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**Stress-induced gastric lesions in newborns  
treated in intensive care - occurrence,  
risk factors and therapy**

*University of Tampere  
Tampere 1999*

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## **ACADEMIC DISSERTATION**

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ISBN 951-44-4707-7  
ISSN 1456-954X

"To understand a man's stomach one must  
understand the man"

(Stewart Wolf 1981)

To Markku and our sons: Kimmo, Timo, Aki

## **CONTENTS**

### **LIST OF ORIGINAL PUBLICATIONS**

### **ABBREVIATIONS**

### **INTRODUCTION**

### **REVIEW OF THE LITERATURE**

**Impact of stress-induced gastric lesions**

**Risk factors for stress-induced gastric lesions in patients treated in intensive care**

**Frequency of stress-induced gastric lesions**

**Appearance of the gastric mucosa in patients under stress**

**Pathogenesis of stress-induced gastric lesions**

**Gastric pH and the newborn**

*Monitoring of gastric pH*

**Diagnosis of stress-induced gastric lesions in newborns**

**Prevention and treatment of stress-induced gastric lesions**

*Histamine -H<sub>2</sub>- receptor antagonists*

*Effectiveness of preventive medication of stress-induced gastric complications*

### **AIMS OF THE STUDY**

### **SUBJECTS AND METHODS**

**Patients**

**Gastrosopies and biopsy samples**

**Intraluminal gastric pH monitoring**

**Treatment**

**Statistical analysis**

**Ethics**

**RESULTS**

**Frequency of stress-induced gastric lesions in newborns treated in intensive care**

**Risk factors for stress-induced gastric lesions in newborns**

**Ranitidine treatment and stress-induced gastric lesions in newborns**

**DISCUSSION**

**Gastroscopy**

**Visual and histological evaluation**

**Frequency of the lesions and symptoms**

**Evaluation of risk factors**

**Optimisation of treatment of stress-induced gastric lesions**

**SUMMARY**

**FINNISH SUMMARY**

**ACKNOWLEDGEMENTS**

**REFERENCES**

**ORIGINAL PUBLICATIONS**

## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following communications, referred to in the text by the Roman numerals I-IV. In addition, previously unpublished data are presented.

I Mäki M, Ruuska T, Kuusela A-L, Karikoski-Leo R and Ikonen RS (1993): High prevalence of asymptomatic oesophageal and gastric lesions in preterm infants in intensive care. Crit Care Med 21: 1863-1867.

II Kuusela A-L, Mäki M, Ruuska T, Laippala P: Stress-induced gastric findings in critically ill newborn infants - frequency and risk-factors. Submitted for publication

III Kuusela A-L, Ruuska T, Karikoski R, Laippala P, Ikonen RS, Janas M, Mäki M (1997): A randomized, controlled study of prophylactic ranitidine in preventing stress-induced gastric mucosal lesions in neonatal intensive care unit patients. Crit Care Med 25: 346-351.

IV Kuusela A-L (1998): Long-term gastric pH monitoring in determining the optimal dose of ranitidine for critically ill preterm and term newborns. Arch Dis Child; 78: F151-153.

## ABBREVIATIONS

VLBW	very-low-birth-weight
NICU	neonatal intensive care unit
cAMP	cyclic adenosine monophosphate
H <sub>2</sub>	Histamine-2-
CI	confidence interval
OR	odds ratio



## INTRODUCTION

It is only during the past three decades that modern neonatal intensive care has evolved. Artificial ventilators have become more sophisticated and a variety of systems of ventilation can be used effectively even in neonatology: we may thus really speak of neonatal intensive care. With these advances increasing numbers of severely ill and more preterm infants have begun to survive. As always, however, progress has its prize. It is easy to understand that in many ways preterm newborns are more fragile than adults, and therefore also more vulnerable to stress, which in turn has an influence on their survival.

The presence of erosive and necrotic lesions in the gastrointestinal tract of burn victims was first described over 150 years ago (Bounous 1982, Ricour 1989). Since that time substantial evidence has accrued showing that upper gastrointestinal mucosal lesions complicate treatment in 60% to 100% of intensive care unit patients (Anand 1993). For this reason it is nowadays acceptable to use prophylactic treatment for stress-induced gastric lesions in adults treated in intensive care, who have certain risk factors (Wilcox and Spenny 1988, Schuster 1993).

