–442.

Penston JG, Wormsley KG. Maintenance treatment with H2-receptor antagonists for peptic ulcer disease. Aliment Pharmacol Ther 1992; 6: 3–29.

Peterson WL. Clinical risk factors. Gastrointest Endosc 1990; 36: 14–15.

Peterson WL. Bleeding peptic ulcer. Epidemiology and nonsurgical management. Gastroenterol Clin North Am 1990; 19: 155–170.

Petlem H, Peetsalu A. Gastroduodenaalverejooksude diagnoosimine ja ravi. Nõukogude Eesti Tervishoid. 1973; 3: 216–219.

Pitcher JL. Therapeutic endoscopy and bleeding ulcers: historical overview. Gastrointest Endosc 1990; 36: 2–7.

Powell KU, Bell GD, Bolton Gh, Burridge SM, Bowden AF, Rameh B, Hart l, Bradley P, Harrison G, Gant PW, Jones PH, Trowell JE, Brown C. Helicobacter pylori eradication in patients with peptic ulcer disease: clinical consequences and financial implications. Quart J Med 1994; 87: 283–290.

Poxon VA, Keighley MRB, Dykes PW, Heppinstall K, Jaderberg M. Comparison of minimal and conventional surgery in patients with bleeding ulcer: a multicentre trial. Br J Surg 1991; 78: 1344–1345.

Pärna K, Rahu K, Rahu M. Patterns of smoking in Estonia. Addiction 2002; 97: 871–876.

Qvist P, Arnesen KE, Jacobsen, Rosseland AR. Endoscopic treatment and restrictive surgical policy in the management of peptic ulcer bleeding. Five years` experience in a central hospital. Scand J Gastroenterol 1994; 29: 569–576.

Rauws EA, Tytgat GN. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990; 335: 1233–1235.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. Lancet 1996; 347: 1138–1140.

Rockall TA, Logan RFA, Devlin HB, Northfield TC, and the steering committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. Risk assessment after acute upper gastroitestinal haemorrhage. Gut 1996; 38: 316–321.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. BMJ 1995; 311: 222–226.

Rodriguez LAG, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994; 343: 769–772.

Rollhauser C, Fleischer DE. Nonvariceal upper gastrointestinal bleeding: an update. Endoscopy 1997; 29: 91–105.

Rorbaek-Madsen M, Fischer L,Thomsen H, Wara P. Late outcome of bleeding gastric ulcer. Five to eight years' follow-up. Scand J Gastroenterol 1994; 29: 983–987.

Ruigomez A, Rodriguez LAG, Hasselgren G, Johansson S, Wallander M-A. Overall mortality among patients surviving an episode of peptic ulcer bleeding. J Epidemiol Comm Health 2000; 54: 130–133.

Rulli A. Maomahla koostise muutusist peale mao resektsiooni Reichel-Polya järele. Eesti Arst 1939; 18: 453–457.

Röher H-D, Imhof M, Goretzki PE, Ohmann C. Ulcus'96 — Methodenwahl im Notfall. Chirurg 1996; 67: 20–25.

Sacks HS, Chalmers TC, Blum AL, et al. Endoscopic hemostasis — an effective therapy for bleeding peptic ulcers. JAMA 1990; 264: 494–499.

Sanderson JD, Taylor RFH, Pugh S, Vicary FR. Specialized gastrointestinal units for the management of upper gastrointestinal haemorrhage. Postgrad Med J 1990; 66: 654–656.

Santander C, Gravalos RG, Gomez-Cedenilla A, Cantero J, Pajares JM. Antimicrobial therapy for Helicobacter pylori infection versus long-term maintenance antisecretion treatment in the prevention of recurrent hemorrhage from peptic ulcer: Prospective nonrandomized trial on 125 patients. Am J Gastroenterol 1996; 91: 1549–1552.

Sarv J. Haavandtõve kirurgilise ravi aktuaalseid küsimusi. Nõukogude Eesti Tervishoid 1968; 1: 5–9.

Savage RL, Moller PW, Ballantyne CL, Wells JE. Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. Arthritis Rheum 1993; 36: 84–90.

Schwesinger WH, Page CP, Sirinek KR, Gaskill HV 3rd, Melnick G, Strodel WE. Operations for peptic ulcer disease: Paradigm lost. J Gastrointest Surg 2001; 5: 438–443.

Selby NM, Chodera J, Kubba AK. Meta-analysis of the efficacy of acid-reducing agents in the management of patients with peptic ulcer haemorrhage. Br J Surg 2000; 87: 636.

Shafi MA, Fleischer DE. Risk factors of acute ulcer bleeding. Hepato-Gastroenterol 1999; 46: 727–731.

Sibul U, Truve R. Mao resektsiooni ulatuse määramisest. Nõukogude Eesti Tervishoid 1968; 1: 9–12.

Sillakivi T, Lang A, Tein A, Peetsalu A. Evaluation of risk factors for mortality in surgically treated perforated peptic ulcer. Hepato-Gastroenterol 2000; 47: 1765–1768.

Sillakivi T, Lang A., Soplepmann J, Tein A, Peetsalu A. Incidence of perforated peptic ulcer correlated with suicide rate in Estonia in 1981–2000. Proceedings of the Eurosurgery 2002. Monduzzi Editore. Lisbon (Portugal), June 5–7, 2002: 199–204.

Simeone DM, Hassan A, Scheiman JM. Giant peptic ulcer: a surgical or medical disease? Surgery 1999; 126: 474–478.

Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol 1999; 26 (Suppl 56):18–24.

Skok P. The epidemiology of haemorrhage from the upper gastrointestinal tract in the mid-nineties — has anything changed? Hepato-Gastroenterol 1998; 45: 2228–2233.

Spiegel BMR, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: Is sooner better? A systematic review. Arch Int Med 2001; 161: 1393–1404.

Stabile BE, Stamos MJ. Surgical management of gastrointestinal bleeding. Gastroenterol Clin North Am 2000; 29: 189–222.

Stack WA, Atherton JC, Hawkey GM, Logan RF, Hawkey CJ. Interactions between Helicobacter pylori and other risk factors for peptic ulcer bleeding. Aliment Pharmacol Therap 2002; 16: 497–506.

Statistical Yearbook of Estonia 1999. Chapter: Labour market. The Statistical Office of Estonia, Tallinn, Estonia, 1999:183.

Swain CP, Storey DW, Bown SG, Heath J, Mills TN, Salmon PR, Northfield TC, Kirkham JS, O`Sullivan JP. Nature of the bleeding vessel in recurrently bleeding gastric ulcers. Gastroenterology 1986; 90: 595–608.

Swain CP, Salmon PR, Northfield TC. Does ulcer position influence presentation or prognosis of upper gastrointestinal bleeding? (abstract). Gut 1986; 27: A632.

Swain CP. Pathophysiology of bleeding lesions. Gastrointest Endosc 1990; 36: 21–22.

Thomopoulos KC, Mitropoulos JA, Katsakoulis EC, Vagianos CE, Mimidis KP, Hatziargiriou MN, Nikolopoulou VN. Factors associated with failure of endoscopic injection haemostasis in bleeding peptic ulcers. Scand J Gastroenterol 2001; 36: 664–668.

Truve R, Sibul U, Lutsuver A. Selektiivse vagotoomia tulemused kaksteistsõrmiksoole haavandtõve ravis. Nõukogude Eesti Tervishoid 1973; 1: 3–7.

Turner IB, Jones M, Piper DW. Factors influencing mortality from bleeding peptic ulcers. Scand J Gastroenterol 1991; 26: 661–666.

Vaira D, Menegatti M, Miglioli M. What is the role of Helicobacter pylori in complicated ulcer disease? Gastroenterology 1997; 113: 78–84.

van Lanschot JJB, van Leerdam M, van Delden OM, Fockens P. Management of bleeding gastroduodenal ulcers. Dig Surg 2002; 19: 99–104.

van Leerdam ME, Rauws EAJ, Geraedts AAM, Tytgat GNJ. Management in peptic ulcer hemorrhage: a Dutch national inquiry. Endoscopy 2000; 32: 935–942.

van Leerdam ME, Tytgat GNJ. Review article: *Helicobacter pylori* infection in peptic ulcer haemorrhage. Aliment Pharmacol Ther 2002; 16 (Suppl 1): 66–78.

Vardja T, Peetsalu A, Peetsalu M, Soplepmann J, Tein A, Väli T. Surgical treatment of duodenal ulcer disease: A long term follow-up study. Acta Medica Baltica 1996; 3: 256–263.

Villanueva C, Balanzo J. A practical guide to the management of bleeding ulcers. Drugs 1997; 53: 389–403.

Vorobjova T, Kisand K, Haukanõmm A, Maaroos H-I, Wadström T, Uibo R: The prevalence of Helicobacter pylori antibodies in a population from southern Estonia. Eur J Gastroenterol Hepatol 1994; 6: 529–533.

Vorobjova T, Grunberg H, Oona M, Maaroos HI, Nilsson I, Wadstrom T, Covacci A, Uibo R. Seropositivity to Helicobacter pylori and CagA protein in schoolchildren of different ages living in urban and rural areas in southern Estonia. Eur J Gastroenterol Hepatol 2000; 12: 97–101.

Vreeburg EM, Levi M, Rauws EAJ, Deventer SJHV, Snel P, Bartelsman JWFM, Ten Cate JW, Tytgat GNJ. Enhanced mucosal fibrinolytic activity in gastroduodenal ulcer haemorrhae and the beneficial effect of acid suppression. Aliment Pharmacol Ther 2001; 15: 639–646.

Wara P. Incidence, diagnosis, and natural course of upper gastrointestinal hemorrhage. Prognostic value of clinical factors and endoscopy. Scand J Gastroenterol 1987; 22 (Suppl 137): 26–27.

Weil J, Langman MJS, Wainwright P, Lawson DH, Rawlins M, Logan RFA, Brown TP, Vessey MP, Murphy M, Colin-Jones DG. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 2000; 46: 27–31.

Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter non-steroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. Arch Intern Med 1994; 154: 42–46.

Williams RA, Vartany A, Davis IP, Wilson SE. Impact of endoscopic therapy on outcome of operation for bleeding peptic ulcers. Am J Surg 1993; 166: 712–715.

Wu X, Zen D, Xu S, Zhang L, Wang P. A modified surgical technique for the emergent treatment of giant ulcers concomitant with hemorrhage in the posterior wall of the duodenal bulb. Am J Surg 2002; 184: 41–44.

Zed PJ, Loewen PS, Slavik RS, Marra CA. Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers. Ann Pharmacother 2001; 35: 1528–1534.

Zittel TT, Jehle EC, Becker HD. Surgical management of peptic ulcer disease today – indication, technique and outcome. Langenbeck`s Arch Surg 2000; 385: 84–96.

SUMMARY IN ESTONIAN

Peptilise haavandi verejooks Eestis:
epidemioloogia, prognostilised faktorid, ravi ja selle tulemused

Peptilise haavandi verejooks (PHV) on haavandtõve sagedasim tüsistus. Seoses *H. pylori* infektsiooni vähenemisega on haavandtõbi viimaste aastate vältel arenenud maades vähenemas. Samal ajal PHV esinemissageduses olulist langust ei täheldata (Bloom *et al.*, 1990; Schwesinger *et al.*, 2001). Kuigi verejooksu haigete hulgas väheneb nooremate osakaal, tagab PHV esinemissageduse stabiilsuse verejooksude märkimisväärne sagenemine vanemaealiste hulgas (Bloom *et al.*, 1990; Higham *et al.*, 2002). Sellise tendentsi põhjuseks peetakse mittesteroidsete põletikuvastaste ravimite (NSAID) üha sagenevat tarvitamist (McCarthy, 1991). Patsientide vanuse tõusust tulenevalt on järjest suuremal osal PHV patsientidest rasked kaasuvad haigused.

Olemasolevad andmed PHV kohta Eestis on ärevusttekitavad. Eesti Vabariigi Sotsiaalministeeriumi andmeil tõusis PHV esinemissagedus 1993. aasta 40 juhtult 100 000 elaniku kohta aastas 77 juhuni 2001. aastal. Arenenud maades on vastav näitaja 25–65 (Panos and Walt, 1993; Cutler and Mendeloff, 1981; van Leerdam and Tytgat, 2002).

Ravitulemused on viimase kümne-viieteistkümne aasta jooksul paranenud ning suremus on paremates keskustes langenud varasemalt 10%-lt 5%-le (Zittel *et al.*, 2000) vaatamata vanematele ja raskemate kaasuvate haigustega patsientidele.

Tulemuste paranemisel on oluline osa endoskoopilise ravi arengul. Verejooksu endoskoopiline peetamine on muutunud PHV ravivõtete esmavalikuks (Lanschot *et al.*, 2002) kombinatsioonis tänapäevase antisekretoorse raviga (Cash, 2002). Mitmed randomiseeritud uuringud näitavad, et endoskoopilise raviga väheneb PHV haigetel vereülekannete ja kirurgilise ravi vajadus, langeb märkimisväärselt kordusverejooksude arv ning väheneb suremus (Lee and Leung, 1997; Gralnek *et al.*, 1998).

PHV kirurgiline ravi osakaal on küll oluliselt vähenenud (Williams *et al.*, 1993; Asaki, 2000), kuid 5–10% patsientidest vajavad seda siiski (Qvist *et al.*, 1994; Zittel *et al.*, 2000). Operatsioon on näidustatud kui (1) on tegemist raske jätkuva verejooksuga, mis ei allu algsele intensiivravile, (2) endoskoopilise ja medikamentoosse raviga ei õnnestu jätkuvat või korduvat verejooksu kontrolli alla saada ja (3) kui esineb kaasnev teine operatsiooninäidustus, perforatsioon, stenoos või maliigse protsessi kahtlus (Stabile and Stamos, 2000). Operatsiooninimeetoditest on viimasel ajal saanud valdavaks mittedefinitiivsed, haavandtõve patogeneesi mittemõjutavad meetodid nagu veritseva haavandipõhja üleõmblus ning haavandi ekstsisioon. Nende pooldajad väidavad, et operatsioonijärgne *H. pylori* eradikatsioon likvideerib haavandtõve ning selle tüsistuste taastekke võimaluse (Ohmann, 2000; Röher *et al.*, 1996). Samas pole *H. pylori* esinemis-

sagedus PHV haigetel ja selle roll PHV tekkes üheselt ja kindlalt määratud (Millat *et al.*, 2000). Ka pole *H. pylori* eradikatsiooni tulemused kaugeltki absoluutsed (Vaira *et al.*, 1997; Maaroos *et al.*, 2001). Lisaks on paljude verit-sevate haavandite tekkes juhtivaks põhjuseks NSAIDid. Nimetatud asjaolud muudavad mittedefinitiivsed operatsioonid kaugtulemuste suhtes ebakindlaks. Definitiivseid operatsioone, vagotoomiat ja maoresektsiooni teevad veel vaid mõned keskused, kus vastavad kirurgilised oskused on säilinud. Operatsioon on küll keerulisem, kuid tagab parema tulemuse varases operatsioonijärgses perioodis, tõstmata seejuures suremuse riski (Poxon *et al.*, 1991; Kubba *et al.*, 1996), ning annab paremad kaugtulemused kui mittedefinitiivne operatsioon.

Antud uurimistöö eesmärgiks oli uurida PHV epidemioloogiat, ravi ja selle tulemusi kuna Eestis pole seda seni süstemaatiliselt tehtud.

Uurimistöö eesmärgid

1. Iseloomustada PHV epidemioloogiat Tartu maakonnas, hõlmates esinemis-sagedust, patsientide vanuselist ja soolist koosseisu, soodustavaid faktoreid, *H. pylori* infektsiooni taset, haavandi asukohta ja patsientide suremust (publikatsioonid I–IV).
2. Määrata PHV haigete suremuse prognostilised faktorid (publikatsioon IV).
3. Hinnata muutusi PHV ravitaktikas viimastel aastatel. Anda hinnang en-doskoopilise ja kirurgilisele ravi rollile PHV puhul ning nende meetodite mõjule ravitulemustele (publikatsioon VII).
4. Uurida konseravtiivselt ja operatiivselt ravitud PHV haigete kaugtulemusi (publikatsioon V).
5. Selgitada Helwingi ja Herfarthi poolt gigantsete veritsevate duodeenumi tagaseina haavandite puhuks väljapakutud operatsioonimeetodite kaugtule-mused (publikatsioon VI).

Patsiendid ja uurimismeetodid

Seitsmes eraldi planeeritud uurimistöös koguti ja analüüsiti ühtekokku 1270 PHV haige andmed. Uuringugrupid on osalt kattuvad.

Esimeses, retrospektiivses pilootuuringus võrreldi endoskoopiakabineti registreerimiskaartide alusel seedetrakti ülaosa verejooksude põhjuseid ning patsientide struktuuri kahel perioodil, 1979–81 (206 patsienti) ja 1989–91 (401 patsienti).

SA Tartu Ülikooli Kliinikumi arvutiandmebaasi ja haiguslugude alusel tehtud teises, retrospektiivses uuringus analüüsiti haavandtõve tüsistuste, PHV ja peptilise haavandi perforatsiooni esinemissagedust Tartu maakonnas 15-aas-tase ajavahemiku vältel (1979–1993).

Kolmas oli prospektiivne uuring, milles võrreldi seedetrakti ülaosa verejooksude epidemioloogiat Tartu maakonnas ja Kesk-Soome piirkonnas. Analüüsiti kõigi 1.8.1992–31.7.1994 ravil viibinud 263 Tartumaa ja 263 Kesk-Soome haige andmeid.

Prospektiivselt kogutud andmed 1992–93. aastal ravitud 144 Tartumaa PHV haige kohta analüüsiti neljandas, PHV epidemioloogiat ja suremuse prognostilisi faktoreid hindavas töös. Prospektiivsetes epidemioloogilistes uuringutes oli uuringu piirkond defineeritud — Tartu maakond (Tartu linn ja Tartumaa). Esinemissagedus arvutati uute juhtudena 100 000 elaniku kohta aastas. Haigeid intervjueeriti põhjaliku küsitlusprotokolli alusel, kliinilised andmed saadi haiguslugudest. Neljandas uuringus võeti PHV haigetel *H. pylori*ga infitseerituse määramiseks mao limaskesta biopsiad (värviti Giemsa meetodil).

Viiendas, prospektiivses randomiseerimata uuringus võrreldi 1.1.1992–30.6.1994 (2,5 a.) ravil viibinud 61 opereeritud ja 102 konservatiivselt ravitud PHV haige ravi kaugtulemusi Visicki elukvaliteedi skaala alusel. Visicki elukvaliteedi skaala: Visick I — väga hea: kaebused puuduvad; Visick II — hea: vähesed, normaalset elu ja töötamist mittesegavad kaebused; Visick III — rahuldav: mõõdukad, teatud määral elutegevust ja töötamist segavad kaebused; Visick IV — halb: rasked sümptoomid või endoskoopial kindlakstehtud haavand.

Kuuenda uuringu objektiks olid kuusteist 1984–93. aastal Helwingi ja Herfarthi meetodite järgi opereeritud duodeenumi tagaseina gigantse veritseva haavandiga patsienti, kellel hinnati ravimeetodi kaugtulemusi Visicki elukvaliteedi skaala alusel. Uuritud Helwingi ja Herfarthi operatsioonimeetodid seisnevad järgmises. Helwingi meetodi korral (Figure 1, publ. VI) resetseeritakse duodenumi eessein ja vabastatakse oraalne tagasein haavandi servast. Haavandit ei ekstsideerita. Järgnevalt nihutatakse duodeenumi oraalne ots üle haavandipõhja ja anastomoseeritakse aboraalse otsaga, jättes niimoodi haavandi väljaspoole duodeenumi valendikku, s.o. haavand eksterioriseeritakse. Herfarthi meetodi korral (Figure 2, publ. VI) tehakse duodenaalhaavandit ekstsideerimata antrumektoomia. Järgnevalt nihutatakse maokönt üle haavandi põhja ja anastomoseeritakse duodeenumiga, eksterioriseerides haavandi. Mõlemal juhul tehakse lisaks vagotoomia.

Seitsmendas uuringus võrreldi 1992–93. aastal ravitud 212 PHV haige ja 1999–2000. aastal ravitud 177 PHV haige andmeid eesmärgiga hinnata endoskoopilise ja kirurgilise ravi rolli ja tulemust.

Statistiliseks andmetöötluseks sisestati andmed arvuti andmebaasidesse.

Uurimistööst tulenevad järeldused

1. Peptilise haavandi verejooks on kõige sagedasem seedetrakti ülaosa verejooksu põhjus, moodustades Tartu maakonnas, Eestis kõigist verejooksudest üle poole. Naishaiged on vanemad, on enne peptilise haavandi verejooksu

enamusel juhtudest kasutanud NSAIDe (64%) ja peamiselt on neil tegemist verejooksuga maohaavandist, võrreldes meeshaigetega, kes on nooremad, on harvem kasutanud NSAIDe (36%) ja kelle verejooksu põhjuseks on sage-damini duodenaalhaavand.