The most important problems in the case of premature infants are connected with respiration, and in most cases mechanical ventilation is needed over one to several weeks. Mechanical ventilation is the single most prominent risk factor underlying upper gastrointestinal problems in adults treated in intensive care (Schuster et al. 1984). In children some studies on stress-induced gastric lesions have shown that the incidence does not differ from that of adults (Cochran et al. 1992, López-Herce et al. 1992). Most paediatric intensivists consider upper gastrointestinal bleeding a clinically significant problem (Lacroix et al. 1992), and prophylactic treatment is

commonly used even though the effectiveness of this approach is not well established in the case of children (Lacroix and Gauthier 1990).

The precise aetiology of stress-induced gastric lesions in infants treated in intensive care are poorly substantiated. Any stressful event during pregnancy or labour or soon after birth may be inducive of mucosal lesions and bleeding from the upper gastrointestinal tract (Pugh et al. 1979, Wen et al. 1992). A number of case reports from the thirties to the nineties describe massive bleeding after birth and perforations during the first week of life (Stanley-Brown and Stevenson 1965, Adeyemi et al. 1979, Bell et al. 1981, Holgersen 1981, Ng et al. 1991, Pelizzo et al. 1998). The reports in question were based on clinical symptoms, surgery or post-mortem findings. Technical improvement in gastroscopes, especially the development of fiberoptic endoscopes (Liebman et al. 1978, Olives 1989), has made it possible to evaluate gastric lesions even in infants before any serious complications have evolved (Chang et al. 1983). Recent advances allow gastroscopies to be performed even on very-low-birth-weight (VLBW) infants. The aim of this present study was to ascertain the clinical significance and optimal treatment of stress-induced gastric lesions of preterm and term infants treated in neonatal intensive care units (NICU).

## **REVIEW OF THE LITERATURE**

### **Impact of stress-induced gastric lesions**

Gastric ulcers are rare among infants in the neonatal period (Mezoff and Balistreri 1995), and when they do occur in the newborn they usually arise secondary to serious underlying illness. The digestive system is particularly sensitive to stress, and this sensitivity is increased in children, especially in infants (Touloukian et al. 1972). Although massive bleeding seldom occurs it is always life-threatening for critically ill patients. Some gastrointestinal complications of stress are avoidable, most are amenable to treatment if recognised early, and all are potentially lethal.

Any physiological stress impairs the ability of the intact gastric mucosa to maintain homeostasis and results in the formation of multiple superficial gastric erosions. Stress ulceration, however, develops in the setting of severe physiological stress - hypotension, respiratory insufficiency, uraemia, sepsis, major burns and in association with intracranial disease (Marrone and Silen 1984). In such seriously ill patients acute stress ulcers usually begin as multiple shallow erosions. Mucosal injury is present within hours of stressful events. Upon endoscopic examination performed in adult patients treated in intensive care, multiple gastric erosions have been observed in all patients within 72 hours of admission to intensive care (Lucas et al. 1971). As patients recover from the stressful event the erosions gradually decrease in size and depth and usually disappear within 10 to 14 days without significant episodes of bleeding (Marrone and Silen 1984). Males and females are equally affected.

In a varying percentage of patients stress ulceration leads to clinically significant gastrointestinal haemorrhage. Even after the lesion becomes sufficiently deep to cause severe and life-threatening haemorrhage, it causes no pain, and the symptoms are usually delayed for several days (Adeyemi et al. 1979). Hence, especially in infants, once stress ulcers do cause significant haemorrhage, the likelihood of mortality approaches 40% (Bell et al. 1981). However, the influence of gastric ulcers on mortality has not been conclusively defined. There are case reports (Bickler et al. 1993) on gastric perforations in infants treated in intensive care, but there is no convincing evidence connecting these with stress-induced lesions. That stress may even cause perforations in infants has nevertheless been surmised.