Tartu maakonnas on peptilise haavandi verejooksu esinemissagedus ala-tes 1991. aastast peaaegu kahekordistunud. Peptilise haavandi verejooksu esinemissagedus Tartu maakonnas on võrreldes arenenud maade andmetega kõrge, seda tänu tunduvalt kõrgemale esinemismäärale nooremaealise elanikkonna seas. Vanemaealistel on peptilise haavandi verejooksu esine-missagedus madalam kui arenenud maades.

H. pylori infektsioon on peptilise haavandi verejooksuga haigetel sage (89%).

2. Olulisemad suremust mõjutavad prognostilised faktorid peptilise haavandi verejooksu korral on kaasuv südamehaigus, kordusverejooks, vererõhu näit hospitaliseerimisel alla 100 mmHg, patsiendi vanus üle 65 aasta ja hemo-globiini väärtus hospitaliseerimisel alla 80 g/l.

3. Endoskoopilise injektsioonravi intensiivsem rakendamine peptilise haavandi verejooksude korral on oluliselt vähendanud kirurgilise ravi vajadust ning haigete suremust.

4. Vahelduvat ravi H_2 blokaatoritega peale peptilise haavandi verejooksu epi-soodi tuleb vältida, kuna sellel on sageli ebarahuldavad kaugtulemused (retsidiivhaavandid, korduvad verejooksud).

Definitiivsed operatsioonimeetodid tagavad peptilise haavandi verejooksu korral valdaval enamusel head kaugtulemused.

5. Helwingi ja Herfarthi operatsioonimeetodite kasutamine gigantsete, pank-reasse penetreerunud veritsevate duodeenumi tagaseina haavandite kirurgili-ses ravis annab head kaugtulemused.

ACKNOWLEDGEMENTS

The present study was carried out at the Clinic of Surgery of Tartu University Clinics.

I would like to express my sincere gratitude to:

PUBLICATIONS

ENDOSCOPIC FINDINGS IN UPPER GASTROINTESTINAL TRACT HEMORRHAGE IN TARTU UNIVERSITY SURGICAL CLINIC: COMPARISON OF TWO PERIODS, 1979-81 AND 1989-91.

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The incidence of upper gastrointestinal hemorrhage (UGIH) is 50-160 per 100 000 inhabitants [1, 2, 3].

Peptic ulcer, gastritis, esophageal varices and Mallory-Weiss syndrome are responsible for 64-80% of UGIH [4, 5, 6].

Though elective ulcer surgery has dramatically declined in the past 15 years [7, 8], the admission rate [9, 10] and emergency surgery [7, 11] for peptic ulcer bleeding has not decreased.

Non-steroidal anti-inflammatory drugs (NSAID) are often considered to be responsible for hemorrhagic gastritis and ulcer formation [12, 13]. People using these drugs are put to a higher risk of gastrointestinal bleeding [14, 15]. Consumption of NSAID is increasing in the whole world, especially in the elderly [16, 17] and probably due to this there has been a major change in the age structure of UGIH. The percentage of the elderly has significantly risen in hemorrhage patients [1, 18].

Mortality rate of UGIH ranges from 3,7 to 11,8% [19, 20].

These data show that UGIH remains a challenging problem for surgical departments.

During more than two decades of development and extensive spread, endoscopy has shown its exactness and usefulness in diagnosing and treating UGIH. It is essential for the accurate diagnosis of the cause of hemorrhage and its localisation.

The main causes of hemorrhage according to esophagogastroduodenoscopy are depicted in Table 1.

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Table 1

Causes of UGIH according to endoscopy.

%	Villar et al. 1977	Peetsalu A. et al. 1987	Allum W.H. et al. 1990
Duodenal ulcer	26,0	24,9	34,6
Gastric ulcer	10,4	27,0	18,7
Gastritis	18,2	15,7	
Esophageal varices	15,1	6,3	6,3
Mallory – Weiss s.	7,8	5,8	5,0
Esophagitis	3,6		9,1
Gastric tumor	3,6	8,1	2,7
Miscellaneous	7,8	5,5	14,1
No diagnose	7,3	6,8	9,5

The aim of our study was to assess the possible alterations of UGIH in the light of the epidemiological changes in the world, enhanced NSAID consumption and changes in the Estonian society during the last years.

PATIENTS AND METHODS

Esophagogastroduodenoscopic investigation of UGIH in Tartu University Clinic began in 1978. Since then all patients with UGIH (excluding a small number of those with very poor general condition, patients operated urgently after admission due to severe bleeding and those refusing endoscopy) were examined endoscopically. Majority of the investigations were performed within 12 hours after the admission, all within 48 hours.

Fiberoptic instruments that have been used are the following: GIF-D3, TYF-2D, GIF-K, ACMI, PUTSCHOK.

Every result of endoscopy is recorded on a special card.

We analysed all the cards of two separate periods - 1979-81 (I period) and 1989-91 (II period) in order to study the cause, sex and age distribution of UGIH and changes in these variables.

206 patients (148 male and 58 female) were investigated in I period and 401 (273 male and 127 female) in II period.

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In the study of the causes of UGIH all pyloric and prepyloric ulcers were classified into the duodenal ulcer group. Erosions, acute ulcerations and intramucosal bleeding spots of stomach were classified as gastropathy according to Z. Maratka et al. The group "miscellaneous" consists of the causes of bleeding with less than 2% occurrence (duodenopathy, stomal peptic ulcer, esophageal cancer, gastric hemangioma, duodenal tumors, chemical corrosion of esophagus, pancreatic cancer infiltrating duodenal wall etc.). In some cases endoscopy didn't reveal a lesion responsible for the bleeding - classified as "no diagnose".

As the study includes all the endoscopic records of UGIH patients, not only of those coming from Tartu and Tartu region, but also of other parts of southern Estonia, it doesn't reveal the incidence .

RESULTS

During I period (1979-81) 206 patients and during II period (1989-91) 401 patients with UGIH were examined endoscopically.

Figure 1 depicts the causal distribution of UGIH in both periods.
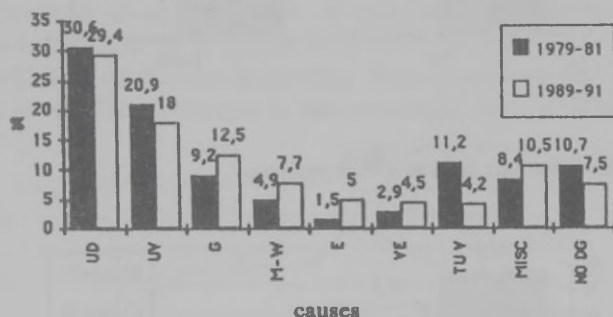
Fig.1. Causes of bleeding according to endoscopy (UD - duodenal ulcer, UV – gastric ulcer, G - gastropathy, M-W - Mallory-Weiss syndrome, E – esophagitis, VE - esophageal varices, TU V - gastric tumor, MISC – miscellaneous, NO DG - no diagnose)

Duodenal ulcer, gastric ulcer and gastropathy are responsible respectively for approximately 30, 20 and 10% of all the bleedings. I and II period don't differ significantly in any of the causes of hemorrhage. The rate of miscellaneous causes and "no diagnose" group hasn't changed either.

Figure 2 compares UGIH sex rates.

The overall sex rates indicate a nearly 2:1 relation, with 71,8% men and 28,2% women in I period and 68,2% versus 31,8% in II period. There is no significant difference between the two periods (Fig. 2a.).

In the duodenal ulcer hemorrhage group the percentage of male patients has decreased from 77,8% to 65,3% and there is a respective increase of female patients from 22,2% to 34,7% (Fig. 2b.). However, the change is not statistically significant. There is an analogical situation in the gastric ulcer hemorrhage group (Fig. 2c.). In both these groups the male to female ratio is approximately 2:1 in II period.

In gastropathy patients the male to female ratio is 3:1 with no remarkable change.
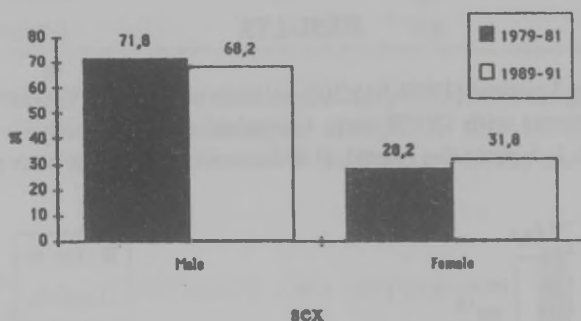
Fig. 2a. Total sex ratio in UGIH patients
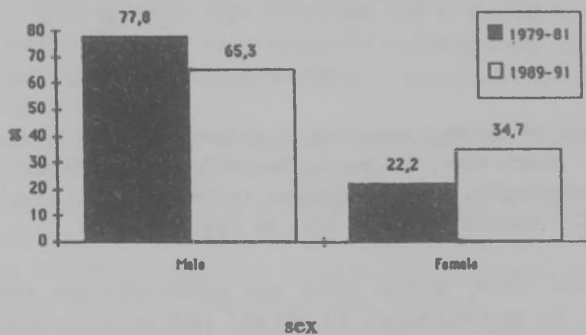
Fig. 2b. Sex ratio in duodenal ulcer hemorrhage patients

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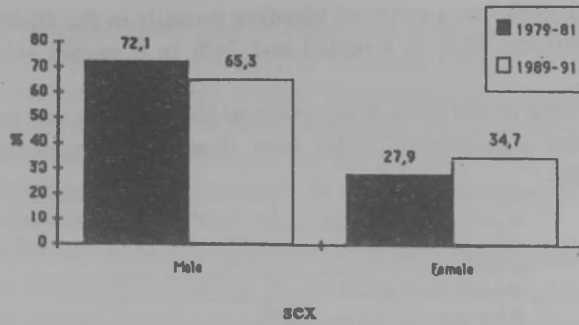
Fig. 2c. Sex ratio in gastric ulcer hemorrhage patients

The sex rates of the "no diagnose" group don't differ significantly through the two periods. The same can be said about bleeding from gastric malignancies, the male:female ratio being 1:1 in II period.

Male patients predominate in Mallory - Weiss tear group. The relation 9:1 has not changed during the ten years.

The age structure of the three main causes of UGIH during the two periods is represented in Figure 3.

Duodenal ulcer occurrence is relatively equal through the age groups in I period. In II period there is a rise in the age group 50-69 years (42% of all the bleedings) (Fig. 3a.). Comparing the two periods shows no significant changes in the occurrence rates of different ages.
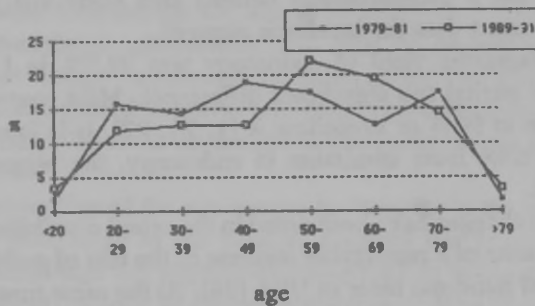
Fig. 3a. Age and duodenal ulcer hemorrhage

The incidence of gastric ulcer hemorrhage rises with the age in both periods. Patients over 60 years constitute 51% of all the cases in I period and 58% in II period (Fig. 3b.).

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Gastropathy as a cause of bleeding prevails in the 40-69 years old in both periods, 69% in I period and 74% in II period belong to this group.

Collation of the three main causes of UGIH shows that gastric ulcer patients are significantly older than those with duodenal ulcer or gastropathy.
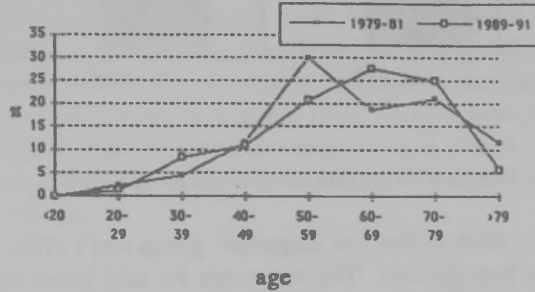
Fig. 3b. Age and gastric ulcer hemorrhage

DISCUSSION

The absolute number of UGIH patients examined endoscopically has increased twofold in a decade in Tartu University Surgical Clinic. A remarkable rise in the incidence of UGIH could be suspected, but this research is not a geographically defined area study and so does not provide the exact data for incidence changes.

The diagnostic yield of endoscopy was 89,3% in I period and 92,5% in II period (no significant difference). Most centres report of results close to 90% or exceeding it [1, 21, 22]. It is known that the shorter the time from admission to endoscopy, the bigger the information [23].

Certain changes have been noted in the causal distribution of UGIH _ Kurata reports of a remarkable increase of the rate of gastric ulcer and a decrease of duodenal ulcer in USA [24]. At the same time the overall rates of hemorrhage have not changed in the United Kingdom [25] and a Finland study shows a decrease of gastric ulcer and increase of duodenal ulcer hemorrhage [26]. These variations are suspected to be related to geographical and life-style determined differences [18]. However in most works peptic ulcer is claimed to be the reason of UGIH in about 50% of the cases [3, 9, 19].

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Our analysis shows also that duodenal ulcer and gastric ulcer have been the main causes of UGIH in southern Estonia through the last decade, with no remarkable change. They contribute respectively 30 and 20% so alltogether a half of all the bleedings. These two lesions together with gastropathy and esophageal varices (up to 15% of all cases) seem to be predominating in the world. In our study esophageal varices are the source of bleeding in less than 5% of cases.

There is a 7% decline in the rate of gastric malignancies. That may be due to diagnosing of earlier stages of tumors the last years. The rate of gastric cancer bleeding is yet somewhat higher than found by others [2, 26, 22].

The sex distribution of UGIH patients didn't change significantly neither in the overall rates nor in the rates of the main causes of UGIH. Various rates of male predominance are seen in every cause of UGIH. The overall male to female ratio is 2:1.

In peptic ulcer hemorrhage there is a trend, yet not significant, of changing sex proportions towards the increase of female rate, especially in duodenal ulcer, where the male to female ratio changed from 3,5:1 to 2:1 in ten years. In gastric ulcer the change is from 2,5:1 to 2:1. Works on peptic ulcer show that in uncomplicated cases the ratio is similar [18, 25] to the one found by us in II period. A Norwegean study shows a reversed male:female ratio - 0,7:1 [27]. Maybe, the character of the disease is changing, the social roles of sexes are changing, women are consuming more NSAID etc. This may have a certain impact on peptic ulcer hemorrhage sex ratio.

In hemorrhagic gastropathy the male to female ratio had an unsignificant change - a decrease of male rate by 5%. Mallory - Weiss tear is generally related to previous alcohol consumption, so mostly men are in risk here. There is no change in this group in our material with a ratio 9:1.

The proportion of the age groups is changing in the world the last years. The percentage of the elderly, admitted due to peptic ulcer or gastritis hemorrhage has significantly increased in both sexes [18, 25]. This is evidently related to changing patterns of NSAID use. And not that the gastrointestinal mucosa of the elderly is more prone to the damage caused by NSAID [13], but the elderly are consuming these drugs remarkabely more than years ago.

Our study shows that the over 60 years age group has increased by 5% (from 32% to 37%) in duodenal ulcer and 7% (from 51% to 58%) in gastric ulcer patients during 10 years. However, the change is not

significant. No change has occurred in gastropathy, where the >60 patients made up 37% in 1979-81 and 38% in 1989-91. It is evident that gastric ulcer hemorrhage occurs relatively more often in the older age than duodenal ulcer or gastropathy bleeding.
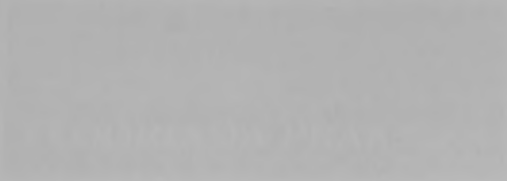
As a conclusion we can say, that there has been no major change in the cause, sex and age distribution of UGIH patients in Tartu University Surgical Clinic during the past 10 years, but certain minor changes show the similar trends as described in the world literature.

REFERENCES

1. Gilbert D.A. Epidemiology of upper gastrointestinal bleeding. Gastrointestinal Endoscopy. 1990; 36: 8-13

2. Henriksson A.E., Svensson J.-O. Upper gastrointestinal bleeding with special reference to blood transfusion. Eur. J. Surg. 1991; 157: 193-6

3. Wara P. Incidence, diagnosis, and natural course of upper gastrointestinal hemorrhage. Prognostic value of clinical factors and endoscopy. Scand. J. Gastroenterol. 1987; 22 (Suppl. 137): 26-7

4. Villar H.V., Roberts Fender H., Watson L.C., Thompson J.C. Emergency diagnosis of upper gastrointestinal bleeding by fiberoptic endoscopy. Ann. Surg. 1977; 185: 367-74

5. Пээтсалу А.Я., Вяли Т., Пооме М.Э. Экстренная эндоскопия при кровотечениях из верхних отделов желудочно-кишечнего тракта. Acta et commentationes Universitatis Tartuensis. 1987; 790: 37–41

6. Allum W.H., Brearley S., Wheatley K.E., Dykes P.W., Keighley M.R.B. Acute hemorrhage from gastric malignancy. Br. J. Surg. 1990; 77: 19-20

7. Paimela H., Tuompo P.K., Peräkylä T., Şaario I., Höckerstedt K., Kivilaakso E. Peptic ulcer surgery during the H_2 -receptor antagonist era: a population - based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987. Br. J. Surg. 1991; 78: 28-31

8. Cuttat J.F., Ruchat P., Chapuis G. La maladie ulcereuse gastro-duodenale: que reste t il des indications chirurgicales? Schweiz. Med. Wochenschr. 1989; 119: 729-30

9.   **Peetsalu A., Vardja T., Peetsalu M., Väli T., Lumiste R.**
     Peptilise haavandi verejooksud ja perforatsioonid. Eesti NSV
     gastroenteroloogide I kongressi materjalid. 1989: 19-21
10. **Gustavsson S., Kelly K.A., Melton L.J., Zinsmeister A.R.**
     Trends in peptic ulcer surgery. A population - based study in
     Rochester, Minnesota, 1956-85. Gastroenterology. 1988; 94: 688-
     94
11. **Herrington J.L., Davidson J.** Bleeding gastroduodenal ulcers:
     choice of operations. World J. Surg. 1987; 11: 304-14
12. **Aabakken L.** NSAIDs and the gastrointestinal tract - case closed?
     Scand. J. Gastroenterol. 1991; 26: 801-5
13. **Moore J.G., Bjorkman D.J., Mitchell M.D., Avots-Avotins A.**
     Age does not influence acute aspirin - induced gastric mucosal
     damage. Gastroenterology. 1991; 100: 1026-9
14. **Laporte J.-R., Carné X., Vidal X., Moreno Y., Juan J.** Upper
     gastrointestinal bleeding in relation to previous use of analgesics
     and non - steroidal anti - inflammatory drugs. Lancet. 1991; 337:
     85-9
15. **Holvoet J., Terriere L., Van Hee W., Verbist L., Fierens E.,
     Hautekeete M.L.** Relation of upper gastrointestinal bleeding to
     non - steroidal anti - inflammatory drugs and aspirin: a case -
     control study. Gut. 1991; 32: 730-4
16. **Papp J.P.** Management of upper gastrointestinal bleeding. Clin.
     Geriatr. Med. 1991; 7: 255-64
17. **Martio J., Jukka E., Isomäki H.** Ulkustauti ja tulehduskipulääk-
     keet. Suomen Lääkärilehti. 1991; 27: 2493–5
18. **Bardhan K.D., Cust G., Hinchliffe R.F.C., Williamson F.M.,
     Lyon C., Bose K.** Changing pattern of admissions and operations
     for duodenal ulcer. Br. J. Surg. 1989; 76:230-6
19. **Holman R.A.E., Davis M., Gough K.R., Gartell P., Britton
     D.C., Smith R.B.** Value of centralised approach in the
     management of haematemesis and melaena: experience in a district
     general hospital. Gut. 1990; 31: 504-8
20. **Clason A.E., Macleod D.A.D., Elton R.A.** Clinical factors in the
     prediction of further haemorrhage or mortality in acute upper
     gastrointestinal haemorrhage. Br. J. Surg. 1986; 73: 985-7
21. **Sanderson J.D., Taylor R.F.H., Pugh S., Vicary F.R.**
     Specialized gastrointestinal units for the management of upper
     gastrointestinal haemorrhage. Postgrad. Med. J. 1990; 66:654-6

24

22. **Mäkelä J., Haukipuro K., Laitinen S., Kairaluoma M.I.** Endoscopy for the diagnosis of acute upper gastrointestinal bleeding. Scand. J. Gastroenterol. 1991; 26: 1082-8

23. **Forrest J.A.H., Finlayson N.D.C., Shearman D.J.C.** Endoscopy in gastrointestinal bleeding. Lancet. 1974; 2: 394-7

24. **Kurata J.H., Honda G.D., Frankl H.** Hospitalisation and mortality rates for peptic ulcers: a comparison of a large health maintenance organisation and United States data. Gastroenterology. 1982; 83: 1008-16

25. **Bloom B.S., Fendrick A.M., Ramsey S.D.** Changes in peptic ulcer and gastritis/duodenitis in Great Britain, 1970-1985. J. Clin. Gastroenterol. 1990; 12: 100-8

26. **Leivonen M., Kivilaakso E.** Peptic ulcer bleeding today: risk factors and characteristics of the disease. Scand. J. Gastroenterol. 1991; 26: 1013-9

27. **Bernersen B., Johnsen R., Straume B., Burhol P.G., Jenssen T.G., Stakkevold P.A.** Towards a true prevalence of peptic ulcer: the Sørreisa gastrointestinal disorder study. Gut. 1990; 31: 989-92

4

Vardja T, Peetsalu M, Soplepmann J, Peetsalu A.
Natural history, results of surgery and the costs of treatment
of duodenal ulcer disease. Estonian Physician 1995; 2: 113–116
(in Estonian, summary in English).

TEOORIA JA PRAKTIKA

Kaksteistsõrmiku-haavandtõve kulg, kirurgilise ravi tulemused ja ravi hind

Tõnis Vardja   Margot Peetsalu
Jaan Soplepmann   Ants Peetsalu

kaksteistsõrmikuhaavandtõbi, kirurgilise ravi tulemused, ravi hind

Kaksteistsõrmikuhaavandtõbi on krooniline haigus, millel on kalduvus retsidiveeruda aastakümnete jooksul ja seda ka pärast medikamentoosset ravi H2—retseptorite blokaatoritega (H2RB) (4). Samuti on seda haigust põdejail risk verejooksu, perforatsiooni ja püloroduodenaalse stenoosi tekkeks (8).

Nende haigete pikaajaline ravi ja ravi taktika ei ole siiani lõplikult lahendatud, sest haiguse kulg on individuaalne ja seda on raske ennustada. Kaksteistsõrmikuhaavandtõve laadi on muutnud ka tänapäevane ravi H2RB—ga ja tänapäevane kirurgiline ravi (4,8). Selle haiguse ravis tulevad arvesse järgmised peamised võimalused: vahelduv või säilitav ravi H2RB—ga, ravi prootonpumba blokaatoritega, *Helicobacter pylori* kolmikravi ja kirurgiline ravi (eeskätt elunditsäilitavad operatsioonid — vagotoomia ilma või koos drenaažoperatsiooniga). Üldjuhul on medikamentoosne ravi valitud tüsistumata ja kirurgiline ravi tüsistunud kaksteistsõrmikuhaavandi korral. Selline taktika ei ole absoluutne (näiteks kirurgiline ravi tüsistuste ennetamiseks). Enam tähele-

Tõnis Vardja, Margot Peetsalu, Jaan Soplepmann, Ants Peetsalu — Tartu Ülikooli Kirurgiakliinik

panu pööratakse ka ravi majanduslikule aspektile, s.t. missugune ravi ja millal tuleb see ühiskonnale odavam (9). Uurimistöö eesmärk oli selgitada kaksteistsõrmikuhaavandtõve laadi ja kulgu Tartu piirkonna haigeil, kirurgilise ravi tulemusi ja ravi hinda.
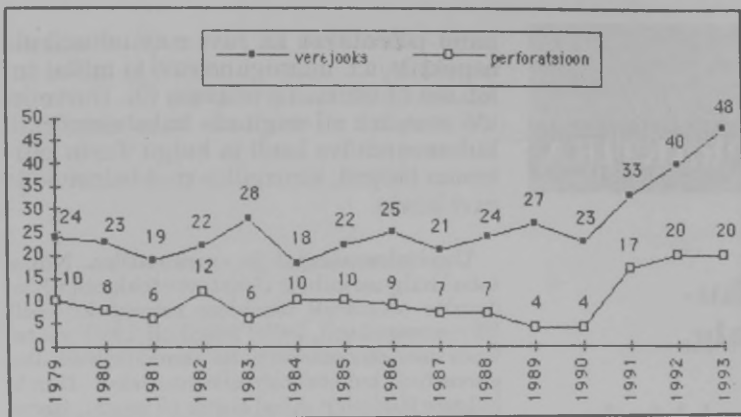
Uurimismaterjal ja –metoodika. Nimetatud haiguse kuluja tüsistuste tekkimise hindamise eesmärgil uurisime retrospektiivselt 54 meespatsienti, kellel kõigil oli 1979. aastal ühes endoskoopiakabinetis esmakordselt diagnoositud kaksteistsõrmikuhaavand. Nende haigete jälgimisperiood kestis 10 aastat. Kasutasime Tartu polikliiniku ambulatoorsete kaartide andmeid, 16 küsimusest koosneva ankeetküsitluse ja ambulatoorse vestluse vastuseid ning patsiendi nõusolekul 1989. aastal tehtud panendoskoopia tulemusi.

Peptiliste haavandite verejooksude ja perforatsioonide esinemist Tartu linnas ja maakonnas uurisime Tartu Kliinilises Haiglas ravil viibinud haigete haiguslugude alusel kahel perioodil: aastail 1979—1988 oli 356 peptilise haavandi verejooksuga ja 132 haavandi perforatsiooniga haiget, aastail 1990—1993 olid need arvud vastavalt 144 ja 57.

Kirurgilise ravi tulemuste hindamiseks kasutasime 482 kroonilist kaksteistsõrmikuhaavandtõbe põdeja prospektiivse uuringu andmeid, kellel oli ajavahemikul 1977—1984 Tartus tehtud elunditsäilitav või elunditsäästev operatsioon (vagotoomia ilma või koos drenaažoperatsiooniga või vagotoomia koos antrumektoomiaga). Operatsiooni näidustuseks oli 69%-l kaksteistsõrmikuhaavandi tüsistus ja 31%-l mitteefektiivne medikamentoosne ravi. Järeluuringud (spetsiaalne küsimustik, vestlus, panendoskoopia, happesekretsiooni uuringud) tegime 418 haigel (87%-l) 5—12 aastat, keskmiselt 8 aastat pärast operatsiooni. Tulemusi hindasime Visicki skaala järgi: Visick I — väga hea: kaebusteta; Visick II — hea: kerged, mitteolulised vaevused; Visick III — rahuldav: kerged või keskmised vaevused, mis põhjustavad enesetunde halvenemise või töövõime häire; Visick IV — halb tulemus: rasked vaevused või retsidiivhaavand.

Kaksteistsõrmikuhaavandtõve ravi hinna arvutamisel lähtusime EV Sotsiaalministeeriumi määrusest nr. 5 11. märtsist 1993 ja nr. 53 5. septembrist 1994 "Ravikindlustuse terviseuuringute ja raviteenuste hinnakiri". Medikamentoosse ravi hinna selgitamisel võtsime aluseks firma TAMDA pakutava ranitidiini preparaadi *Ranisan*'i hulgimüügihinna, mille järgi 150 mg–se tableti hind on 1,4 krooni. Kirurgilise ravi hinna arvestamiseks hindasime

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legend: verejooks — perforatsioon

50
45
40
35
30
25 24   23   22   22   25   24   27   23
20   19   18   21   17   20   20
15 10   12
10   8   6   6   10   10   9   7   7
5   4   4
0
1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993

(values above line near right: 28, 33, 40, 48)

Joonis. Peptilise haavandi verejooksu ja perforatsiooni esinemissagedus Tartu piirkonnas aastail 1979—1993 (100 000 inimese kohta).

aastail 1992—1993 Tartu Ülikooli Kirurgiakliinikus plaanilises korras kaksteistsõrmikuhaavandtõve tõttu opereeritud (vagotoomia koos drenaažoperatsiooniga) 31 haige ravil viibimist. Patsiendid viibisid statsionaaris kokku keskmiselt 17 voodipäeva, nendest 6 päeva enne ja 11 pärast operatsiooni (4 päeva intensiivravipalatis).

Uurimistulemused. 10 aasta jooksul õnnestus meil kaksteistsõrmikuhaavandtõve kulgu uurida 54 meespatsiendist 43 patsiendil. Jälgimisperioodil suri kolm haiget: üks kusepõievähki, üks maksavähki ja üks teadmata põhjusel. Andmeid ei õnnestunud saada 8 haige kohta. Selgus, et kaksteistsõrmikuhaavandtõbi oli tüsistunud 16 juhul (37%–l). 10–l oli tekkinud stenoos (23%–l), kolmel verejooks (7%–l) ja ühel penetratsioon (2%–l). Kahel haigel (5%–l) esines üheaegselt kaks tüsistust — stenoos ja penetratsioon. 27 juhul (63%–l) tüsistusi ei tekkinud. Jälgimisperioodil opereeriti 17 haiget (40%), kellest 12–l oli operatsiooni näidustuseks kaksteistsõrmikuhaavandtõve tüsistus ja 5–l mitteefektiivne medikamentoosne ravi. Kõigil 17 opereeritul oli haavandtõbi agressiivset tüüpi ja põhjustas elukvaliteedi langust (haiguse sage retsidiveerumine, vajadus kasutada perioodiliselt või regulaarselt ravimeid, korduv viibimine haiglas medikamentoossel ravil, vajadus muuta töötingimusi või elukutset), mis oli samuti operatsiooni näidustuseks. Opereerimata 26 juhust esines neljal samuti kaksteistsõrmikuhaavandtõve tüsistus

(kahel stenoos, kahel verejooks) ja seitsmel juhul oli haigus seotud elukvaliteedi langusega.

Peptilise haavandi verejooksu ja perforatsiooni esinemissageduse analüüs Tartu linnas ja maakonnas 100 000 täiskasvanu kohta näitas, et mõlema tüsistuse esinemissagedus aastail 1979—1990 kõikus suhteliselt vähe (vt. joonis). Verejooksu puhul oli see 18—28 ja perforatsiooni puhul 4—12 juhtu aastas. Kaksteistsõrmikuhaavandtõbi moodustas verejooksujuhtudest 55% ja perforatsioonidest 92%. Mõlema tüsistuse esinemissageduse märgatav suurenemine algas 1991. aastal ja saavutas 1993. aastaks taseme, mil verejooksu esines 48 ja perforatsioone 20 juhtu aastas.

482 haige kirurgilise ravi analüüs näitas, et operatsioonijärgne letaalsus oli 0,8% (4 surmajuhtu). Kõigil neljal juhul oli haavandtõbi tüsistunud ja kolmel oli operatsioon erakorraline. Operatsiooniga seotud tüsistusi esines 42 haigel (8,7%–l), neist 30–l oli kaksteistsõrmikuhaavandtõbi tüsistunud ja 12–l tüsistumata. Hilistulemustest moodustasid väga head ja head tulemused 90% (378 418–st), rahuldavad 3% (12 418–st) ja halvad 7% (28 418–st). Kõikide halbade tulemuste põhjuseks olid retsidiivhaavandid, millest 4 (14%) olid asümptomaatilised.

Vahelduva medikamentoosse ravi ühe ravikuuri hind oli 213 ja ühe aasta säilitava ravi hind 640 krooni (vt. tabel 1). Kirurgilise ravi hind oli 6181 krooni (vt. ta-

Uuring/raviteenus	Vahelduva ravi 1 kuuri (300 mg Ranisan'i 30 päeva) hind (kr.)	Säilitava ravi (Ranisan'i 150 mg päevas) 1 aasta hind (kr.)
Esmane arsti konsultatsioon	19.—	19.—
Panendoskoopia	100.—	100.—
Ranisan	84.—	511.—
Korduv arsti konsultatsioon	10.—	10.—
Hind kokku	213.—	640.—

Tabel 2. Kirurgilise ravi hind

Uuring/raviteenus	Hind (kr.)
Esmane kirurgi konsultatsioon	19.—
Panendoskoopia	100.—
Mao happesekretsiooni test	20.—
Rindkere röntgenoskoopia	40.—
EKG	20.—
VI kategooria operatsioon	3200.—
Anesteesia	1000.—
Intensiivravipäevad, 4 päeva á 250.—	1000.—
Kirurgiaosakonna ravipäevad, 6 päeva á 74.—	444.—
Pikaravipäevad, 7 päeva á 44.—	308.—
Operatsioonijärgsed korduvad kirurgi konsultatsioonid 1., 3., 5. aastal, 3 päeva á 10.—	30.—
Hind kokku	6181.—

bel 2). Kirurgilise ja medikamentoosse ravi hinna võrdlemine näitas, et kirurgilise ravi hind on võrdne 29 vahelduva ravikuuri või 9,7 aasta säilitava ravi hinnaga.

Arutelu. Kaksteistsõrmikuhaavandtõbi on jätkuvalt probleemiks ka tänapäeval (3), sest umbes 10% lääneriikide elanikkonnast haigestub mingil eluperioodil peptilisse haavandtõvesse (4). Haavandi retsidiivi tekkimise risk nendel haigetel aga on suur: ühe aasta jooksul pärast haavandi paranemist tekib vähemalt üks retsidiiv 80%-l haigetest ja viie aasta jooksul praktiliselt kõigil (8).

54 mehe kaksteistsõrmikuhaavandtõve kulu jälgimisel aastail 1979—1988 selgus, et kõige sagedam tüsistus oli püloroduodenaalstenoos (27%-l), mille esinemissagedus on suurem kirjanduse andmetel

esinevast 11%-st (8). Samuti viitavad kirjanduse andmed stenoosijuhtude vähenemisele, põhjendades seda tänapäevase efektiivsema medikamentoosse raviga (7). Meie patsientidel aga ei olnud sel perioodil H2RB-ravi kättesaadav, mis võiks seletada sellist stenoosijuhtude esinemist. 10 aasta jooksul opereeriti 40% uurituist. Operatsiooni põhjuseks oli 70%-l kaksteistsõrmikuhaavandtõve tüsistus ja 30%-l mitteefektiivne medikamentoosne ravi. Kõigil opereerituil oli enne operatsiooni tegemist elukvaliteedi langusega.

Elukvaliteedi hindamist, kuigi see on subjektiivne ja ei ole täpselt standardiseeritud (2), peetakse krooniliste haiguste, ravi tulemuste ja ravi ökonoomsuse aspektist oluliseks näitajaks (2, 6). Opereerimata 27 haigest oli neljal kaksteistsõrmikuhaavandtõve tüsistus ja seitsmel elukvaliteedi langus. Arvatavasti oleks ka nende puhul arvesse tulnud kirurgiline ravi.

Kirjanduse andmed kinnitavad, et oluliselt ei ole muutunud peptilise haavandi verejooksude ega perforatsioonide esinemissagedus, seda vaatamata H2RB kasutamisele (7). Andmed on ka nende tüsistuste sagenemise kohta ja seda eeskätt vanematel inimestel (üle 65-aastastel) ja mittesteroidsete põletikuvastaste ravimite kasutajatel (3, 4, 5). Tartu piirkonna elanike analüüs näitas, et peptilise haavandi verejooksude ja perforatsioonide esinemissagedus püsis suhteliselt stabiilsena aastail 1979—1990. 1991. aastast alates aga ilmnes mõlema tüsistuse aastase esinemissageduse selge suurenemistendents. Ka meie andmeil oli verejooks sageli (45%-l) seotud mittesteroidsete põletikuvastaste ravimite kasutamisega, seda eeskätt vanematel naistel (10).

Kirurgiline ravi (elunditsäilitavad operatsioonid) on mõjutanud kaksteistsõrmikuhaavandtõve kulgu ja laadi. Pärast suurte kogemustega kirurgide operatsioone oli retsidiivhaavandeid 10 aasta kohta umbes 10%, samas kui pärast H2RB-ravi oli retsidiivhaavandite arv 18 kuu järel umbes 100% (4). Samuti on pärast kirurgilist ravi retsidiivhaavand parema iseloomuga, retsidiveerub harvem ning võib

olla ka sümptoomideta, on paremini me-
dikamentidega ravitav ja võib mitte kor-
duda (1).

Uurimistulemuste alusel olid elundit-
säästvad operatsioonid ohutud (operat-
sioonijärgne letaalsus oli 0,8%). Keskmi-
selt 8 aastat pärast operatsiooni moodus-
tasid väga head ja head tulemused 90%.
Probleemiks on retsidiivhaavand, kuid
nende arv, 6,7% kõigist kontrollitud hai-
getest ja 8% endoskopeeritutest, on suhte-
liselt väike. Elukvaliteet aga oli langenud
40–l (12–l Visick III ja 28 retsidiivhaavan-
diga patsiendil) ehk 10%–l.

A. Sonnebergi andmeil on USA–s kaks-
teistsõrmikuhaavandtõve ravi hinna as-
pektist kõige tasuvam säilitav H2RB–ravi
(9), sest kirurgiline ravi (proksimaalne
vagotoomia) on kallis oma alghinna tõttu
ja see muutub odavamaks, kui vahelduv
või säilitav ravi on kestnud vastavalt 29
ja 32 aastat. Saksamaal aga on kirurgili-
ne ravi odavam juhul, kui säilitav ravi on
kestnud 6 aastat. Arvestades Eestis toi-
muvaid suuri muutusi arstiabis, kajastab
ravi hind vaid hetkeseisu ja see võib lähi-
tulevikus oluliselt muutuda. Medikamen-
toosse ravi hinna arvutamiseks valisime
H2RB–ravi hinna, sest need ravimid on
praegu kättesaadavad. Ravi prootonpum-
ba blokaatoritega on kallis ravimi kõrge
hinna tõttu ja Helicobacter pylori kolmik-
ravi ei ole leidnud laialdast kasutamist
puuduliku diagnoosimise ja mitte alati si-
hipärase ravitaktika tõttu.

Meie tulemused näitavad, et kirurgiline
ravi on odavam, kui säilitav ravi on kest-
nud 9,7 aastat. Kirurgilise ravi hinda
oleks meil võimalik vähendada operat-
sioonieelse perioodi lühendamise teel.
Enamik operatsioonieelseid uuringuid ja
vajaduse korral medikamentoosset ravi
(haavandipiirkonnas lokaalset turset vä-
hendav ja sellega opereerimist tehniliselt
kergendav) on võimalik teha ambulatoor-
selt.

Ravimeetodi valik iga kaksteistsõrmi-
kuhaavandtõve põdeja korral on indivi-
duaalne. Nõustume taani kirurgi A. Am-
drupi öelduga, et haige ei ihalda gastro-
enteroloogi, kes kunagi ei soovita
operatsiooni, ega kirurgi, kes soovitab
seda alati.

Järeldused.
1. Tartus ajavahemikul 1979—1988
uurituist tüsistus kaksteistsõrmikuhaa-
vandtõbi 37%–l, sagedam tüsistus oli pü-
loroduodenaalstenoos. Opereeriti 40%
haigeist. Nende kõigi puhul oli tegemist
elukvaliteedi langusega enne operatsioo-
ni.
2. 1990–ndatel aastatel oli Tartu piir-
konnas elavate inimeste peptiliste haa-
vandite verejooksude ja perforatsioonide
esinemissagedus aastas suurenemisten-
dentsiga võrreldes 1980–ndate aastatega.
Verejooks on sageli seotud mittesteroidse-
te põletikuvastaste ravimite kasutamise-
ga.
3. Elunditsäilitavad operatsioonid
kaksteistsõrmikuhaavandtõve ravis on
ohutud ja heade hilistulemustega, taga-
des 90%–le hea elukvaliteedi.
4. Kirurgilise ravi hind on võrdne 9,7
aasta säilitava H2RB–ravi hinnaga.

KIRJANDUS: 1. *Byrne, D. J., Brock, B. M., Mor-
gan, A. G. a.o.* Br. J. Surg., 1988, 75, 869—872. —
2. *Fraser, S. C. A.* Br. J. Surg., 1993, 80, 163—169.
— 3. *Jibril, J. A., Redpath, A., Macintyre, I. M. C.*
Br. J. Surg., 1994, 81, 87—89. — 4. *Johnson, A. G.*
Br. J. Surg., 1994, 81, 161—163. — 5. *McQuaid, K.
R., Isenberg, J. I.* Surg. J. Clin. North Am., 1992, 72,
285—316. — 6. *O'Boyle, C. A.* Br. J. Surg., 1992, 79,
395—398. — 7. *Paimela, H., Tuompo, P. K., Peräky-
lä, T. a.o.* Br. J. Surg., 1991, 78, 28—31. — 8. *Pens-
ton, J. G.* Scand. J. Gastroenterol., 1990, 25, 1—7.
— 9. *Sonneberg, A.* Gastroenterology, 1989, 96,
1445—1452. — 10. *Soplepmann, J., Peetsalu, M.,
Väli, T., Tein, A., Peetsalu, A.* In: The Joint Spring
Meeting of the Estonian Surgical Society and the
Finnish Surgical Society. Kirurgiayhdistyksen koti-
mainen julkaisusarja, 1994, 15, 42.

Summary

**Natural history, results of surgery and the
costs of treatment of duodenal ulcer disease.** In
Tartu, during the years 1979—1988 the duodenal
ulcer disease complicated in 37% of the patients stu-
died. The most frequent complication was pyloro-
duodenal stenosis. In the 1990s there is a tendency
towards a rising frequency of peptic ulcer haemor-
rhages and perforations, as compared to the 1980s.
In 482 organ preserving operations the postopera-
tive lethality was 0,8%, and complications occurred
in 8,7%. Averagely 8 years after the operation the
proportion of the excellent and good results was 90%,
satisfactory — 3%, and poor — 7%. The cost of sur-
gical treatment today is equal to that of 9,7 year
maintenance treatment.