### **Risk factors for stress-induced gastric lesions in patients treated in intensive care**

Although there are many reports of stress-induced gastric lesions causing overt and occult bleedings, it has not been convincingly shown that prevention of these bleedings by treating all intensive care patients with any kind of medication alters overall morbidity or mortality (Shuster et al. 1984, Tryba 1991a). Certainty as to who is likely to bleed would bring precision to the approach, and this might reduce the side-effects of the therapy given and could also influence morbidity (Cook et al. 1994). There have therefore been numerous both retrospective and prospective evaluations attempting to delineate the risk factors for stress-induced gastric lesions (Leivonen et al. 1991, Metz et al. 1993, Ill et al. 1996).

It has been shown that there are certain risk factors which play an important role in the development of stress-induced gastric lesions. Cook and coworkers (1994) have described two strong independent risk factors for bleeding among 2252 adult patients treated in intensive care: respiratory failure and coagulopathy. Within the group of patients with these risk factors the mortality rate was 48.5 percent. The end points were overt bleeding and clinically important bleeding. Respiratory failure was defined as need for mechanical ventilation for at least 48 hours and coagulopathy if the a platelet count was less than 50 000 per cubic millimetre or partial-tromboplastin time more than twice the upper limit of normal. Upper gastrointestinal endoscopy was not performed during the study. These risk factors have in fact been described mostly in adult patients treated in intensive care (Table 1), but infants treated in neonatal intensive care are particularly vulnerable to these factors, and modern neonatological treatment enables even VLBW infants to survive (Rennie 1999). Because infants are especially sensitive to gastric lesions (Ricour 1989), even small disturbances in homeostasis may increase the probability of gastric lesions.

The most common changes in the gastric mucosa occur rapidly and almost universally following surgery or major trauma. Stress ulcers are associated with shock, respiratory failure, sepsis, hypoglycaemia, severe burns and intracranial lesions. These ulcers usually present as medical emergencies with perforation or haemorrhage.

Factors such as mechanical ventilation (Garland et al. 1985), various medications (Alpan et al. 1985, Butt et al. 1986, O'Neil et al. 1992), and difficulties during pregnancy (Pugh et al. 1979) have been implicated in the development of gastric lesions, bleeding from the gastrointestinal tract and ulcers and perforations in newborns. All risk factors increase the severity of the illness also in the neonatal context and thereby aggravate the stress itself. VLBW infants require several invasive

interventions to survive. These are mostly painful, and pain itself is of course another stress-causing factor. Contrary to previous beliefs it has now been conclusively shown that premature infants are also sensitive to pain and need adequate pain assessment and relief (Pokela 1994).

**Table 1. Risk factors for stress-induced gastric lesion according to the literature.**

<b>Risk factor</b>	<b>References</b>
Mechanical ventilation	Schuster et al. 1984, Marrone and Silen 1984, Geus and Lamers 1990, Ben-Menachem et al. 1994, Cook et al. 1994, Mezzoff and Balistreri 1995, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997
Shock, any haemodynamic problems	Marrone and Silen 1984, Geus and Lamers 1990, Cochran et al. 1992, Ben-Menachem et al. 1994, Mezzoff and Balistreri 1995, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997
Sepsis, especially peritonitis	Marrone and Silen 1984, Geus and Lamers 1990, Lacroix et al. 1992, Ben-Menachem et al. 1994, Mezzoff and Balistreri 1995, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997
Coagulopathy	Schuster et al. 1984, Lacroix et al. 1992, Ben-Menachem et al. 1994, Cook et al. 1994, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997
Intracranial diseases, neurosurgery	Geus and Lamers 1990, Mezzoff and Balistreri 1995, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997
Hepatic failure	Marrone and Silen 1984, Geus and Lamers 1990, Ben-Menachem et al. 1994, Cook et al. 1996, Lu et al. 1997
Burns	Geus and Lamers 1990, Mezzoff and Balistreri 1995, Cook et al. 1996, Lu et al. 1997, Tryba and Cook 1997, Geus and Lamers 1990
Renal failure	Marrone and Silen 1984, Geus and Lamers 1990, Ben-Menachem et al. 1994, Cook et al. 1996, Lu et al. 1997
Multiple trauma	Geus and Lamers 1990, Lacroix et al. 1992, Cochran et al. 1992
Corticosteroids	Ben-Menachem et al. 1994, Cook et al. 1996
Tetraplegia	Tryba and Cook 1997,
Multiple organ failure	Tryba and Cook 1997,
Jaundice	Lu et al. 1997
Hypoglycaemia	Mezzoff and Balistreri 1995
Cardiac arrest	Ben-Menachem et al. 1994
Mother's stress during pregnancy	Pugh et al. 1979

## **Frequency of stress-induced gastric lesions**

Little research has been done on the frequency of stress-induced gastric lesions in children and especially in infants treated in neonatal intensive care. As noted in studies among adult intensive care patients, the frequency varies according to the method used in evaluation. When the gastric lesions are diagnosed with an endoscope, the frequency rises to 100 % (Lucas et al. 1971). In the few studies made of children treated in intensive care the frequency has been defined without endoscopy and has varied from 5% to 25 % (Cochran et al. 1992, Lacroix et al. 1992, Lopez-Herce et al. 1992). Since these stress-induced gastric lesions are mostly painless (Adeyemi et al 1979), and other symptoms such as overt gastrointestinal bleeding appear late, and their frequency is underestimated if evaluated by symptoms alone. Painlessness and delayed manifestation are the reason why in most intensive care units prophylactic treatment is used to counter these lesions before overt symptoms develop. Prophylactic treatment reduces the incidence of severe stress-induced gastric lesions from 71% to 33% as examined by endoscope (Behrens et al. 1994). In modern adult intensive care management the overall incidence of clinically important stress ulcer bleeding may be in the range of 0.1 to 3% and the incidence of overt bleeding between 3-13%, depending on whether there are regarded as risk factors or not (Cook et al 1994, Zandstra et al. 1994).

The literature includes no studies on the frequency of upper gastrointestinal bleeding and/or stress-induced gastric lesions in newborns treated in neonatal intensive care. However, a number of case reports on so-called spontaneous gastric perforation during the neonatal period have been published throughout the 20th century. Some authors connect these perforations to stress (Sarna et al. 1981) or specific risk factors such as mechanical ventilation (Garland et al. 1985), corticosteroids (Wolf



et al. 1991), indomethacin (Nagaraj et al. 1981) or tolazoline treatment (Wilson et al. 1985, Butt et al. 1986). Patients in these case reports or retrospective analyses have received a variety of medications or enteral feedings, which confuses the results. Prophylactic, but empirical, treatment has also been used in newborns by prescribing antacid or histamine - 2 – (H<sub>2</sub>) receptor blockers (Agarwal et al. 1989, Kelly et al. 1993). However, these studies allow no conclusions as to how many infants actually need prophylactic treatment and for how long. Table 2 lists case reports and retrospective studies on stress-induced perforations and gastric ulcers or symptomatic gastrointestinal bleeding associated with stress in newborns treated in intensive care.

**Table 2: Previous reports on perforations, gastric or duodenal ulcers or gastrointestinal haemorrhage in newborns treated in intensive care.**

Author	Number of preterm/term infants	Symptoms and findings	Age at symptoms	Treatment	Mortality	Type of study
Liebman et al. 1978	0/1	Haematemesis, superficial erosions	6 h	lavage	0	Case report
Adeyemi 1979	0/4	Perforations	5wk - 8mo	surgery	2/4	Case report
Sarna et al. 1981	0/38	Gastric bleeding	0 - 4 days	ranitidine	0	Controlled study
Bell 1981	2/8	Haemorrhage, perforations	3 days - 6 mo	surgery	4/10	Retrospective study
Garland et al. 1985	18/2	Perforations	0 - 5 days	surgery	5/20	Retrospective study
Agarwal et al. 1989	0/77	Gastric bleeding	0 - 30 days	cimetidine	7/77	Case-control study
O'Neil et al. 1992	3/0	Ulcer, perforation, haemorrhage	10 - 28 days	surgery and H <sub>2</sub> -blocker	2/3	Retrospective study
Bruce et al. 1993	7/3	Pneumoperitoneum	22h - 14 days	surgery	4/10	Retrospective study
Fontana et al. 1993	0/30	Haematemesis	under 2 days	ranitidine	0	Prospective evaluation
Aslam et al. 1995	3/0	Pneumoperitoneum	10 - 30h	surgery	0	Case report
McDonnell and Evans 1995	3/0	Pneumoperitoneum, haemorrhage	12 - 16 days	cimetidine surgery lavage	1/3	Case report
Pelizzo et al 1998	7/4	Haematemesis	12h - 3 days	Surgery or ant-acids or H <sub>2</sub> -blockers	3/11	Case report