III

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Soplepmann J, Udd M, Peetsalu A, Palmu A.
Acute upper gastrointestinal haemorrhage in Central Finland province,
Finland, and in Tartu County, Estonia. Annales Chirurgiae et Gynaecologiae 1997;
86: 222–228.

ACUTE UPPER GASTROINTESTINAL HAEMORRHAGE IN CENTRAL FINLAND PROVINCE, FINLAND, AND IN TARTU COUNTY, ESTONIA

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ABSTRACT

Background and Aims: A comparative study of the epidemiology of acute upper gastrointestinal haemorrhage (UGIH) was carried out in Central Finland province (CF), Finland, and in Tartu county (TC), Estonia.

Patients and Methods: All patients from CF and TC aged ≥ 15 who were treated in the Central Hospital of Central Finland and in Tartu University Hospital for UGIH, entered the prospective study during 1 August 1992 – 31 July 1994. Altogether 298 patients (198 men, 100 women) were treated in CF and 270 patients (159 men, 104 women) in TC.

Results and Conclusions: The overall incidence of UGIH was 68.3/100,000 adults per year in CF and 98.6 in TC. The incidence increased considerably with age: from 3.1 in those aged 20–29 to 314.1 in those ≥ 80 in CF, and from 13.2 to 299.1 in TC, respectively. Incidence rates were twice as low in younger age groups in CF compared to TC, almost equalized in those ≥ 60 and became even higher in those ≥ 80. 63 % of the patients (55 % men, 79 % women) in CF and 49 % (35 % men, 70 % women) in TC were ≥ 60. NSAID use before UGIH was equally common (46 %) in both regions. Peptic ulcer accounted for over 50 % of UGIH cases both in CF and TC. Mortality rate was 8.1 % in CF and 9.9 % in TC. The main epidemiological differences between the regions are the lower overall incidence of UGIH, due to the lower incidence of haemorrhage in the younger age groups, and the higher proportion of the elderly patients in CF compared to TC.

KEY WORDS: EPIDEMIOLOGY; INCIDENCE; MORTALITY; NONSTEROIDAL ANTI-INFLAMMATORY DRUGS; PEPTIC ULCER; UPPER GASTROINTESTINAL HAEMORRHAGE

INTRODUCTION

Upper gastrointestinal haemorrhage (UGIH) is by no way a single entity, but a number of features common for the development, clinical course, principles of diagnosing and treatment and finally also outcome risk factors have made it useful to consider different causes of bleeding together.

The incidence of UGIH is estimated at 48 to 150 per 100,000 population per year (1, 2).

Approximately half of UGIH episodes are accounted for by duodenal and gastric ulcer. Acute gastroduodenal mucosal lesions, oesophageal varices, oesophagitis and Mallory – Weiss tear are responsible for one-third of the episodes (3, 4, 5). Various minor causes of bleeding have an incidence of about

10 %; in up to 10 % of the patients no lesions can be detected by endoscopy (5, 6).

Peptic ulcer (PU) haemorrhage has been reported to rise in the elderly (7, 8). This trend could be related to the taking of NSAIDs (9). Obviously, PU bleeding, haemorrhagic and erosive gastritis are closely related to previous NSAID use (10, 11, 12, 13). There is evidence that these drugs may play a role in all types of gastrointestinal bleeding (14). NSAID consumption is increasing, especially in the elderly (15, 16), while women use these drugs more often than men (9, 17).

Mortality rates of 8–10 % for UGIH, that have not significantly changed during recent decades in most centres seem to be related to the increasing proportion of elderly patients (18).

TABLE 1

Socio-economic development and nonsteroidal anti-inflamma-
tory drug (NSAID) consumption in Finland and Estonia.

	Finland	Estonia
GNP *per capita* 1991	23 930	3 970
HDI world ranking 1992	16	29
NSAID use 1989 (DDD)	66.7	49.9

GNP = gross national product per capita per year ex-
pressed in USD
HDI = human development index
DDD = defined daily doses per 1 000 inhabitants per day

To evaluate the significance of the problem, we performed a prospective study of UGIH epidemiology in the province of Central Finland (257,000 inhabitants, 1993) and in Tartu county, Estonia (159,000 inhabitants, 1993), as no publication has until now dealt with UGIH in these regions. The study is valuable in providing comparable information about UGIH in case of kindred nations living on the opposite coasts of the Gulf of Finland. There are certain differences between the countries that could have an impact on the epidemiology of UGIH. Finland and Estonia have a similar cultural background but Finland has a six-fold higher gross national product per capita and a higher socio-economic level of development, according to the United Nations "Human Development Report 1994" (Table 1). Table 1 also contains data on NSAID consumption in the two countries, expressed by defined daily dose methodology in 1989 (19, 20).

The aim was to study the incidence of UGIH, the patient population structure, possible predisposing factors, causes of haemorrhage and mortality in the two regions.

PATIENTS AND METHODS

We assessed data on all cases of patients aged ≥ 15 years treated for acute UGIH in the Central Hospital of Central Finland, Jyväskylä, Finland, and in Tartu University Hospital, Tartu, Estonia, during 01 August 1992 – 31 July 1994. Acute UGIH was defined as melaena and/or haematemesis of ≤ 1 week duration before admission, or onset of signs of bleeding in hospital.

Only patients from the province of Central Finland and from Tartu county were included in the study. Altogether 298 patients with haemorrhage were treated in Central Finland and 263 patients in Tartu county.

The patients were questioned about previous UGIH, as well as of smoking habits, alcohol and NSAID consumption before the onset of bleeding. The final diagnosis was established by endoscopy, X-ray technique (one case in Tartu), surgery or autopsy. 96.3 % of the patients underwent endoscopy in the Central Hospital of Central Finland where the Pentax videoendoscopy system was used, and 95.1 % in Tartu University Hospital, Estonia, where Olympus fiberoptic endoscopes were employed. In 6 patients (2.0 %) in Central Finland and in 9 patients (3.4 %) in Tartu no endoscopy, operation or autopsy was performed and so the causes of UGIH were not established. These patients were included in the evaluation of incidence, patient profile and mortality but excluded from the analysis of the causes of haemorrhage.

Prepyloric and pyloric ulcers were considered in the duodenal ulcer group, haemorrhagic gastropathy and gastric mucosal erosions, in the acute gastric mucosal lesion group.

Population characteristics for Central Finland were obtained from "Population Structure 1993. Official Statistics of Finland" published by Statistics Finland, and for Tartu county from "Population Age Structure. Counties of Estonia 1990–1991" issued by the Viljandi County Statistics Bureau, Estonia. Incidence rates were calculated from the number of new UGIH cases diagnosed during one year and expressed per 100,000 population per year.

Statistical analysis of the significance of differences was performed using the chi-square test. Yates' correction was applied to approximate the chi-square test where necessary.

RESULTS

There were 298 episodes of UGIH (198 in men and 100 in women) in 270 patients in Central Finland with 23 patients (8.5 %) admitted more than once. In Tartu 243 patients were treated on 263 occasions (159 men and 104 women) with 16 patients (6.6 %) admitted more than once.

INCIDENCE

The overall incidence of UGIH per 100,000 adults per year was 68.3 in Central Finland and 98.6 in Tartu county. In Central Finland the incidence rate increased 100-fold with age, from 3.1 in patients aged 20–29 years to 314.1 in those ≥ 80 years of age, in Tartu county 23-fold, from 13.2 to 299.1, respectively. Incidence rates by sex and age are depicted in Table 2.

TABLE 2

Incidence rate of upper gastrointestinal haemorrhage by age groups per 100,000 population per year in Central Finland and in Tartu county.

Age groups	Central Finland			Tartu county		
	Total	Males	Females	Total	Males	Females
15–19	0	0	0	7.9	16.1	0
20–29	3.1	5.9	0	13.2	26.2	0
30–39	23.1	42.2	2.7	43.6	75.3	13.4
40–49	51.7	85.2	12.8	116.4	196.2	45.1
50–59	77.2	104.1	50.3	150.2	234.0	82.5
60–69	120.4	186.4	65.2	164.1	230.7	122.7
70–79	206.2	351.7	122.5	250.2	282.6	235.7
≥ 80	314.1	361.5	303.7	299.1	451.6	247.9
Total	68.3	92.3	45.4	98.6	133.4	70.3

PATIENT PROFILE

The total male to female ratio was 2:1 in Central Finland and 1.5:1 in Tartu, which showed no significant difference between the regions.

The mean age of the patients was 64.2 in Central Finland and 58.8 in Tartu. In Central Finland the proportion of the patients aged ≥ 60 was 62.7 %, which is significantly higher than 49.1 % in Tartu (*P* = 0.001). In Central Finland 79.0 % of the women and 55 % of the men were aged ≥ 60, in Tartu 70.2 % and 35.2 %, respectively. The distribution of age groups is depicted in Fig. 2.

CAUSES OF HAEMORRHAGE

A lesion responsible for bleeding was revealed on endoscopy, operation or autopsy in 90.4 % of the patients in Central Finland and in 92.9 % in Tartu. The most frequent cause of haemorrhage was PU, accounting for more than half of the total number of cases in both centres. Duodenal ulcer prevailed in both sexes in Central Finland, accounting for 31.3 % of all cases in women and for 27.0 % of cases in men. In Tartu county, gastric ulcer was more common in women (30.0 % of all cases) and duodenal ulcer in men (38.3 % of all cases). In Central Finland, PU haemorrhage was followed by oesophageal varices and oesophagitis, in Tartu, by acute gastric mucosal lesions and Mallory – Weiss tear. The distribution of the causes of UGIH is presented in Fig. 1.

PREDISPOSING FACTORS

One-third of the patients in Central Finland and one-fourth in Tartu had suffered from previous UGIH (Table 3).

46.1 % of the patients in Central Finland and 46.8 % in Tartu county had taken NSAIDs prior to bleeding. The elderly had used these drugs significantly more often than younger patients. Women had used NSAIDs significantly more frequently than men in Tartu county. In Central Finland the difference was not significant (Table 3).

Smoking habits showed no difference, but the men admitted to the Central Hospital of Central Finland had consumed alcohol prior to bleeding significantly more often than the men admitted in Tartu (Table 3).

MORTALITY

Mortality rate was 8.1 % in Central Finland and 9.9 % in Tartu county. Patients ≥ 65 years of age accounted for 63 % of the total mortality in Central Finland and for 69 % of the total mortality in Tartu county. In Tartu the mortality rate was four-fold higher for those ≥ 65 years of age compared to younger patients, which was mainly due to the high mortality rate (24.1 %) in women aged ≥ 65. There were neither sex nor age related differences in mortality rates in Central Finland (Table 4).
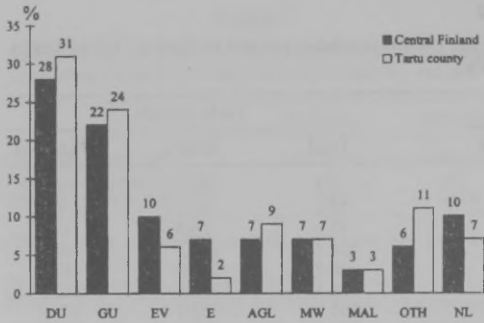
Fig. 1. Causes of upper gastrointestinal haemorrhage in Central Finland and in Tartu county.

DU = duodenal ulcer   MW = Mallory-Weiss tear
GU = gastric ulcer   MAL = malignancies
EV = oesophageal varices   OTH = others
E = oesophagitis   NL = no lesion revealed
AGL = acute gastric mucosal lesions

Fig. 2. Age distribution of upper gastrointestinal haemorrhage patients in Central Finland and in Tartu county.

DISCUSSION

The overall incidence of UGIH was 68.3 per 100,000 adults per year in Central Finland and 98.6 in Tartu county. The incidence rate seems to be relatively low in Central Finland and medium in Tartu county, considering the range of incidence rates from 48 to 150 as reported from elsewhere (1, 2). In both centres the incidence showed a substantial increase with age. Incidence rates in younger age groups were considerably lower in Central Finland than in Tartu county but became almost equal for those ≥ 60 years of age and were even higher for those aged ≥ 80. In both centres the incidence of UGIH in men compared to women was more than double in all age groups except in those ≥ 80 in Central Finland and in those ≥ 70 in Tartu county. A similar pattern has been reported in a study from the United Kingdom (1).

Several studies report ageing trends in UGIH patients during recent decades (18, 21). Indeed, the proportion of the elderly was high in Central Finland: two-thirds of the patients and as many as 79 % of all the women with haemorrhage were aged ≥ 60 there. The proportion of the elderly was significantly lower in Tartu. Half of the patients and 70 % of the women were ≥ 60 years of age there. The discrepancy in the share of the elderly is not the result of the different proportion of the elderly in the population of the regions studied. According to demographic data, people ≥ 60
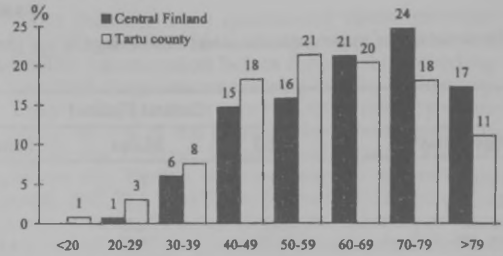
years of age constitute 19 % of the whole population in Central Finland and 18 % in Tartu county.

The above age related differences could be associated with the more extensive NSAID use in Finland (Table 1). It is also possible that different *Helicobacter pylori* infection rates reported recently in both countries have an impact on the incidence and age structure of UGIH, because this bacterium is related to the development of PU disease. Studies have shown an extremely high prevalence, 73–87 %, of *Helicobacter pylori* infection among the population of Estonia in three regions; the prevalence is as high as 68–83 % even in those born in 1955–70 (22, 23). In Finland the prevalence of *Helicobacter pylori* related gastritis is high (70–80 %) in cohorts born at the beginning of the century, lower (40–50 %) in those born in the decade following World War II and still lower (20–35 %) in those born in recent decades (24). This discrepancy, presumably related to differences in the level of socioeconomic development between the countries, may result in the higher prevalence of PU disease and subsequently higher haemorrhage rates among the younger population in Tartu county, as well as in the predominance of the elderly in Central Finland. It could be expected that in Central Finland PU haemorrhage may become less common after some decades due to the *Helicobacter pylori* cohort effect, whereas in Tartu county it will maintain the position of the most frequent cause of UGIH for a longer period.

The main cause of UGIH was PU disease both in Central Finland and in Tartu county, accounting for more than half of the total number of cases. On the whole, the rate of duodenal ulcer haemorrhage prevailed that of gastric ulcer haemorrhage 1.3-fold in both re-

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TABLE 3

Predisposing factors of upper gastrointestinal haemorrhage patients in Central Finland and in Tartu county.

Predisposing factors	Central Finland		Tartu county		P
	Number/patients	%	Number/patients	%	
Previous haemorrhage	105/298	35.2	60/229	26.2	< 0.05
once	57/298	19.1	37/229	16.2	NS
more	48/298	16.1	23/229	10.0	NS
Smoking	90/283	31.8	77/229	33.6	NS
men	79/187	42.2	67/139	48.2	NS
women	11/96	11.5	10/90	11.1	NS
Alcohol prior to bleeding	103/281	36.7	46/230	20.0	< 0.001
men	91/185	49.2	38/141	27.0	< 0.001
women	12/96	12.5	8/89	9.0	NS
NSAIDs prior to bleeding	129/280	46.1	108/231	46.8	NS
men	77/182	42.3	53/139*	38.1	NS
women	52/98	53.1	55/92	59.8	NS
NSAIDs in < 65 patients	50/127**	39.4	59/150+	39.3	NS
NSAIDs in ≥ 65 patients	79/153	51.6	49/81	60.5	NS
NSAIDs prior to bleeding					
gastric ulcer	39/58	67.2	28/55	50.9	NS
duodenal ulcer	44/78	56.4	31/72	43.1	NS
acute gastric lesions	6/19	31.6	13/20	65.0	NS

NS = not significant
*   P < 0.01 when compared to NSAIDs prior to bleeding in women in Tartu county
**   P < 0.05 when compared to NSAIDs in ≥ 65 patients in Central Finland
+   P < 0.01 when compared to NSAIDs in ≥ 65 patients in Tartu county

TABLE 4

Mortality by sex and age of upper gastrointestinal haemorrhage patients in Central Finland and in Tartu county.

Sex/age (years)	Mortality				P
	Central Finland		Tartu county		
	Number/patients	%	Number/patients	%	
Men	15/198	7.6	10/159	6.3	NS
age < 65	7/108	6.5	6/122	4.9	NS
age ≥ 65	8/90	8.9	4/37	10.8	NS
Women	9/100	9.0	16/104	15.4	NS
age < 65	2/30	6.7	2/46*	4.3	NS
age ≥ 65	7/70	10.0	14/58	24.1	= 0.056
Total	24/298	8.1	26/263	9.9	NS
age < 65	9/138	6.5	8/168**	4.8	NS
age ≥ 65	15/160	9.4	18/95	18.9	< 0.05

NS = not significant
*   P < 0.05 when compared to women aged ≥ 65 in Tartu county
**   P < 0.001 when compared to patients aged ≥ 65 in Tartu county

gions. However, gastric ulcer haemorrhage was more common in women in Tartu county. The distribution of the causes of UGIH is similar in both observed regions and is close to that reported from other centres (3, 4). There is only one major difference between the two regions: a higher incidence of oesophageal disease (oesophagitis and oesophageal varices) in Central Finland, the reason of which has remained unclear.

The incidence rates of UGIH were notably lower for younger women than for men in

both regions but showed a more pronounced increase with age and almost equalized in the older age groups. This indicates that there exist also other factors than *Helicobacter pylori* contributing to age and sex related discrepancies. One of these is the circumstance that certain causes of haemorrhage are observed mostly in younger men (Mallory – Weiss tear that is mostly related to alcohol abuse), whereas others are more likely to occur in older women (gastric ulcer). It has also been found that elderly women consume more NSAIDs than men (17), which places them at a higher risk of NSAID related lesions, particularly of gastric ulcer. NSAID use prior to haemorrhage was equally frequent in both regions. Nearly half of the patients had received NSAIDs, while the elderly had used them significantly more often than younger patients. The same observation has been made elsewhere as well (17).

Compared to duodenal ulcer development, gastric ulcer development (25) as well as gastric ulcer bleeding (10) are reported as being related more to NSAID use. However, NSAID use prior to gastric ulcer haemorrhage was slightly but not significantly higher than NSAID use prior to duodenal ulcer haemorrhage in both regions.

Mortality rates of UGIH are mostly reported to be around 10 % (26, 27). Several specialized units have achieved rates as low as 3.7–4.8 % (5, 28). The mortality rate was 8.1 % in Central Finland and 9.9 % in Tartu, without significant differences. However, patients aged ≥ 65 had a significant, nearly four-fold higher mortality compared to those < 65 of age in Tartu county. The reason for this was the high, 24.1 % mortality in women aged ≥ 65 years there. In Central Finland the relative risk of mortality was 1.3-fold higher for patients aged ≥ 65 collated with that of younger ones.

It can be concluded that in Central Finland the incidence of UGIH is somewhat lower than in Tartu county. This is mainly due to low rates among the younger population, while in the elderly the rates are nearly equalized. While the distribution of the causes of UGIH is basically the same and there is no difference in sex ratios between the regions, the proportion of the elderly is significantly higher in Central Finland. These findings could partly result from higher NSAID consumption in Finland. The difference in *Helicobacter pylori* infection rate, a factor connected with different levels of socio-economic development, could also have an impact on the described age related discrepancies. Therefore further time related epidemiological studies in the regions under study would be of interest.