mo = month, h = hour, wk = weeks

## **Appearance of the gastric mucosal lesions in patients under stress**

The appearance of the gastric mucosa in patients under stress may be evaluated visually using gastroscopy, by histopathology of biopsy specimens, or at autopsy. The development of fiberoptic gastroscopes has greatly extended our knowledge of gastrointestinal tract mucosal lesions. Recently, it has become routine to perform upper gastrointestinal endoscopy also in infants on the occurrence of certain symptoms (Ruuska 1994, Ruuska et al. 1996). By this means mucosal changes may be demonstrated with high precision. These studies have been open and descriptive in design.

Lucas et al. (1971) have described gastric mucosal visual lesions in adult patients treated in intensive care. Very early during stress, hyperaemia and small petechiae can be seen as markers of mucosal friability. Thereafter haemorrhage spreads and up to 1- to 2- mm erosions are present. After 72 hours severe stress induces multiple gastric erosions predominantly in the fundic region, these lesions being observed in 100 per cent of patients (Lucas et al. 1971). The lesions are highly likely to bleed if blood coagulation is somehow disturbed, for which reason the newborn are especially prone to bleed (Reverdiau-Moalic et al. 1996). After recovery the erosions gradually decrease in size and depth and usually disappear within two weeks (Marrone and Silen 1984). During continuous exposure to a risk factor such as mechanical ventilation for several weeks the lesions spread and become deeper, forming ulcers and erosions which eventually lead to perforations.

In infants the first description of this kind of gastric lesions was published by Liebman et al., in 1978, since when there have been several case reports on ulcers and erosions in infants treated in neonatal intensive care. These lesions

apparently progress to perforation if neither the stress is eliminated nor treatment started (Garland et al. 1985). No connection of gastric perforation to stress has been conclusively demonstrated, and findings have often been associated with other factors such as indomethacin (Nagaraj et al. 1981) or corticosteroid treatment (Ng et al. 1991).

The histopathology of gastric lesions is generally classified according to the inflammatory cells in the gastric mucosa (Toukan et al. 1985). In stress-induced lesions, however, few inflammatory cells are present in the lamina propria (Tryba 1994), and it is therefore difficult to classify these injuries according to the gastritis classification (Misiewicz et al. 1990). Under stress only severe haemorrhage is usually seen, and erosions appear later together with inflammatory cells. Histopathological descriptions are lacking in the case of newborns, because no biopsies have been taken at endoscopy; most of the data available are based on autopsy findings.

Cystic glands of the gastric mucosa with gastritis have been described after gastric surgery for duodenal or gastric ulcer (Niv and Turani 1991), and their association with gastritis raises the possibility of their being secondary to the inflammatory process. These cysts have been considered a premalignant condition (Honoré et al. 1979), but may in neonatal patients be a sign of immaturity. Such lesions have never been connected to stress-induced gastric lesions or described in infancy.

## Pathogenesis of stress-induced gastric lesions

The formation of gastric mucosal stress lesion and ulceration is a multifactorial system. It can be described as a balance between aggressive and defensive factors (Tryba 1994, Mezoff and Balistreri 1995) (Table 3).

**Table 3: List of the factors influencing the formation of stress-induced gastric lesions according to Tryba 1994 and Mezoff and Balistreri 1995**

Aggressive factors	Defensive factors
Acid	Bicarbonate
Bile acids	Blood flow in the mucosa
Drugs	Cell turnover
Free radicals	Hydrophobic layer
Gastrin	Mucus
Pepsin	Prostaglandins

In the absence of harmful events such as stress all these factors are balanced. In the normal state the gastric mucosa tolerates high acid secretion and this secretion increases the blood flow in the mucosa, which in turn improves the function of the defensive factors. It has been shown that high acid secretion alone cannot induce stress ulceration. If, however, the gastric mucosal barrier is somehow broken, acidity worsens the lesions. Thus while gastric acid plays an important role in the development of acute gastric erosions, the dynamic process is also dependent on changes in gastric blood flow, mucosal permeability, the secretory status of the mucosa and the overall acid-base balance.

In certain stress situations it has also been shown that even though there is no hypersecretion of acid and intraluminal acidity is not lowered, gastric lesions are present (Tryba 1994). Direct injury to the gastric mucosa usually results from exposure to drugs (e.g. corticosteroids, nonsteroidal anti-inflammatory agents), hypersecretion of acid and pepsin or reflux of bile salts. This latter takes place when motility is decreased and the pylorus is poorly closed under stress (Miller 1987). Under stress all these mechanisms act in concert to break the mucosal barrier and induce the development of lesions.

The functional activity of the respective aggressive and defensive factors is under cephalic, gastric and intestinal control. Vagal stimulation is the most important component in cephalic activity. Anything which causes vagal stimulation changes the acid base balance in the gastric mucosa towards acidity (Glavin et al. 1991). It is this stimulation which contributes largely to spontaneous secretion in the unfed or basal state. The second mechanism is direct gastric control, where secretion is stimulated by distension or food in the stomach, while the third component in the control system is intestinal stimulation, which increases gastrin secretion. All three mechanisms stimulate gastric acid secretion directly or by causing decreased function of the defensive factors. Vagal stimulation also inhibits gastric motility and directly increases acidity in the gastric lumen.

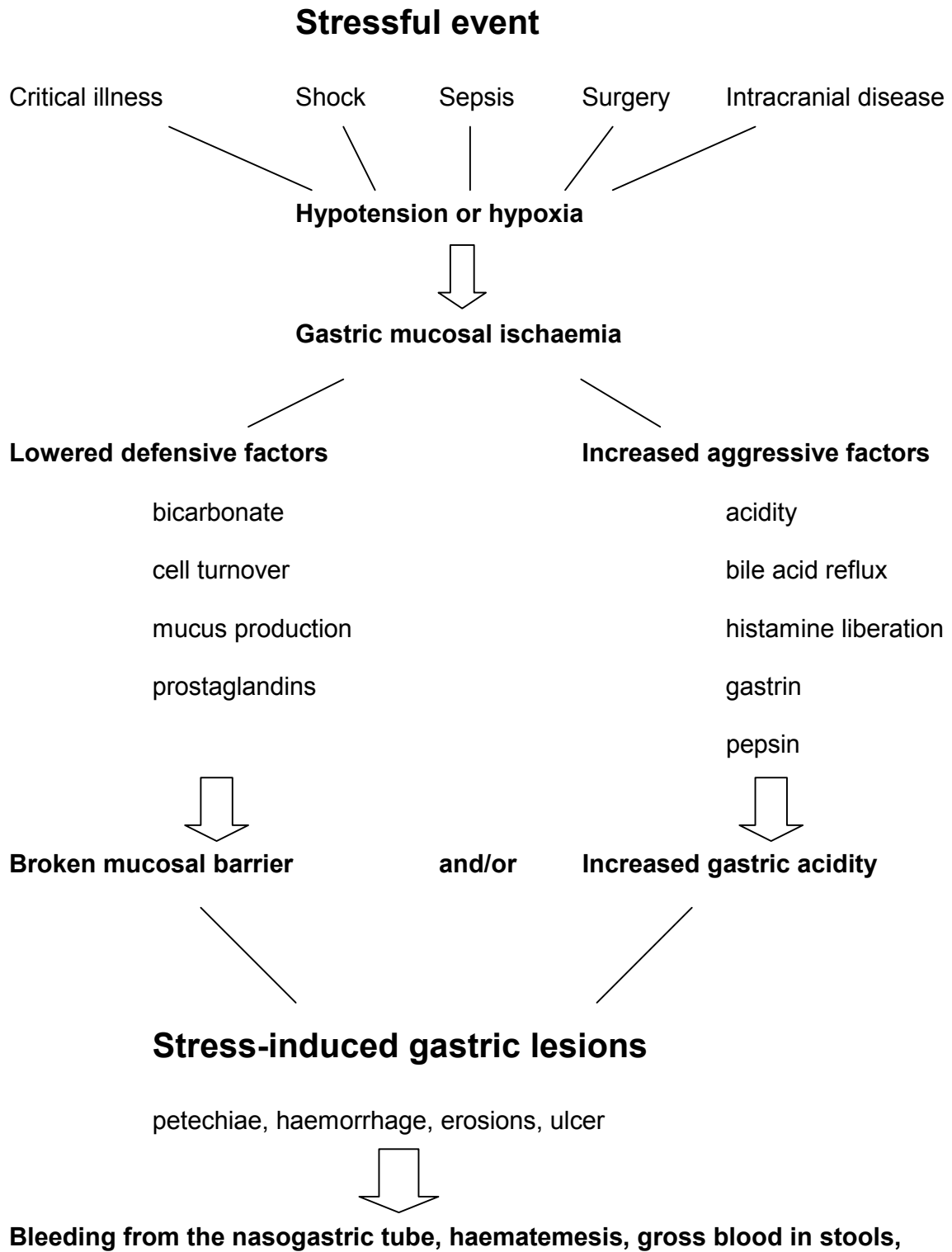
The stomach possesses a very rich blood and lymphatic circulation. This is one reason why during hypotension the gastrointestinal tract is the first area to develop ischaemia and the last to recover from it (Casado-Flores et al. 1998). Even a slightly decreased blood volume entailing no changes in systemic arterial pressure has been shown to reduce splanchnic perfusion by up to 40%. Any degree of ischaemia will induce changes in energy metabolism and will also result in discontinued back diffusion of hydrogen ions. Hypoxia increases local free radicals in the stomach and these radicals are partly causative in oxidative damage of the