REFERENCES

1. *Rockall TA, Logan RFA, Devlin HB, Northfield TC:* Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Br Med J 311: 222–226, 1995
2. *Cutler JA, Mendeloff AI:* Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. Dig Dis Sci 26: 90–96, 1981
3. *Wara P:* Incidence, diagnosis, and natural course of upper gastrointestinal haemorrhage. Prognostic value of clinical factors and endoscopy. Scand J Gastroenterol 22 (Suppl 137): 26–27, 1987
4. *Henriksson AE, Svensson J-O:* Upper gastrointestinal bleeding with special reference to blood transfusion. Eur J Surg 157: 193–196, 1991
5. *Sanderson JD, Taylor RFH, Pugh S, Vicary FR:* Specialized gastrointestinal units for the management of upper gastrointestinal haemorrhage. Postgrad Med J 66: 654–656, 1990
6. *Allum WH, Brearley S, Wheatley KE, Dykes PW, Keighley MRB:* Acute haemorrhage from gastric malignancy. Br J Surg 77: 19–20, 1990
7. *Bardhan KD, Cust G, Hinchliffe RFC, Williamson FM, Lyon C, Bose K:* Changing pattern of admissions and operations for duodenal ulcer. Br J Surg 76: 230–236, 1989
8. *Bloom BS, Fendrick AM, Ramsey SD:* Changes in peptic ulcer and gastritis/duodenitis in Great Britain, 1970–1985. J Clin Gastroenterol 12: 100–108, 1990
9. *McCarthy DM:* Acid peptic disease in the elderly. Clin Geriatr Med 7: 231–254, 1991
10. *Wilcox CM, Shalek KA, Cotsonis G:* Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal haemorrhage. Arch Intern Med 154: 42–46, 1994
11. *Rodriguez LAG, Jick H:* Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 343: 769–772, 1994
12. *Holvoet J, Terriere L, Van Hee V, Verbist L, Fierens E, Hautekeete ML:* Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. Gut 32: 730–734, 1991
13. *Chamberlain CE:* Acute haemorrhagic gastritis. Gastroenterol Clin North Am 22: 843–873, 1993

14. *Lanas A, Sekar MC, Hirshowitz BI:* Objective evidence
    of aspirin use in both ulcer and nonulcer upper and
    lower gastrointestinal bleeding.
    Gastroenterology 103: 862–869, 1992
15. *Glise H:* Epidemiology in peptic ulcer disease. Scand
    J Gastroenterol 25 (Suppl 175): 13–18, 1990
16. *Leivonen M, Kivilaakso E:* Peptic ulcer bleeding today:
    Risk factors and characteristics of the disease.
    Scand J Gastroenterol 26: 1013–1019, 1991
17. *Savage RL, Moller PW, Ballantyne CL, Wells JE:* Varia-
    tion in the risk of peptic ulcer complications with
    nonsteroidal antiinflammatory drug therapy.
    Arthritis Rheum 36: 84–90, 1993
18. *Gilbert DA:* Epidemiology of upper gastrointestinal
    bleeding. Gastrointest Endosc 36 (Suppl 5): 8–13, 1990
19. Finnish Statistics on Medicines 1990. Edited by the
    Finnish Committee on Drug Information and Statis-
    tics. Kelan omatarvepaino, Helsinki, Finland, 1991,
    pp. 145–150
20. *Kiivet RA, Bergman U, Sjöqvist F:* The use of drugs in
    Estonia compared to the Nordic countries.
    Eur J Clin Pharmacol 42: 511–515, 1992
21. *Martio J, Jukka E, Isomäki H:* Ulkustauti ja tuleh-
    duskipulääkkeet. Suomen Lääkärilehti 27: 2493–2495,
    1991 (in Finnish)
22. *Maaroos H-I:* Helicobacter pylori infection in Eston-
    ian population: Is it a health problem?
    Ann Med 27: 613–616, 1995
23. *Vorobjova T, Kisand K, Haukanõmm A, Maaroos H-I,
    Wadström T, Uibo R:* The prevalence of Helicobacter
    pylori antibodies in a population from southern Es-
    tonia. Eur J Gastroenterol Hepatol 6: 529–533, 1994
24. *Sipponen P, Helske T, Järvinen P, Hyvärinen H, Seppälä
    K, Siurala M:* Fall in the prevalence of chronic gastri-
    tis over 15 years: analysis of outpatient series in Fin-
    land from 1977, 1985, and 1992.
    Gut 35: 1167–1171, 1994
25. *Langman MJS, Brooks P, Hawkey CJ, Silverstein F, Yeo-
    mans N:* Non-steroidal anti-inflammatory drug asso-
    ciated ulcer: Epidemiology, causation and treatment.
    Eur J Gastroenterol Hepatol 6: 442–449, 1991
26. *Katschinski B, Logan R, Davies J, Faulkner G, Pearson J,
    Langman M:* Prognostic factors in upper gastrointes-
    tinal bleeding. Dig Dis Sci 39: 706–712, 1994
27. *Clason AE; Macleod DAD, Elton RA:* Clinical factors
    in the prediction of further haemorrhage or mortal-
    ity in acute upper gastrointestinal haemorrhage.
    Br J Surg 73: 985–987, 1986
28. *Holman RAE, Davis M, Gough KR, Gartell P, Britton
    DC, Smith RB:* Value of a centralised approach in the
    management of haematemesis and melaena: experi-
    ence in a district general hospital.
    Gut 31: 504–508, 1990

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Soplepmann J, Peetsalu A, Peetsalu M, Tein A, Juhola M.
Peptic ulcer haemorrhage in Tartu County, Estonia: epidemiology and
mortality risk factors. Scandinavian Journal
of Gastroenterology 1997; 32: 1195–1200.

Peptic Ulcer Haemorrhage in Tartu County, Estonia: Epidemiology and Mortality Risk Factors

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Background: The aim of the study was to assess the epidemiology and mortality risk factors of peptic ulcer haemorrhage (PUH) in Tartu County, Estonia. *Methods:* In a prospective unselected defined area study, data for 144 patients aged ≥15 years with new cases of PUH were analysed during a 2-year period. *Results:* The incidence of PUH was 57 per 100,000 adult population per year, increasing from 12 in patients aged 20–29 years to more than 135 in those ≥70 years. The incidence was 2.3-fold higher for men. The incidence of gastric ulcer haemorrhage was 26 (men, 33; women, 20) and that of duodenal ulcer 22 (men, 39; women, 9). Of the women 72% and of the men 37% were ≥60 years. Nonsteroidal anti-inflammatory drugs (NSAIDs) were used by 45% of the patients (64% of women, 36% of men). *Helicobacter pylori* infection was present in 93% of the duodenal ulcer patients and in 81% of the gastric ulcer patients. Mortality (8%) was related to age, shock, haemoglobin <80 g/l, cardiac comorbidity, and recurrence of haemorrhage. *Conclusions:* The incidence of PUH is relatively high owing to a high incidence among the younger population in Tartu County. Women with PUH are older, have consumed more NSAIDs, and have mainly gastric ulcer; men are younger, have consumed less NSAIDs, and are prone to duodenal ulcer haemorrhage. *H. pylori* infection is common in PUH patients. Mortality risk factors coincide with those reported by other researchers.

Key words: Epidemiology; haemorrhage; *Helicobacter pylori*; incidence; mortality; nonsteroidal anti-inflammatory drugs; peptic ulcer

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A continuous decrease in hospital admissions (1) and surgery (1–3) for peptic ulcer (PU) disease during recent decades has been repeatedly reported from different regions. However, emergency admissions and surgery for PU complications lack such a trend (1, 3, 4).

Peptic ulcer haemorrhage (PUH) is estimated to have an incidence of 25–58 per 100,000 population per year (5, 6). The incidence rates of PUH are significantly higher in the elderly, and time trends show a continuous increase in the proportion of elderly persons (4).

Recent studies have pointed out the significant role of *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) in ulcer development. NSAID consumption is related to an enhanced risk of ulcer haemorrhage (7, 8). The use of NSAIDs is increasing (9), and the elderly are more prone to take them owing to diseases of the locomotor system. The growing proportion of elderly persons could be a reason that the PUH mortality rates have persisted around 8–10% for decades. Still, some units have achieved death rates as low as 3–5.5% (10–12).

The aim of our study was to establish the epidemiology of PUH, covering incidence, patient profile, *H. pylori* infection

rate, predisposing factors, mortality, and mortality risk factors in Tartu County, Estonia. No such information has been available about the region until now.

PATIENTS AND METHODS

A prospective unselected defined area study of PUH was carried out at Tartu University Hospital, Estonia, from 1 January 1992 to 31 December 1993. Tartu County, with 160,000 inhabitants, served as a defined catchment area, since all patients with gastrointestinal haemorrhage from this county are treated only in Tartu University Hospital. Thus the incidence of PUH estimated by our study group is close to the actual rate.

The study included all departments of surgery and internal medicine and intensive care units. All patients ≥15 years of age with new cases of PUH during a year were included, either presenting with haemorrhage within 10 days of the first sign of bleeding or developing it during hospital treatment for some other disease.

During the study period a total of 271 new cases of upper

Table I. Distribution of age groups in the population of Tartu County and the incidence of peptic ulcer haemorrhage per 100,000 population per year

Age group, years	Share of the whole population (%)	Incidence of peptic ulcer haemorrhage		
		Men	Women	All
15–19	7.4	—	—	—
20–29	16.2	22.5	—	11.5
30–39	13.5	23.7	9.0	16.2
40–49	11.5	150.1	15.4	78.8
50–59	11.6	132.7	43.9	83.6
60–69	10.0	150.9	76.4	105.5
70–79	5.3	209.7	102.4	135.6
≥80	3.1	198.5	119.1	139.0
Total	78.5	82.7	36.1	57.1

gastrointestinal haemorrhage were recorded, of which PUH accounted for 144 cases (53.1%).

Haemorrhage was defined as haematemesis or melaena, a drop in the haemoglobin/haematocrit value, or clinical evidence of blood loss. PU as a cause of haemorrhage was established at endoscopy (139 cases), at operation (2 cases of urgent operation due to clinically active bleeding), or at autopsy (3 cases of exsanguination). Endoscopy was performed within 48 h of admission, in most cases (77%) within 24 h. PU was classified in accordance with location: gastric ulcer, prepyloric ulcer (within 0.5 to 3 cm proximal of the pyloric ring), pyloric ulcer, and duodenal ulcer. Shock was defined as systolic blood pressure <100 mmHg, and rebleeding as any sign of bleeding recurring within 10 days of admission.

All patients capable of adequate communication were questioned about their history and symptoms of ulcer disease, PUH, and other major diseases, and about smoking, alcohol consumption, NSAID use (both aminosalicylic acid (ASA) and non-ASA), and signs of bleeding. An ulcer was considered asymptomatic when there were no complaints (epigastric pain or discomfort) typical of PU within 2 weeks before the onset of PUH. By NSAID use and alcohol consumption is meant the use of these agents within 48 h before the first sign of bleeding. Regular NSAID use is the daily use of these drugs for more than 1 week. Clinical data, results of laboratory analyses, and endoscopy, surgical, and autopsy findings were obtained from the case histories.

In 120 PUH cases 2 gastric mucosal biopsy samples were taken from the antrum and 2 from the corpus, stained in accordance with Giemsa, and investigated microscopically for the presence of *H. pylori* infection.

The evaluation of incidence was based on the publication of the Statistical Office of Estonia, 'Population Age Structure. Towns and Counties of Estonia. January 1, 1995'. Incidence rates were calculated per 100,000 population per year.

The data were analysed by means of StatView Student for the Macintosh. Medians with 95% confidence intervals (CI) were calculated for age. Absolute numbers were compared by means of the chi-square test with continuity correction.

RESULTS

Incidence

The incidence of PUH was 57.1 per 100,000 adults per year. It was 82.7 for men and 36.1 for women, with a 2.3-fold higher relative risk for men. Incidence rate (IR) increased considerably with age, from 11.5 in those aged 20–29 years to more than 135 in those ≥70 years (Table I). The incidence of gastric ulcer was 25.8 (men, 32.6; women, 20.2), of duodenal ulcer 22.2 (men, 38.7; women, 8.7), of prepyloric ulcer 5.5 (men, 5.2; women, 5.7), and of pyloric ulcer 1.6 (men, 3.5; women, 0). The male to female IR ratio was 1.6:1 for gastric ulcer and 4.4:1 for duodenal ulcer.
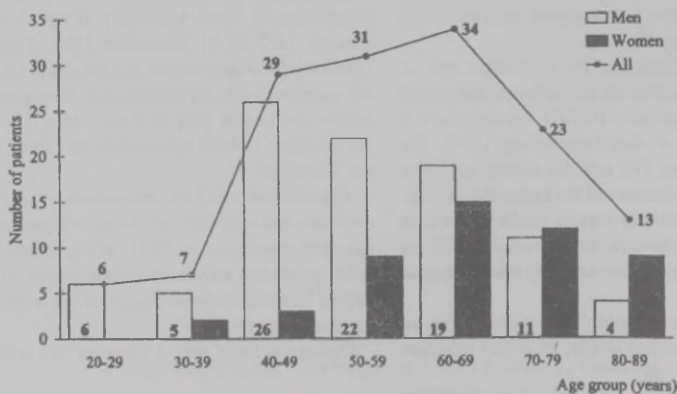

Fig. 1. The number of patients with peptic ulcer haemorrhage by age and sex.

Table II. Predisposing factors of peptic ulcer haemorrhage by sex and age

Predisposing factors	Men		Women		All	
	n/patients	(%)	*n*/patients	(%)	*n*/patients	(%)
NSAID consumption	32/90	(35.6)	30/47*	(63.8)	62/137	(45.3)
Age <60 years	19/57	(33.3)	9/14	(64.3)	28/71	(39.4)
Age ≥60 years	13/33	(39.4)	21/33	(63.6)	34/66	(51.5)
Regular NSAID use	15/90	(16.7)	16/47†	(34.0)	31/137	(22.6)
Age <60 years	5/57	(8.8)	5/14	(35.7)	10/71	(14.1)
Age ≥60 years	10/33‡	(30.3)	11/33	(33.3)	21/66§	(31.8)
Alcohol consumption	12/93	(12.9)	2/46	(4.3)	14/139	(10.1)
Smoking	56/94	(59.6)	7/47¶	(14.9)	63/141	(44.7)

* *P* = 0.003 compared with men.

† *P* = 0.004 compared with men.

‡ *P* = 0.019 compared with men aged <60 years.

§ *P* = 0.023 compared with all aged <60 years.

¶ *P* = 0.0001 compared with men.

Patient profile

There were 144 new cases of PUH during the study period, with a male to female ratio of 1.9:1 (94 men and 50 women). The median age of the patients was 59 (95% CI, 56–62). The median age of male patients was 53.5 (95% CI, 50–58), and that of female patients 66.5 (95% CI, 63–71). Of the patients 49.3% were ≥60 years old, and 72% of the women and 37.2% of the men were aged ≥60 years (*P* = 0.0001). Age and sex distribution is depicted in Fig. 1.

Helicobacter pylori *infection*

Of the PUH patients, 89.2% (107 of 120) had *H. pylori* infection. It was present in 100% (14 of 14) of prepyloric ulcer patients, in 93.5% (43 of 46) of duodenal ulcer patients, and in 81.1% (43 of 53) of gastric ulcer patients. The differences were not significant.

Predisposing factors

Of the patients 17.9% (25 of 140) had previously had PUH, and 45% (63 of 140) had a previously verified ulcer diagnosis.

Altogether, 45.3% of the patients had used NSAIDs 48 h before the onset of bleeding, and half of these had been receiving regular NSAID treatment longer than 1 week. Of the patients 42.9% (6 of 14) of those with prepyloric ulcer versus 13.5% (7 of 52) of those with duodenal ulcer had been receiving regular NSAID treatment (*P* = 0.038). For gastric ulcer the percentage was 25.8 (16 of 62) without a significant difference from the above-mentioned ulcer locations. Data on NSAID use, smoking, and alcohol consumption are depicted in Table II.

Causes of haemorrhage

Gastric ulcer was the commonest cause of PUH (45.1%), followed by duodenal ulcer (38.9%) and others. The distribution of causes of haemorrhage differed between the sexes (Table III). Duodenal ulcer prevailed in men, and gastric ulcer in women.

Endoscopy showed active bleeding (Forrest I) in 10.1% (14 of 139) of the patients, stigmata of recent bleeding (Forrest II) in 54.7% (76 of 139), and ulcer without stigmata (Forrest III) in 35.2% (49 of 139) of the patients.

Asymptomatic ulcers

In 27.3% (38 of 139) of the patients complaints (pain, epigastric discomfort) typical of PU were lacking. Of these, 3 had active bleeding, 19 had stigmata of recent bleeding, and 16 had ulcer without stigmata. In patients aged ≥60 years asymptomatic ulcer accounted for 32.8% (22 of 67) and in younger patients for 22.2% (16 of 72) of the cases, in regular NSAID users for 33.3% (10 of 30) and in nonusers for 27.2% (28 of 103) of the cases. Asymptomatic ulcer occurred in 28.3% (26 of 92) of the men and in 25.5% (12 of 47) of the

Table III. Distribution of the causes of haemorrhage by sex in peptic ulcer haemorrhage patients

Diagnosis	Men	(%)	Women	(%)	All	(%)
Gastric ulcer	37	(39.4)	28	(56)	65	(45.1)
Duodenal ulcer	44	(46.8)	12*	(24)	56	(38.9)
Prepyloric ulcer	6	(6.4)	8	(16)	14	(9.7)
Pyloric ulcer	4	(4.2)	—		4	(2.8)
Marginal ulcer	2	(2.1)	—		2	(1.4)
Others†	1	(1.1)	2	(4)	3	(2.1)
Total	94	(100)	50	(100)	144	(100)

* *P* = 0.013 compared with duodenal ulcer in men.

† Combined ulcers: one patient with prepyloric and gastric ulcer, two patients with prepyloric and duodenal ulcer.

Table IV. Mortality risk factors in patients with peptic ulcer haemorrhage

| Risk factors | No. of patients | Mortality | | Chi-square, P |
		n	%	
Sex: men/women	94:50	5:7	5.3:14.0	0.140
Age: ≥65/<65 years	54:90	9:3	16.7:3.3	0.013
Gastric ulcer/duodenal ulcer	65:56	8:3	12.3:5.4	0.313
Previous PUH/no	25:109	1:7	4.0:6.4	0.994
NSAID use/no	62:75	6:3	9.7:4.0	0.323
Age <65 years, regular NSAID therapy/no	14:73	2:1	14.3:1.4	0.104
Age ≥65 years, regular NSAID therapy/no	17:33	3:3	17.6:9.1	0.673
Haematemesis/no	63:73	8:2	12.7:2.7	0.059
Shock/no	22:114	7:5	31.8:4.4	0.0002
Pulse rate <100/≥100	85:47	7:4	8.2:8.5	0.784
Haemoglobin <100 (g/l)/≥100	85:59	9:3	10.6:5.1	0.385
Haemoglobin <80 (g/l)/≥80	40:104	7:5	17.5:4.8	0.033
Major cardiac disease/no	21:121	7:3	33.3:2.5	0.0001
Admitted ≤24/>24 h after PUH	66:71	7:4	10.6:5.6	0.450
Forrest I/Forrest II, III*	14:125	3:6	21.4:4.8	0.068
Recurrent haemorrhage/no	27:117	8:4	29.6:3.4	0.0001

* Forrest I = active bleeding; Forrest II = stigmata of recent bleeding; Forrest III = no stigmata of recent bleeding. PUH = peptic ulcer haemorrhage; NSAID = nonsteroidal anti-inflammatory drug.

women. Of the duodenal ulcers 28.3% (15 of 53) and of the gastric ulcers 19.0% (12 of 63) were asymptomatic. None of these differences proved to be statistically significant.

Mortality and mortality risk factors

The overall mortality of PUH patients was 8.3%. The median age of the patients who died was 66 (95% CI, 59–73 years) and that of the patients who survived 57 (95% CI, 54–62 years). Patients aged ≥65 years accounted for 75% of the deaths. The death rate was 4.8 per 100,000 adult population per year.

The mortality was significantly related to older age, shock, haemoglobin <80 g/l, severe cardiac comorbidity, and recurrence of haemorrhage during treatment (Table IV).

DISCUSSION

PU is the commonest cause of gastrointestinal haemorrhage. This fact, the latest data on ulcer pathogenesis, and new prevention and treatment modalities have aroused increased interest in the epidemiology of PUH. Most studies indicate that PU is responsible for at least half of all bleeding episodes from the upper gastrointestinal tract (13, 14). Our study confirms these data, with PUH accounting for 53.1% of all haemorrhage cases.

The incidence of PUH was 57.1 per 100,000 adult population per year in Tartu County, Estonia. This level can be considered high compared with the range of 25–58 per 100,000 per year as estimated by other researchers (5, 6). Haemorrhage has been found to affect elderly persons disproportionately (4). Indeed, IR rose significantly with age in our study, being 10-fold higher for patients aged ≥70 years (more than 135 per 100,000 per year) than for those aged 20–39 years (11.5 per 100,000 per year). Incidence was

higher for men in all age groups. The same age- and sex-related differences have been noted in a German (15) and a U.S. study (6). In women increase in IR with age was steady, whereas in men a sharp sixfold increase in IR appeared in the age group 40–49 years as compared with younger patients in Tartu County (Table I). In the German study IR showed a more uniform growth. Compared with our study, overall IR was twice as low for patients aged <50 years, equalized for those aged 50–79 years, and was twice as high for those ≥80 years. The U.S. study shows a very high incidence (242 per 100,000 per year) in patients more than 65 years of age as compared with the respective rate in Tartu County.

Several studies have found that gastric ulcer is a more frequent cause of PUH than duodenal ulcer (14, 15), whereas others report the contrary (16). In our study gastric ulcer haemorrhage had the highest overall incidence, followed by duodenal ulcer and prepyloric ulcer. However, in men duodenal ulcer incidence was higher, whereas in women gastric ulcer prevailed, and the incidence of duodenal ulcer was low, close to that of prepyloric ulcer.