gastric mucosa induced by stress (Das et al. 1996). Foetal or neonatal hypoxia may be the first step to gastric lesion in newborns, leading to focal intestinal perforation (Raghuveer et al. 1996).

All the said defensive factors require ample local oxygenation. An appropriate cell turnover is necessary for mucus regeneration. However, a basic requirement is good blood circulation and oxygenation, both of which are very often disturbed during a severe illness such as those calling for treatment in intensive care. Also the production of mucus and bicarbonate requires good circulation and oxygenation. Bicarbonate secretion by surface epithelial cells provides a buffer to the harmful effects of gastric acid. This secretion correlates with the circulation of the stomach and is depressed during hypoxia and hypotension.

The mechanisms of stress-induced gastric lesions have been studied in experimental conditions (Holgersen 1981) or in adults (Tryba 1987) under stress. It may be assumed that the mechanisms underlying these lesions are the same in newborns, since both the maturation and the function of the gastrointestinal tract are already relatively advanced during early foetal life (Hamosh 1994).

A schematic presentation of various factors possible contributing to the pathogenesis of stress-related mucosal injury is given in Figure 1.



**Figure 1: Pathophysiology of acute gastric mucosal lesions**



## **Gastric pH and the newborn**

Knowledge of gastric acid secretion of infants has increased during the last few years. Structurally mature cells, with the proton pump in parietal cells in the body and antrum of the foetal stomach have been shown to exist as early as at 13 weeks of gestation (Kelly and Newell 1994). Thus even the most immature infants can secrete hydrogen ion to form gastric acid. Some studies, however, have shown that immediately after birth the gastric pH is alkaline, partly in consequence of swallowed amniotic fluid (Avery et al. 1967), and only during the first days of life becomes increasingly acidic (Sondheimer et al. 1985). During the first months of life, gastric pH is variable but often is below 4 before feeding in healthy and critically ill neonates (Chhattriwalla et al. 1980). The reasons for these changes are poorly understood.