The distribution of PUH patients (Fig. 1) shows a predominance of younger men and elderly women: 72% of the women and 37.2% of the men were aged ≥60 years. Several studies show a high proportion of the elderly among PUH patients. In studies from the United Kingdom 81% (12) and 74% (16) of the patients were aged ≥60 years; in an Australian study their share was 69% (17). In the Tartu region the proportion of patients aged ≥60 years, 49.3%, was lower than in the mentioned studies. This difference can be partly explained by the lower proportion of elderly persons in the whole population of Estonia. The other possible contributing factor is high *H. pylori* infection rate among the inhabitants of Estonia. The role of *H. pylori* in PU development has recently been established. It has been shown that eradication of this

bacterium reduces ulcer recurrence (18, 19) and bleeding relapses (18, 20). It is suggested that *H. pylori* infection rate depends on the socioeconomic level. According to the United Nations 'Human Development Report 1994', Estonia ranks behind developed countries with regard to the level of socioeconomic development. This could be the reason why *H. pylori* infection is commoner in Estonia than in Western countries, affecting 73–87% of the population in three regions studied (21). Even younger people from cohorts born in 1955–70 had infection rates as high as 68–83% (21, 22). Comparable data from Western countries show significantly lower *H. pylori* infection rates among those born in recent decades, ranging from 10% to 20% (23). The high *H. pylori* infection rate might result in a high prevalence of PU disease and account for the subsequent higher PUH rate among the younger population found in our study.

H. pylori infection was frequently observed in the gastric mucosa of PUH patients. Its presence was slightly higher in prepyloric and duodenal ulcer patients than in gastric ulcer patients.

The recently reported somewhat lower NSAID consumption among the population of Estonia than in developed countries (24) may have an impact on age distribution, as these drugs are more often used by the elderly. This could explain the lower IR among the elderly compared with other countries (6, 15).

NSAID use has been established as carrying enhanced risk of PU genesis and of PUH development. Studies show the use of these drugs in 34.6% to 89% (12, 25) of cases. According to our study, 45.3% of the patients had used NSAIDs before the onset of bleeding. Regular NSAID treatment before PUH was significantly more often observed in the elderly. Women used these drugs considerably more frequently than men. In case patients with PUH, presumably caused by NSAIDs, were excluded, the discrepancy between the male to female incidence ratio (2.3:1) would be even greater. Could such a sex-related difference be caused by other factors like stress, smoking, and alcohol consumption? Of the possible predisposing factors of ulcer haemorrhage, smoking was significantly more frequent in men than in women in our study.

NSAIDs seem to be more related to prepyloric and gastric ulcers than to duodenal ulcers (7, 9). Our study confirms this finding: the proportion of regular NSAID users among patients with prepyloric ulcer (42.9%) was slightly higher than among gastric ulcer patients (25.8%) and significantly higher than among duodenal ulcer patients (13.5%).

In one-fourth of the patients from Tartu County haemorrhage developed from asymptomatic ulcers. Asymptomatic ulcers present a major problem, as no preventive measures can be applied against life-threatening ulcer complications. It has been found that in older people ulcer symptoms can be vaguely expressed, and NSAID use is often present in such cases (26). The presence of ulcer symptoms was not related to NSAID use in a previous study (7). According to our study,

ulcer symptoms before bleeding were not related to age, sex, diagnosis, or NSAID use.

The mortality rates of PUH vary widely, from 3% (10) to 16.9% (27). Although not close to the lowest rates, the 8.3% mortality in Tartu County is comparable to rates observed in most centres. Some authors have reported lower mortality rates, relating it to specialized unit management, strict protocol (11), aggressive approach (28), and restrictive blood transfusion policy (29).

In our patients death was associated with higher age, shock, haemoglobin level <80 g/l, major cardiac disease, and recurrent bleeding. These risk factors coincide with those established by other researchers (12, 16, 17).

To conclude, our study indicates that despite the lower IR of PUH in the elderly and owing to the higher IR in the younger population, the overall incidence is relatively high in our study compared with that reported from elsewhere. These differences could be the result of the synchronous interaction of different factors. Lower NSAID consumption among the Estonian population and higher prevalence of *H. pylori* infection among the young seem to play the key role. Unfortunately, no time-related data are currently available for the region. Therefore further studies directed to changes in epidemiology would be of importance.

ACKNOWLEDGEMENTS

REFERENCES

1. Kurata JH, Corboy ED. Current peptic ulcer time trends. J Clin Gastroenterol 1988;10:259–68.
2. Penston JG, Crombie IK, Waugh NR, Wormsley KG. Trends in morbidity and mortality from peptic ulcer disease: Tayside versus Scotland. Aliment Pharmacol Ther 1993;7:429–42.
3. Paimela H, Tuompo PK, Peräkylä T, Saario I, Höckerstedt K, Kivilaakso E. Peptic ulcer surgery during the H_2-receptor antagonist era: a population-based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987. Br J Surg 1991; 78:28–31.
4. Bloom BS, Fendrick AM, Ramsey SD. Changes in peptic ulcer and gastritis/duodenitis in Great Britain, 1970–1985. J Clin Gastroenterol 1990;12:100–8.
5. Panos MZ, Walt RP. Current management of bleeding peptic ulcer. Drugs 1993;46:269–80.
6. Cutler JA, Mendeloff AI. Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. Dig Dis Sci 1981;26 Suppl:90–6.
7. Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E, Hautekeete ML. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. Gut 1991;32:730–4.
8. Savage RL, Moller PW, Ballantyne CL, Wells JE. Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. Arthritis Rheum 1993;36:84–90.
9. Glise H. Epidemiology in peptic ulcer disease. Current status

and future aspects. Scand J Gastroenterol 1990;25 Suppl 175:13–8.

10. Gostout CJ, Wang KK, Ahlquist DA, Clain JE, Hughes RW, Larson MV, et al. Acute gastrointestinal bleeding. Experience of a specialized management team. J Clin Gastroenterol 1992; 14:260–7.

11. Sanderson JD, Taylor RFH, Pugh S, Vicary FR. Specialized gastrointestinal units for the management of upper gastrointestinal haemorrhage. Postgrad Med J 1990;66:654–6.

12. Holman RAE, Davis M, Gough KR, Gartell P, Britton DC, Smith RB. Value of a centralised approach in the management of haematemesis and melaena: experience in a district general hospital. Gut 1990;31:504–8.

13. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol 1995;90:206–10.

14. Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. Arch Intern Med 1994;154:42–6.

15. Ohmann C, Thon K, Hengels K-J, Imhof M, DÜSUK Study Group. Incidence and pattern of peptic ulcer bleeding in a defined geographical area. Scand J Gastroenterol 1992;27:571–81.

16. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Br Med J 1995;311:222–6.

17. Turner IB, Jones M, Piper DW. Factors influencing mortality from bleeding peptic ulcers. Scand J Gastroenterol 1991;26:661–6.

18. Labenz J, Börsch G. Role of Helicobacter pylori eradication in the prevention of peptic ulcer bleeding relapse. Digestion 1994;55:19–23.

19. Seppälä K, Färkkilä M, Nuutinen H, Hakala K, Väänänen H, Rautelin H, et al. Triple therapy of *Helicobacter pylori* infection in peptic ulcer. A 12-month follow-up study of 93 patients. Scand J Gastroenterol 1992;27:973–6.

20. Graham DY, Hepps KS, Ramirez FC, Lew GM, Saeed ZA. Treatment of *Helicobacter pylori* reduces the rate of rebleeding in peptic ulcer disease. Scand J Gastroenterol 1993;28:939–42.

21. Maaroos H-I. Helicobacter pylori infection in Estonian population: is it a health problem? Ann Med 1995;27:613–6.

22. Vorobjova T, Kisand K, Haukanõmm A, Maaroos H-I, Wadström T, Uibo R. The prevalence of Helicobacter pylori antibodies in a population from southern Estonia. Eur J Gastroenterol Hepatol 1994;6:529–33.

23. The EUROGAST Study Group. Epidemiology of, and risk factors for, Helicobacter pylori infection among 3194 asymptomatic subjects in 17 populations. Gut 1993;34:1672–6.

24. Kiivet RA, Bergman U, Sjöqvist F. The use of drugs in Estonia compared to the Nordic countries. Eur J Clin Pharmacol 1992; 42:511–5.

25. Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology 1992;103:862–9.

26. Katz J. The course of peptic ulcer disease. Med Clin North Am 1991;75:831–40.

27. Clason AE, Macleod DAD, Elton RA. Clinical factors in the prediction of further haemorrhage or mortality in acute upper gastrointestinal haemorrhage. Br J Surg 1986;73:985–7.

28. Bender JS, Bouwman DL, Weaver DW. Bleeding gastroduodenal ulcers: improved outcome from a unified surgical approach. Am Surg 1994;60:313–5.

29. Henriksson AE, Svensson J-O. Upper gastrointestinal bleeding with special reference to blood transfusion. Eur J Surg 1991; 157:193–6.

Soplepmann J, Peetsalu M, Tein A, Peetsalu A.
Long-term results of peptic ulcer haemorrhage. European Journal
of Trauma and Emergency Surgery 1999; 22: 177–179.

Long-term results of peptic ulcer haemorrhage

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Summary
Aims. To assess the long-term follow-up results of patients treated operatively and conservatively for peptic ulcer haemorrhage (PUH).
Patients and methods. In a prospective non-randomised study, 163 PUH patients, of whom 61 had passed definitive operative procedures and 102 had been treated conservatively (intermittent therapy with H_2 blockers after hospital treatment), were assessed for mortality, causes of death, ulcer recurrence and ulcer haemorrhage two years after discharge from hospital.
Results. 18 patients died due to causes unrelated to ulcer complications.
Excellent and good results were obtained in 40% (34/86) of the conservatively treated and 79% (37/47) of the operatively treated patients. In 49% (42/86) of conservatively treated patients, recurrence of peptic ulcer was diagnosed during follow-up and 14 of them re-bled within two years. Of the operatively treated patients 13% (6/47) suffered from recurrent ulcer and three of them had another haemorrhage during follow-up.
Conclusions: Intermittent H_2 blocker therapy after hospital treatment for PUH fails to control recurrence of peptic ulcer and ulcer haemorrhage. Definitive operations for PUH are efficient in avoiding recurrence of peptic ulcer and its complications in long term.

Key words peptic ulcer haemorrhage, long-term results, operative treatment, H_2 blockers.

The world-wide tendency of decline in hospital treatment and surgery (1-3) of uncomplicated peptic ulcer disease has not been reflected either in the frequency of peptic ulcer haemorrhage (PUH) or in the need for surgical intervention due to PUH (1,3,4).

For decades the greatest concern has been reducing hospital morbidity and mortality of PUH patients. Few works have emphasised the importance of long-term results, therefore, we studied the two-year follow-up results of the patient treated conservatively and operatively for PUH.

Patients and methods

During a period of 2,5 years (1.01.92 - 30.06.94) a prospective non-randomised study of long-term results of peptic ulcer haemorrhage has been carried out at Tartu University Hospital, Estonia. Inclusion criteria were age, ≥ 15 years, and residence in Tarty county (160,000 inha-

bitants) where Tartu University Hospital is the only hospital serving gastrointestinal haemorrhage patients. Peptic ulcer, as the source of haemorrhage, was established endoscopically and a total of 170 patients were treated for PUH on 184 occasions.

To investigate the long-term results of PUH only the first occasions of either conservative or operative treatment during the 2,5-year period were included. Six patients managed conservatively on the first occasion had another haemorrhage requiring operation, they were included both in the conservatively and operatively treated groups for follow-up. 13 patients, who died during the hospital stay were excluded; two of them had passed emergency operation and 11 had been treated conservatively.

There were 163 patients left for analysis, of whom 61 had been operated and 102 had been treated conservatively. Of the 102 patients treated conservatively 67 were men and 35 were women, their mean age was 58.4 (SE ± 1.66). Of the 61 patients treated operatively 45 were men and 16 were women, their mean age was 55.2 (SE ± 1.73). Emergency operations had been undertaken in 21 patients for persistent or recurrent bleeding. In 40 patients early elective operation after stabilisation of the condition had been carried out. The indications were giant and/or penetrating ulcer with a visible vessel or adherent clot, previous episodes of ulcer bleeding, stenosis, and need for regular extensive NSAID therapy. In all cases definitive operations with ulcer removal were performed. In gastric ulcers partial gastrectomy was carried out. Praepyloric ulcers were treated with partial gastrectomy or truncal vagotomy with antrumectomy. In case of duodenal ulcer, vagotomy (truncal or proximal selective vagotomy) with either antrumectomy or ulcer excision with pyloroplasty according to Holle were used. Conservatively treated patients passed a 4-6-week H_2 blocker treatment after discharge from hospital and were thereafter all on intermittent treatment on demand. No *Helicobacter pylori* eradication was used. Two years after hospital treatment data were collected for assessment of long-term results.

Data on mortality and causes of death for the two-year follow-up were obtained from the Registry Office of Tartu County Government. Data on recurrence of haemorrhage during two years from hospital treatment were obtained from statistical database of Tartu University

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Hospital. In a mean time of 17 months (range 12-31 months) the patients who had neither died nor suffered from recurrent haemorrhage passed a follow-up examination in which their subjective quality of life was assessed using a questionnaire. Of these patients 86% (100/116) agreed to undergo endoscopic investigation. The results were graded according to a modified Visick scale. Visick I = excellent: no symptoms; Visick II = good: mild symptoms without impact either on the quality of life or ability to work; Visick III - satisfactory: moderate symptoms causing a certain degree of discomfort or disability; Visick IV = poor: severe symptoms or recurrent ulcer. Eighteen patients, of whom five had passed the follow-up examination, died within two years from hospital treatment. Seven of the conservatively treated patients and ten of the operatively treated patients were lost during follow-up (90% follow-up rate).

Chi-square test with continuity correction was used for statistical analysis.

Results

During the two-year follow-up period there were no deaths related to peptic ulcer haemorrhage. Eleven of the conservatively treated and seven of the operatively treated patients died due to different causes: cardiovascular disease (9 cases), malignancies (5 cases), cerebrovascular disease (2 cases), liver failure (1 case) and drowning (1 case). Recurrence of ulcer bleeding within two years occurred in 16% (14/86) of the conservatively treated and in 6% (3/47) of the operatively treated patients (Table 1). There were no ulcer perforations during the follow-up. Severe symptoms of peptic ulcer disease and/or recurrent ulcer without complications were observed in 33% (28/86) of the conservatively treated and in 6% (3/47) of the operatively treated patients. Excellent and good results were obtained in 40% (34/86) of the conservatively treated and in 79% (37/47) of the operatively treated patients.

Discussion

The surgeon dealing with peptic ulcer haemorrhage is faced with multiple tasks among which the first ones are the stabilisation of patient's condition and the reduction of the risk of recurrent bleeding in the attempt to diminish mortality. These tasks, often discussed by researchers, are accomplished with the use of transfusion, endoscopic therapy, medication and definitive or non-definitive operation. The further goal is to prevent ulcer relapse and subsequent ulcer complications in long term performing medical therapy or definitive operative treatment. However, long-term results of PUH have been rarely assessed in the literature.

In a Hong Kong study (5) the risk of further ulcer complication, both haemorrhage and perforation, has been found to be as high as 32% over a median follow-up period of 36 months. The patients were treated with H_2 blockers until ulcer's healing and received no maintenance therapy thereafter. In a similar study 13% of patients on intermittent H_2 blocker therapy re-bled during a mean follow-up of 48 months (6). The latter study reports the 6% late complication rate of peptic ulcer in definitively operated patients.

Similarly further haemorrhage occurred in 16% of the conservatively treated and in 6% of the operatively treated patients during the two-year follow-up period in our series. However, the difference was not statistically significant. Intermittent therapy with H_2 blockers after conservative hospital treatment resulted in nearly 50% of recurrence of ulcer bleeding, ulcer relapse or severe symptoms and 40% of excellent and good results. This unsatisfactory outcome indicates that intermittent therapy after PUH fails to control peptic ulcer disease and further haemorrhage in long term, and should not be advocated for patients. Ranitidine administered in a maintenance regimen has revealed the capacity to reduce both duodenal ulcer relapse and further ulcer bleeding (7). However, lifelong maintenance therapy for all ulcer haemorrhage patients is expensive. The recent advent of drugs for *Helico-*

Table 1 Long-term results of treatment of peptic ulcer haemorrhage patients.			
Long-term results	Conservatively treated patients No (%)	Operatively treated patients No (%)	Chi square (p)
Visick I*	17 (19.8%)	22 (46.8%)	p=0.0021
Visick II	17 (19.8%)	15 (31.9%)	p=0.1756
Visick III	10 (11.6%)	4 (8.5%)	p=0.7915
Visick IV	42 (48.8%)	6 (12.8%)	p=0.0001
– with bleeding	14 (16.3%)	3 (6.4%)	p=0.1731
– without bleeding	28 (32.6%)	3 (6.4%)	p=0.0014
Deaths related to ulcer bleeding	0	0	
* For Visick grading, see Patients and Methods			

bacter pylori eradication has expanded the possibilities of treating peptic ulcer disease. The first long-term results of the use of these drugs after complications appear to be promising (8,9). Some authors claim that definitive ulcer surgery should be avoided in PUH patients (10) and that only the undersewing of bleeding vessel and its branches should be performed (11). We are of the opinion that when operative treatment is indicated, definitive procedures with ulcer removal should not be abandoned as they provide an immediate and complete control of the bleeding site as well as good long-term results. In our study excellent and good long-term results were achieved in 80% of the patients. Definitive operative treatment is also a safe procedure. No hospital deaths resulted from early elective operation in our patients. The two patients who died has passed emergency operation.

However, although the late prognosis for patients discharged from hospital after treatment due to PUH is poor, most deaths cannot be attributed to recurrent ulcer bleeding (12,13). In our study 18 patients died within two years from hospital treatment due to reasons unrelated toUH. Deaths resulted mainly from cardiovascular disease (9/18) and malignancies of various locations (5/18). Among the latter cases, one patient had been diagnosed with praepyloric ulcer during hospital treatment but died of gastric cancer. Obviously, cancer diagnosis had been previously missed.

Conclusion

To conclude, in patients with PUH the long-term effect of treatment should always be considered. Intermittent H_2 blocker therapy is inadequate and should be avoided. In the Centres with experience in gastroduodenal surgery, definitive operations should not be abandoned in the treatment of PUH patients. Good long-term results can be achieved applying these procedures directed to the pathogenesis of ulcer disease.

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List of abbreviations PUH - peptic ulcer haemorrhage; NSAID - nonsteroidal anti-inflammatory drug.

References

1. Kurata JH, Corboy ED. Current peptic ulcer time trends. An epidemiological profile. J Clin Gastroenterol 1988; 10: 259-68.
2. Paimela H, Tuompo PK, Perakyla T, Saario I, Hockersted K, Kivilaakso E. Peptic ulcer surgery during the H_2-receptor antagonist era: a population-based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987. Br J Surg 1991; 78: 28-31.
3. Bloom BS, Fendrick AM, Ramsey SD. Changes in peptic ulcer and gastritis/duodenitis in Great Britain, 1970-1985. J Clin Gastroenterol 1990; 12: 100-8.
4. Ishikawa M, Ogata S, Harada M, Sakakihara Y. Changes in surgical strategies for peptic ulcer before and after the introduction of H_2-receptor antagonists and endoscopic hemostasis. Jpn J Surg 1995; 25: 318-23.
5. Ng EKW, Chung SCS, Lau JTF, Sung JJY, Leung JWC, Raimes SA, Chan ACW, Li AKC. Risk of further ulcer complications after an episode of peptic ulcer bleeding. Br J Surg 1996; 83: 840-4.
6. Mueller X, Rothenbuehler J-M, Amery A, Meyer B, Harder F. Outcome of peptic ulcer hemorrhage treated according to a defined approach. World J Surg 1994; 18: 406-10.
7. Jensen DM, Cheng S, Kovacs TOG, Randall G, Jensen ME, Reedy T, Frankl H, Machicado G, Smith J, Silpa M, Van Deventer G. A controlled study of ranitidine for the prevention of recurrent hemorrhage from duodenal ulcer. N Engl J Med 1994; 330: 382-6.
8. Jaspersen D, Koerner T, Schorr W, Brennenstuhl M, Raschka C, Hammar C-H. Helicobacter pylori eradication reduces the rate of rebleeding in ulcer hemorrhage. Gastrointest Endosc 1995; 41: 5-7.
9. Labenz J, Tilelnburg B, Peitz U, Borsch G. Long-term consequences of Helicobacter pylori eradication: clinical aspects. Scand J Gastroenterol 1996; 31 Suppl 215: 111-5.
10. Roher H-D, Imhof M, Goretzki PE, Ohmann C. Ulcus '96 - Methodenwahl im Notfall. Chirurg 1996; 67: 20-5.
11. Kolkman JJ, Meuwissen SGM. A review on treatment of bleeding peptic ulcer: a collaborative task of gastroenterologist and surgeon. Scand J Gastroenterol 1996; 31 Supl 218: 16-25.
12. Kubba AK, Choudari C, Rajgopal C, Ghosh S, Palmer KR. Reduced long-term survival following major peptic ulcer haemorrhage. Br J Surg 1997; 84: 265-8.
13. Hudson N, Faulkner G, Smith SJ, Langman MJS, Hawkey CJ, Logan RFA. Late mortality in elderly patients surviving acute peptic ulcer bleeding. Gut 1995; 37: 177-81.

Soplepmann J, Peetsalu M, Väli T, Peetsalu A.
Long-term results of surgical treatment of giant duodenal posterior
wall ulcers complicated with hemorrhage. Langenbeck's Archives
of Surgery 2003 (submitted for publication).

GIANT DUODENAL POSTERIOR WALL ULCERS COMPLICATED WITH HEMORRHAGE: LONG-TERM RESULTS OF SURGICAL TREATMENT

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ABSTRACT

Background: To assess long-term results of the surgical treatment of giant duodenal posterior wall ulcers penetrating into the pancreas, complicated with hemorrhage.

Patients and methods: During 1984–1993, 16 patients were operated using procedures exteriorizing the giant ulcer base from the duodenal lumen. In 13 cases duodenal resection with plasty and in 3 cases antrectomy was performed, both combined with vagotomy. Long-term results were evaluated clinically and endoscopically according to the Visick scale 7–16 years (mean 11 years) after operation in 10 patients. Four patients had died from causes unrelated to peptic ulcer or operation.

Results: Long-term results were excellent or good in 90% (9/10) of the cases. In one patient the long-term result was assessed as satisfactory. Endoscopy revealed no cases of ulcer recurrence.

Conclusions: Ulcer base exteriorizing operations, i.e. duodenal resection with plasty and antrectomy, combined with vagotomy, yield good long-term results in the case of giant duodenal posterior wall ulcers penetrating into the pancreas, complicated with hemorrhage.

INTRODUCTION

The incidence of peptic ulcer hemorrhage varies from 25 to 58 cases per 100, 000 per year [1,2]. In Estonia, the incidence is high, 57 cases per 100 000 adults per year [3]. The need for the surgical treatment of ulcer hemorrhage has significantly decreased mainly owing to the use of endoscopic management both elsewhere [4,5] and in Estonia [6].

When bleeding cannot be stopped endoscopically, or when it recurs after repeated endoscopic procedures, operative management is indicated.

The aim of the surgical treatment of hemorrhage is to stop bleeding, to remove the cause of bleeding, to prevent complications including bleeding recurrence, as well as to obtain good long-term outcome. Since 1977, our method of choice in duodenal ulcer hemorrhage has been excision of ulcer(s), and form and function preserving pyloro- or duodenoplasty after Holle plus vagotomy. This has yielded good or excellent long-term results in 86% of cases, with ulcer recurrence in 10% of cases on average 8 years after operation [7].

The most complicated phase of the operation is ulcer excision, particularly in the case of giant (larger than 2 cm in diameter) duodenal posterior wall ulcers penetrating into the pancreas, which are often combined with stenosis. The operation is time consuming, with the probability of intraoperative bleeding and with the danger of damaging the bile ducts and the pancreas; development of postoperative pancreatitis is possible. To avoid these problems, we have since 1984 introduced duodenal resection with plasty after Helwing et al. [8], combined with vagotomy (DPV) and antrectomy with reconstruction after Herfarth et al. [9], combined with vagotomy (AEV). In these methods, giant duodenal posterior wall ulcers penetrating into the pancreas are not excised but exteriorized, i.e. the ulcer base is left out of the duodenal lumen.

The aim of this investigation was to assess long-term results in patients operated for giant duodenal posterior wall ulcers penetrating into the pancreas, complicated with hemorrhage, using the methods of Helwing and Herfarth, combined with vagotomy.

PATIENTS AND METHODS

1. Patients

Between 1984 and 1993, 16 patients were operated at the Department of Abdominal Surgery of Tartu University Clinics for giant duodenal posterior wall ulcer penetrating into the pancreas, complicated with hemorrhage, using DPV in 13 cases and AEV in 3 cases. Giant duodenal ulcers were defined as ulcers larger than 2 cm in diameter [10]. Patient data were obtained retrospectively from the computer database of the Clinics. The age of the patients at the

time of operation was 29–74 years (mean 55 years). There were three female and thirteen male patients. Endoscopy had been performed in all patients preoperatively and the type of hemorrhage was classified according to the Forrest classification. Four of the patients had persistent bleeding (Forrest I); nine had stigmata of recent bleeding: a visible vessel, a clot in the ulcer base (Forrest II); three patients lacked stigmata of recent bleeding (Forrest III). Stenosis due to giant ulcer occurred in 10 patients of 16.

2. Operative methods

2.1. DPV after Helwing

The duodenum is mobilised employing Kocher maneuver. Further, hemipylorectomy is performed with two semicircular incisions, one above and the other below the pylorus (Fig.1a). A giant duodenal posterior wall ulcer becomes visible (Fig. 1b). Current bleeding is stopped by oversewing of the bleeding vessel. The proximal part of the duodenum is mobilised from the ulcer and the pancreas by severing the duodenum proximal to the ulcer (Fig. 1c). In the case of stenosis, a circular resection of the stenosed region is performed. Thus two separate ends are formed, one on the gastric side and the other on the duodenal side. The posterior wall is then sutured in a one-row manner through all layers of the posterior wall of the gastric end to the distal edge of the giant ulcer with the posterior wall of the duodenal end (Fig. 1d). Thus the mobile posterior gastric wall is shifted to cover the ulcer base, leaving it out of the duodenal lumen, i.e. the ulcer base is exteriorized (Fig. 1e). Then the anterior wall is closed by a two-row suture (Fig. 1f). Further, vagotomy is carried out.

2.2. AEV after Herfarth

Kocher maneuver is performed to mobilize the duodenum. Further, antrectomy is done so that the base of the giant ulcer remains on the pancreas. Current bleeding is stopped by oversewing of the bleeding vessel. Then the gastric stump is closed leaving an opening for the anastomosis. The posterior wall of the opening of the gastric stump is fixed by one-row sutures, involving all gastric layers, to the distal edge of the ulcer and the back wall of the duodenum (Fig. 2a). In this way the posterior wall of the gastric stump is shifted to cover the ulcer base, while the latter is left out of the lumen, i.e. is exteriorized (Fig. 2b). Then the two-row suturing of the anterior wall will restore the integrity of the digestive tract (Fig. 2c). Further, bilateral truncal vagotomy is performed.

3
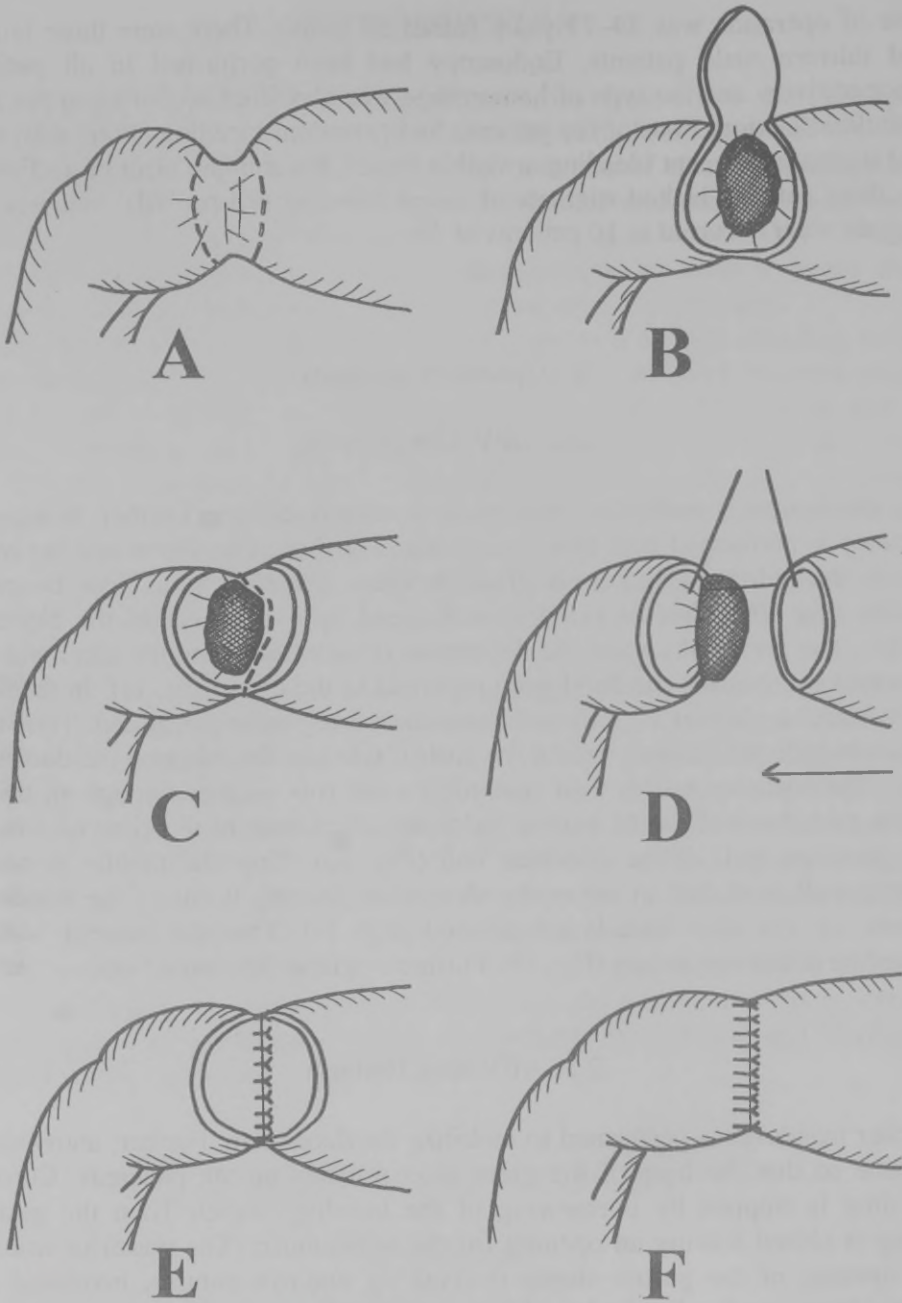
Fig. 1. Duodenal resection with plasty after Helwing. (A) Two semicircular incisions for opening of the duodenum. (B) A giant duodenal posterior wall ulcer is exposed. (C) Severing of the duodenum proximal to the ulcer. (D) The posterior wall is sutured, the gastric end to the distal edge of the ulcer. (E) The posterior wall sutures in place. The ulcer is exteriorized. (F) The anterior wall is sutured.

4
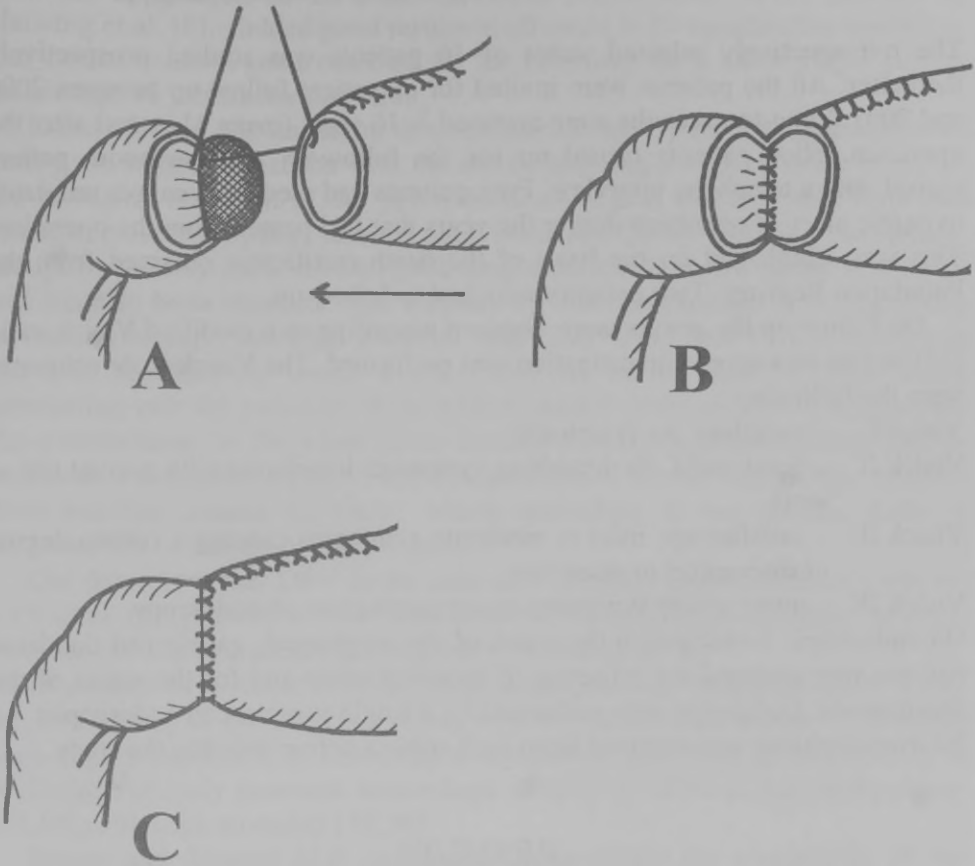
Fig. 2. Antrectomy after Herfarth. (A) Antrectomy has been performed. The posterior wall is sutured, the gastric end to the distal edge of the ulcer. (B) Posterior wall sutures are completed. The ulcer is exteriorized. (C) The anterior wall is sutured.

3. Methods of assessment of long-term outcome

The retrospectively selected series of 16 patients was studied prospectively thereafter. All the patients were invited for outpatient follow-up between 2000 and 2001. Long-term results were assessed 7–16 years (mean 11 years) after the operation. Nine patients turned up for the follow-up and one more patient agreed with a telephone interview. Four patients had died from causes unrelated to peptic ulcer or operation during the years that had passed from the operation. This was established on the basis of the death certificates obtained from the Population Registry. Two patients were lost to follow-up.

On follow-up the results were assessed according to a modified Visick scale [11] and an endoscopic investigation was performed. The Visick scale estimates were the following:

Visick I   – excellent: no symptoms
Visick II   – good: mild, no disturbing symptoms interfering with normal life or work
Visick III   – satisfactory: mild or moderate symptoms causing a certain degree of discomfort or disability
Visick IV   – poor: severe symptoms or recurrent ulcer on endoscopy

On endoscopic investigation the status of the esophageal, gastric and duodenal mucosa was assessed for presence of recurrent ulcer and for the status of the anastomosis. Endoscopy was performed by a single experienced endoscopist. Informed consent was obtained from each subject before entering the study.

RESULTS

The results of the investigation show that 7–16 years (mean 11 years) after operation long-term results were excellent or good in 90% (9/10) of cases according to Visick. In one patient the long-term result was assessed as satisfactory. Endoscopy revealed no cases of ulcer recurrence. The anastomoses after DPV and AEV were sufficiently wide in all cases.

DISCUSSION

Giant duodenal posterior wall ulcers penetrating into the pancreas are often the cause of severe hemorrhage, primarily owing to the erosion of a. gastro-duodenalis [12]. In such cases the choice of the operative method is compli-cated, particularly when ulcer hemorrhage is accompanied with stenosis of the pyloroduodenal zone.

The results of our investigation demonstrate that in these cases, excellent or good long-term results without ulcer recurrence can be obtained in 90% of cases

with the application of DPV or AEV. An earlier study of 15 patients by Helwing et al. [8], yielded good results in all cases 8–24 months after operation. Our results confirm good outcome for the first time for a much longer period, on average 11 years after operation.

In our opinion, the important determinant accounting for the achievement of such good long-term results with the use of Helwing`s method is the focus on the salvaging resection of the pyloroduodenal region together with form and function preserving plasty after Holle`s concept [13,14]. Holle`s pyloroplasty, though not widely used, showed good long-term results in our earlier study [11] and has also been recommended recently by other researchers [15]. According to Holle`s concept, duodenal posterior wall ulcer is excised. This is feasible in the case of relatively small ulcers. However, in the case of giant ulcers penetrating into the pancreas, there arise technical problems. DPV, which uses the exteriorizing of the ulcer base, enables to skip possible hazards and is technically simpler compared with ulcer excision. At the same time, stenosis from scarring around the ulcer, which, according to our present study is frequent, can be simultaneously excised.

Our data show that DPV in the case of a bleeding giant duodenal posterior wall ulcer can prevent several postoperative complications that may develop with the use of other widely used operative techniques.

Some authors have recommended, in duodenal posterior wall ulcer hemorrhage, the oversewing of the bleeding vessel with or without pyloroplasty, combined with vagotomy [16, 17]. However, a significant drawback of oversewing is occurrence of early recurrent hemorrhage in up to 17–23% of operated patients [18,19], with high mortality [19,20].

Bumm and Siewert [21] recommend to combine the oversewing of the bleeding vessel in the ulcer base, through duodenotomy, with the extraluminal ligation of a. gastroduodenalis, a. gastroepiploica dextra and a. pancreatoduodenalis. Although postoperative mortality in this case has been reported as 3–6%, long-term results obtained with this method are not available. Besides, one should also take into account that the mere ligation of the bleeding vessel, or the oversewing of the ulcer does not eliminate stenosis due to giant ulcer.

As an alternative, Billroth II gastric resection is performed in giant duodenal ulcers [18]. However, we consider that Billroth II gastric resection is less appropriate than Billroth I type resection because of the possibility of duodenal leakage following the atypical closure of the duodenal stump, as well as a significantly more frequent occurrence of postgastrectomy syndromes. Therefore, AEV with Billroth I reconstruction after Herfarth should be recommended, where the base of the giant penetrating ulcer is not excised but exteriorized [9], together with truncal vagotomy. A similar method has also been suggested by Herrington and Davidson [22]. Our earlier study of long-term outcome on average 8 years after operation shows that truncal vagotomy with antrectomy in duodenal ulcer patients yields excellent and good results without ulcer recurrence in 98% of cases [11].

7

Recent studies have shown that *H. pylori* eradication results in low recurrent bleeding in cases of conservatively treated peptic ulcer hemorrhage [23,24]. These findings have encouraged some authors to question performance of operations with vagotomy in duodenal ulcer hemorrhage [25,26]. Would it be right to resort to minimal surgery i.e. to attack only the bleeding vessel without vagotomy and to rely on *H. pylori* eradication? However, as Millat et al. have pointed out, the prevalence of *H. pylori* in bleeding peptic ulcers is not well defined and has been assessed to be lower than in uncomplicated ulcers [27]. The success of *H. pylori* treatment has been reported to be 70–80% [28]. Besides, development of giant duodenal ulcers has been associated with the use of NSAIDs [10], representing one of the main risk factors for peptic ulcer bleeding [29]. Moreover, NSAID induced ulcer hemorrhage can develop without *H. pylori* infection. Therefore, we agree with the viewpoint of Stabile and Stamos that until now no data support the efficacy of operation for bleeding duodenal ulcer that does not include vagotomy [30]. Our good long-term results from recent and present studies also serve as an argument for the use of vagotomy.

CONCLUSIONS

Ulcer exteriorizing operations with vagotomy yield good long-term results in giant duodenal posterior wall ulcers, penetrating into the pancreas, complicated with hemorrhage.

REFERENCES

1. Panos MZ, Walt RP (1993) Current management of bleeding peptic ulcer. Drugs 46:269–280
2. Cutler JA, Mendeloff AI (1981) Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. Dig Dis Sci 26 (July Suppl):90–96
3. Soplepmann J, Peetsalu A, Peetsalu M, Tein A, Juhola M (1997) Peptic ulcer haemorrhage in Tartu county, Estonia: Epidemiology and mortality risk factors. Scand J Gastroenterol 32:1195–1200
4. Villanueva C, Balanzo J (1997) A practical guide to the management of bleeding ulcers. Drugs 53:389–403
5. Asaki S (2000) Efficacy of endoscopic pure ethanol injection method for gastrointestinal ulcer bleeding. World J Surg 24:294–298
6. Peetsalu M, Sillakivi T, Väli T, Tein A (2001) Endoscopic diagnoses and treatment of peptic ulcer hemorrhage at the Clinic of Surgery of Tartu University Clinics. Acta Medica Lituanica 7 (Suppl):109
7. Peetsalu A, Vardja T, Peetsalu M, Väli T (1994) Long-term results of surgical treatment of bleeding duodenal ulcers. Br J Surg 81 (Suppl):57
8. Helwing E, Heymann H (1978) Postpylorische Resektion des komplizierten Ulcus der Duodenalhinterwand im Rahmen form- und funktionsgerechter Magenchirurgie. Chirurg 49:29–32
9. Herfarth C, Merkle P, Mattes P (1977) Billroth I-Resektion beim großen penetrierenden Duodenalhinterwand-Ulkus. Chirurg 48:123–124
10. Collen MJ, Santoro MJ, Chen YK (1994) Giant duodenal ulcer. Evaluation of basal acid output, nonsteroidal antiinflammatory drug use, and ulcer complications. Dig Dis Sci 39:1113–1116
11. Vardja T, Peetsalu A, Peetsalu M, Soplepmann J, Tein A, Väli T (1996) Surgical treatment of duodenal ulcer disease: A long term follow-up study. Acta Medica Baltica 3:256–263
12. Swain CP (1990) Patophysiology of bleeding lesions. Gastrointest Endosc 36:21–22
13. Holle F, Hart W (1967) Neue Wege der Chirurgie des Gastroduodenalulkus. Medizinische Klinik 62:441–450
14. Holle FK (1977) The physiopathologic background and standard technique of selective proximal vagotomy and pyloroplasty. Surg Gynecol Obstet 145:853–859
15. Donahue PE (2000) Parietal cell vagotomy versus vagotomy–antrectomy: Ulcer surgery in the modern era. World J Surg 24:264–269
16. Mills PR (1991) Upper gastrointestinal hemorrhage. Curr Opin Gastroenterol 7:920–924
17. Gostout CJ, Wang KK, Ahlquist DA, Clain JE; Hughes RW, Larson MV, Petersen BT, Schroeder KW, Tremaine WJ, Viggiano TR, Balm RK (1992) Acute gastrointestinal bleeding. Experience of a specialized management team. J Clin Gastroenterol 14:260–267
18. Hunt PS, McIntyre RLE (1990) Choice of emergency operative procedure for bleeding duodenal ulcer. Br J Surg 77:1004–1006
19. Kubba AK, Choudari C, Rajgopal C, Palmer KR (1996) The outcome of urgent surgery for major peptic ulcer haemorrhage following failed endoscopic therapy. Eur J Gastroenterol Hepatol 8:1175–1178

20. Kuttila K, Havia T, Pekkala E, Ali-Melkkilä T (1991) Surgery of acute peptic ulcer haemorrhage. Ann Chir Gynaecol 80:26–29
21. Bumm R, Siewert JR (1998) Chirurgisches Vorgehen beim Ulcus ventriculi und Ulcus duodeni. Chirurg 69:588–596
22. Herrington JL, Davidson J (1987) Bleeding gastroduodenal ulcers: Choice of operations. World J Surg 11:304–314
23. Graham DY, Hepps KS, Ramirez FC, Lew GM, Saeed ZA (1993) Treatment of Helicobacter pylori reduces the rate of rebleeding in peptic ulcer disease. Scand J Gastroenterol 28:939–942
24. Labenz J, Börsch G (1994) Role of Helicobacter pylori eradication in the prevention of peptic ulcer bleeding relapse. Digestion 55:19–23
25. Ohmann C, Imhof M, Röher H-D (2000) Trends in peptic ulcer bleeding and surgical treatment. World J Surg 24:284–293
26. Zittel TT, Jehle EC, Becker HD (2000) Surgical management of peptic ulcer disease today — indication, technique and outcome. Langenbeck`s Arch Surg 385:84–96
27. Millat B, Fingerhut A, Borie F (2000) Surgical treatment of complicated duodenal ulcers: Controlled trials. World J Surg 24:299–306
28. Vaira D, Menegatti M, Miglioli M (1997) What is the role of Helicobacter pylori in complicated ulcer disease? Gastroenterology 113:78–84
29. Santander C, Gravalos RG, Gomez-Cedenilla A, Cantero J, Pajares JM (1996) Anti-microbial therapy for Helicobacter pylori infection versus long-term maintenance antisecretion treatment in the prevention of recurrent hemorrhage from peptic ulcer: Prospective nonrandomized trial on 125 patients. Am J Gastroenterol 91:1549–52
30. Stabile BE, Stamos MJ (2000) Surgical management of gastrointestinal bleeding. Gastroenterol Clin North Am 29:189–222

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Soplepmann J, Peetsalu M, Sillakivi T, Tein A, Väli T, Peetsalu A.
Changes in the treatment of peptic ulcer haemorrhage.
Estonian Physician 2002; 81: 468–472 (in Estonian, summary in English).

Muutused peptilise haavandi verejooksu ravis

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peptiline haavand, verejooks, endoskoopiline ravi, kirurgiline ravi, suremus

Peptilise haavandi verejooksu ravitaktika on viimastel aastakümnetel kogu maailmas muutunud - kui varasematel aastatel kasutati verejooksu efektiivseks peetamiseks kirurgilist ravi, siis nüüd on järjest enam kasutusel endoskoopiline meetod. See on kaasa toonud ka hospitaliseerimise ja suremuse mõningase vähenemise. Selles uuringus on võrreldud kahel ajaperioodil, 1992-1993 ja 1999-2000, TÜK kirurgiakliinikus ravil viibinud peptilise haavandi verejooksuga haigete struktuuri, ravitaktikat ja -tulemusi.

Kogu maailmas väheneb peptilise haavandi (PH) tõttu hospitaliseeritute hulk (1). Viimase paarikümne aastaga on peptilise haavandi plaanilise kirurgilise ravi vajadus vähenenud mitu korda (1, 2). Vähenemine on sedavõrd drastiline, et kirjutatakse plaanilisest maokirurgiast kui kaduvast protseduurist (3). Kontrastiks eelnevale pole muutunud PH tüsistuste, verejooksu esinemissagedus ning selle tõttu hospitaliseerimine (1, 2). Peptilise haavandi verejooksu (PHV) esinemissagedus maailmas on 25–58 juhtu 100 000 inimese kohta aastas (4, 5). Eesti vastav näitaja on suur: 57 juhtu 100 000 täiskasvanu kohta aastas (6). Vanemaealiste seas on selle tüsistuse esinemissagedus oluliselt suurem ning vanemaealiste osakaal kõigist PHV-haigetest on pideva kasvutendentsiga. Mitmed autorid on seisukohal, et verejooksuga haigete suremus on viimaste aastakümnete jooksul vaatamata diagnostika ja ravi tõhustumisele püsinud muutumatuna 10% piires (7).

On teada, et 80–85%-l PHV juhtudest on verejooks enne haiglasse saabumist iseeneslikult seiskunud. Kirurgilisest vaatevinklist on probleemiks jätkuva verejooksuga patsiendid ning need, kellel tekib haiglaravil olles korduv verejooks. Uuringud on näidanud, et ainult medikamentoosse raviga ei ole võimalik käigusolevat verejooksu seisata ega haiglaravi ajal korduvat verejooksu vältida (8). Veel

paarkümmend aastat tagasi oli haavandi verejooksu ainukeseks efektiivseks peetamismeetodiks operatsioon. Hemostaasi saavutamine endoskoopilisel teel on PHV-haigete ravis oluline edasiminek. Viimasel aastakümnel on endoskoopiline ravi (ER) tänu tõendatud efektiivsusele muutunud laialdaselt kasutatavaks.

Uuringu eesmärgiks oli iseloomustada PHV ravitaktika muutusi ja selle tulemusi Tartu Ülikooli Kliinikumi (TÜK) kirurgiakliinikus viimasel aastakümnel.

Patsiendid ja meetodid

Ajavahemikul 1.1.1992–31.12.1993 (I periood) korraldati TÜK kirurgiakliinikus prospektiivne PHV-uuring. Uuringusse kaasati kõik PHVga haiglaravil viibinud 212 patsienti. Arvuti andmebaasis fikseeriti nende sugu, vanus, haavandi paiknemine ja verejooksu endoskoopiline tüüp, samuti ka patsiendile teostatud endoskoopiline või kirurgiline ravi ning lõpe.

Analoogiliselt 1992.–93. a tehtud prospektiivse uuringu protokolliga tehti retrospektiivne uuring ajavahemikul 1.1.1999–31.12.2000 (II periood). Aluseks võeti kõigi sel ajal ravil viibinud 177 PHV patsiendi andmed endoskoopiakabineti uuringukaartide alusel. Informatsioon ravi ja selle tulemuste kohta saadi haiguslugudest.

Tabel 1. Peptilise haavandi verejooksuga patsientide iseloomustus aastatel 1992-1993 (I periood) ja 1999-2000 (II periood)

	I periood Patsiendid (%)	II periood Patsiendid (%)	p
Patsientide arv	212	177	NS***
mehed	148 (69,8)	135 (76,3)	NS
naised	64 (30,2)	42 (23,7)	
Keskmine vanus	56	57	
mehed	53	54	
naised	66	68	
≥ 65aastaseid	71 (33,5)	72 (40,7)	NS
mehed	34 (23,0)	46 (34,1)	0,038
naised	37 (57,8)	26 (61,9)	NS
Haavandi lokalisatsioon*			
DH	113 (53,3)	103 (58,2)	NS
MH	97 (45,8)	68 (38,4)	NS
JPH	2 (0,9)	6 (3,4)	NS
Haavandi lok. mehed			
DH	89 (60,1)	86 (63,7)	NS
MH	57 (38,5)	44 (32,6)	NS
JPH	2 (1,4)	5 (3,7)	NS
Haavandi lok. naised			
DH	24 (37,5)	17 (40,5) 2	NS
MH	40 (62,5)	4 (57,1)	NS
JPH	0	1 (2,4)	NS
Verejooksu tüüp**			
Forrest I	24 (11,7)	30 (16,9)	NS
Forrest II	115 (55,8)	97 (54,8)	NS
Forrest IIII	67 (32,5)	50 (28,2)	NS
Informatsioon puudub	6 (-)	0	

* DH - duodenaalhaavand, MH - maohaavand, JPH - *jejunum*'i peptiline haavand;
** Forrest I - haavand jätkuva verejooksuga, Forrest II - haavand hiljutise verejooksu tunnustega (veresoone ots, hüüve haavandi põhjas), Forrest III - haavand hiljutise verejooksu tunnusteta;
*** NS - erinevus statistiliselt mitteoluline.

Duodeenumi, püüloruse ja prepüloorsed (kuni 2,5 cm püüloruse rõngast oraalsemale) haavandid liigitati patogeneetilise mehhanismi sarnasuse alusel duodenaalhaavanditeks ning haavandid alates 2,5 cm püüloorusest oraalsemal kuni *cardia*'ni klassifitseeriti maohaavanditeks (9). Eraldi rühma moodustavad maoresektsiooni-järgsed *jejunum*'i peptilised haavandid.

Verejooksu endoskoopilised tüübid jaotati Forresti klassifikatsiooni alusel (10): Forrest I – jät-kuv verejooks haavandist, Forrest II – hiljutise verejooksu tunnused (nähtav veresoone ots, hüüve haavandi põhjas), Forrest III – haavand hiljutise verejooksu tunnusteta.

Endoskoopilise ravina oli mõlemal perioodil kasutusel injektsioonteraapia. Esimesel perioodil kasutati ainult skleroteraapiat absoluutse alkoholiga (96°). Teisel perioodil kasutati lisaks injektsioonteraapiat epinefriiniga (1 : 10 000), valdavalt kombinatsioonis skleroteraapiaga, kuid ka iseseisva meetodina.

Kahe perioodi andmed töödeldi ja võrreldi arvutiprogrammi StatView® Student for the Macintosh abil. Absoluutarve võrreldi χ^2-testi abil. Yatesi korrektsiooni kasutati vajadusel χ^2-testi täpsustamiseks. Erinevust peeti statistiliselt oluliseks p väärtuse korral alla 0,05.

Tulemused
Patsientide struktuuri kajastab tabel 1. PHVga ravile sattunutest moodustavad enam kui 2/3 mehed. Meeste ja naiste suhe pole uuritaval ajavahemikul oluliselt muutunud (p = 0,154).

Uuritud meeste ja naiste keskmine vanus pole 7 aasta vältel suurenenud. PHVga hospitali-seeritud naiste keskmine vanus on üle 10 aasta

Tabel 2. Peptilise haavandi verejooksu ravitaktika aastatel 1992-1993 (I periood) ning 1999-2000 (II periood)

	I periood ER/Pt* (%)	II periood ER/Pt (%)	p
Endoskoopiline ravi			
Kõik patsiendid	46/212 (21,7)	91/177 (51,4)	0,0001
Forrest I**	13/24 (54,2)	25/30 (83,3)	0,042
Forrest II	32/115 (27,8)	64/97 (66,0)	0,0001
Forrest III	1/67 (1,6)	2/50 (4,0)	NS***
Kirurgiline ravi	85/212 (40,1)	11/177 (6,2)	0,0001
Suremus	14/212 (6,6)	4/177 (2,3)	0,042

* ER - endoskoopiliselt ravitud patsientide arv, Pt - patsientide üldarv;
** Forrest I - haavand jätkuva verejooksuga, Forrest II - haavand hiljutise
verejooksu tunnustega (veresoone ots, hüüve haavandi põhjas),
Forrest III - haavand hiljutise verejooksu tunnusteta;
*** NS - erinevus statistiliselt mitteoluline.

suurem kui meestel. 65 aastaste osakaal kõigist PHV-patsientidest oli I perioodil 34% ja II perioodil 41% (p = 0,143).

Meestel on ülekaalus verejooks duodenaal-haavandist ning naistel maohaavandist. Olulisi muutusi veritseva haavandi paiknemises uuritud ajavahemikul ei olnud. Verejooksu endoskoopiliste tüüpide (Forresti klassifikatsioon alusel) proportsioonis olulisi muutusi ei toimunud (p = 0,289).

PHV ravimeetodeid kajastab tabel 2. Oluliselt enam kasutati II perioodil endo-skoopilise verejooksu peetamise meetodit PHV ravis. Kui 1992.-93. a kasutati ERi 22%-l, siis 1999.–2000. a juba 51%-l patsientidest (p = 0,0001). Verejooksude endoskoopilise ravi osakaal kasvas II perioodil märgatavalt nii Forresti I kui ka Forresti II tüüpi verejooksude korral. Forresti I tüüpi verejooksu korral kasutati I perioodil ERi 54%-l ning II perioodil 83%-l juhtudest (p = 0,042), Forresti II tüüpi verejooksude korral vastavalt 28%-l ning 66%-l juhtudest (p = 0,0001). ERi kasutamisel tüsistusi ei esinenud.

Uuritud ajavahemiku jooksul vähenes märkimisväärselt kirurgilise ravi vajadus. Kui 1992.-93. a opereeriti 40% PHV-patsientidest, siis 1999.-2000. a vaid 6% (p = 0,0001). Samal aja-vahemikul vähenes patsientide suremus 6,6%-lt 2,3%-ni (p = 0,042).

Arutelu

Meie uuringus patsientide vanuselises struktuuris, haavandi paikmetes ega verejooksu endoskoopilistes tüüpides (Forrest) uuritud perioodidel olulisi erinevusi ei olnud. See võimaldab meil usaldusväärselt võrrelda kahte perioodi ravi taktika ja selle tulemuste osas.

Andmed näitavad, et TÜK kirurgiakliinikus kasutati II perioodil ERi peptilise haavandi verejooksu peetamiseks oluliselt sagedamini. Kui 1992.-93. a teostati seda 22%-l patsientidest, siis 1999.-2000. a enam kui pooltel ravitutest. ERi kasutamise aktiivsus jätkuva verejooksu (Forrest I) korral kasvas uuritud ajavahemikul 54%-lt 83%-ni ning hiljutise verejooksu tunnuste (Forrest II) korral 28%-lt 66%-ni.

Uuringud on näidanud, et ilma endoskoopilise ravita tekib ligikaudu pooltel patsientidest haiglas viibimise vältel kordusverejooks. Forresti I tüüpi verejooksuga haigetest jätkub verejooks või tekib kordusjooks 88%-l ning Forresti II tüübi korral tekib retsidiivjooks 43%-l juhtudest. Forresti III tüüpi verejooksu korral on see väga harv – 3% (11). Seetõttu tuleb ERi kasutada patsientidel, kellel on jätkuv verejooks või kordusverejooksu oht endoskoopilisel uuringul nähtav (veresoone ots või hüüve haavandi põhjas). Kui haavandi põhi on puhas, s.t puuduvad hiljutise verejooksu tunnused, peetakse ERi mittenäidustatuks.

Endoskoopilist injektsioonteraapiat peetakse tehniliselt suhteliselt lihtsaks, efektiivseks ja ohutuks (12). Kuigi ERi tüsistusena kirjeldatakse ka kontrollimatu verejooksu teket ning perforatsiooni, esineb neid siiski harva, kuni 0,9%-l (13). Meie patsientidel tüsistusi ei esinenud.

PHV-uuringute metaanalüüsile toetudes leidis Sacks kaastöötajatega 1990. aastal, et ER vähendab oluliselt kordusverejooksude sagedust, erakorralise operatsiooni vajadust ning suremust (14). ERi järel tekib kordusjooks kuni 20%-l PHV-patsientidest (8). Sellisel puhul on näidustatud korduv ER, mille efektiivsus on ligikaudu 75% (15). Kirurgilist ravi peetakse näidustatuks vaid juhtudel, kui medikamentoosse ravi ja ERiga verejooksu seisata ei õnnestu (16). On leitud, et rakendades aktiivselt ERi, vajab operatsiooni vaid 5–6% PHV-patsientidest (17). Jaapani kuue keskuse uuringud on veelgi paremate tulemustega (12).

Meie uuritud perioodi vältel vähenes TÜK kirurgiakliinikus PHV ravis kirurgiline aktiivsus märkimisväärselt, 40%-lt 6%-ni. Oluliselt vähem oli

vaja teha varajasi plaanilisi operatsioone, mida seni oli kasutatud kordusverejooksu suure riskiga patsientidel pärast üldseisundi stabiliseerimist. Kuigi varajasi plaanilisi operatsioone soovitatakse ka praegu (18), on tänu ERi efektiivsusele nende vajadus oluliselt vähenenud. Patsientide suremus vähenes ERi sagedamal kasutamisel 6,6%-lt 2,3%-ni. Mõned autorid on väitnud, et viimastel aastakümnetel pole suremus PHV tõttu vähenenud ja see püsib 10% ringis (7). Samas saavutati paljudes hästi töötavates keskustes juba 1980ndate lõpus suremus alla 5% (19). Kuigi leidub keskusi, kus PHV-haigete suremus on 14% (20), on õigustatud seisukoht, et PHV tänapäevane ravi peaks tagama suremuse alla 5% (21). Selle üheks olulisemaks eelduseks peetakse ERi intensiivsemat kasutamist. Seda kinnitavad ka selle töö tulemused.

Järeldus
Endoskoopilise ravi intensiivsema rakendamisega on TÜK kirurgiakliinikus oluliselt vähenenud peptilise haavandi verejooksuga patsientidel kirurgilise ravi vajadus ning nende suremus.

Kirjandus
1. Kurata JH, Corboy ED. Current peptic ulcer time trends. J Clin Gastroenterol 1988;10:259–68.
2. Schwesinger WH, Page CP, Sirinek KR, Gaskill 3rd HV, Melnick G, Strodel WE. Operations for peptic ulcer disease: paradigm lost. J Gastrointest Surg 2001;5:438–43.
3. Fallahzadeh H. Elective procedure for peptic ulcer: A disappearing operation. Am Surg 1993;59:20–2.
4. Panos MZ, Walt RP. Current management of bleeding peptic ulcer. Drugs 1993;46:269–80.
5. Cutler JA, Mendeloff AI. Upper gastrointestinal bleeding. Nature and magnitude of the problem in the U.S. Dig Dis Sci 1981; Suppl:90–6.
6. Soplepmann J, Peetsalu A, Peetsalu M, Tein A, Juhola M. Peptic ulcer haemorrhage in Tartu county, Estonia: Epidemiology and mortality risk factors. Scand J Gastroenterol 1997;32:1195–200.
7. Iambrenghi OC, Lospalluti M, Piccinni G, Lippolis A. Is endoscopic injection hemostasis of bleeding gastrointestinal ulcers obsolete in 1995? Surg Endosc 1995;9:1090–2.
8. Kolkman JJ, Meuwissen SGM. A review on treatment of bleeding peptic ulcer: A collaborative task of gastroenterologist and surgeon. Scand J Gastroenterol 1996;31 Suppl 218:16–25.
9. Horowitz J, Kukora JS, Ritchie WP. All perforated ulcers are not alike. Ann Surg 1989;209:693–6.
10. Kohler B, Riemann JF. The endoscopic doppler: Its value in evaluating gastroduodenal ulcers after hemorrhage and as an instrument of control of endoscopic injection therapy. Scand J Gastroenterol 1991;26:471–6.

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Special courses

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1999   II Baltic Endoscopy Workshop, Jurmala, Latvia
2000   European School of Oncology colorectal cancer course, Moscow,
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2001   III Baltic Endoscopy Workshop, Vilnius, Lithuania
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Professional employment

1987–1988 Tartu University Surgical Clinic, internship
1988–1988 Department of Surgery, Central Hospital of Rapla County, general
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1988–1991 Chair of General Surgery, Anaesthesiology and Intensive Care of Tartu University, assistant
1996–1999 II Department of Surgery, Tartu University Clinic of Surgery, general surgeon
2000 Department of Surgical Oncology, Clinic of Haematology and Oncology, Tartu University Clinics, oncological surgeon

Scientific work

Main scientific research focuses upon upper gastrointestinal haemorrhage and colorectal cancer.

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1987–1988	Tartu Ülikooli Kirurgiakliinik, intern
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Teadustegevus

Peamisteks uurimisvaldkondadeks on seedetrakti ülaosa verejooks ja kolorektaalne vähk.

Kakskümmend üheksa publikatsiooni.

Kuulub järgmistesse teadusseltsidesse: Eesti Gastroenteroloogide Seltsi, Tartu Kirurgide Seltsi, Eesti Kirurgide Assotsiatsiooni, Eesti Organite ja Kudede Transplantatsiooni Ühingu, Eesti Onkoloogide Seltsi, Eesti Gastrointestinaalse Endoskoopia Ühingu ja European Association for Endoscopic Surgery.

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