Gastric acid secretion from parietal cells is controlled by histamine, acetylcholine and gastrin (Mezoff and Balistreri 1995). Histamine stimulates acid secretion via cyclic adenosine monophosphate (cAMP) and both cholinergics and gastrin increase the amount of intracellular calcium in parietal cells, which influences gastric acid secretion. The parietal cells possess histamine and gastrin receptors, and immaturity of these could explain a lack of response to different stimulations. Such reactions require energy and in ischaemia they are easily disturbed. For example Hyman et al. (1985) failed to reduce gastric acid secretion with a histamine analogue with normal doses 5 mg/kg/day. There are on the other hand several studies which show definitively that H<sub>2</sub>-receptor blocking is effective in reducing intragastric acidity as measured by intraluminal gastric pH also in pre-term and term infants (Sarna et al. 1991, Kelly et al. 1992, Fontana et al. 1993). This apparent conflict of results can be explained by the fact that H<sub>2</sub>-receptor an-

tagonists not only act via histamine receptors but also suppress all modes of gastric acid secretion via central mechanisms (Kelly et al. 1992, Mezzoff and Balistreri 1995)

The role of gastrin secretion in gastric acidity is not clear in the case of preterm infants. Some studies have shown high serum gastrin levels in newborns (Aynsley-Green et al. 1990, Meetze et al. 1992) and that enteral feedings increase gastrin levels (Euler 1979). The role of gastrin could also change during the development of the gastrointestinal tract (Marchini and Uvnäs-Moberg 1992). There are no data as to how the immature stomach responds to gastrin stimulation. It may be that the feedback system of low gastric pH reducing gastrin levels is not functioning adequately in such a state of immaturity. The overall gastric acid secretory response is similar to that in older children and adults, although responsiveness to histamine and gastrin is partly deficient (Harada et al. 1984).

#### *Monitoring of gastric pH*

Measurement of gastric pH is one of the main issues in controlling stress-induced gastric lesions. A pH value of 4.0 is usually considered the demarcation point to initiate or alter therapy. The most common means of monitoring gastric pH is by sampling the gastric juice via a nasogastric tube and determining pH using pH-sensitive litmus paper on which colour change is compared visually to a printed scale (Dobkin et al. 1990). This mode of measurement correlates to the real gastric pH at the time, but the sample is often small and the result can therefore be unreliable (Caballero et al. 1990). Nowadays intraluminal electrodes are used for continuous measurement (Eisenberg et al. 1990). Microelectrodes positioned in the

stomach record pH continuously and any changes are easy to discern. Results of this approach have been criticised in that it does not directly measure acid secretion (Fisher et al. 1996). However, it can be used in patients whose intragastric hydrogen ion concentration must be kept above a specific level. The technique of pH probe - nasogastric tube is simple and is applicable in patients at risk of stress ulcer bleeding. There is conflicting evidence as to the equivalence of litmus paper and intragastric pH probes (Bradley et al. 1998). The use of litmus paper to determine gastric pH is both easy and inexpensive (Levine et al. 1994). With the intraluminal probe gastric pH can be measured even when there is little or no gastric juice, as is often the case in newborns, and the determination is continuous, so that requisite adjustments in treatment can be made swiftly (Eisenberg et al. 1990, Halpern et al. 1992).

Intramucosal gastric pH measurement by gastric tonometry has been used in adults treated in intensive care (Doglio et al. 1991). This is also a non-invasive method of evaluating more specifically mucosal acidity. It has been shown also to estimate the state of homeostasis in the circulation and may thereby be taken as a prognostic index of mortality in critically ill patients. However, the method has only occasionally been used in children, because the electrode is rather large and as yet unsuitable for use in newborns (Krafte-Jacobs et al. 1995, Booker et al. 1996, Casado-Flores et al. 1998).

## **Diagnosis of stress-induced gastric lesions in newborns**

Symptoms and signs should lead to diagnosis. If symptoms are associated with pain, the diagnosis is easier. It is known that stress-induced gastric lesions are painless (Adeyemi et al. 1981) and that bleeding is only a late sign of the lesions. Also bleeding evinces different stages, from hardly noticeable to massive haemorrhage, from occult to overt. It is not unusual that stress-induced bleeding is massive and uncontrolled. Massive upper gastrointestinal bleeding is associated with increased mortality. Judging from findings in adults, it takes considerable time for the lesions to progress to perforation, while reports on newborns mostly merely describe gastric perforations in severely ill newborns (Sherman and Clatworthy 1967). To ensure timely detection of bleeding the gastric juice must thus be repeatedly checked for the presence of blood, and at any sign of bleeding an endoscopic evaluation should be undertaken without delay (Hyams et al. 1985).

The diagnostic capacity of radiological studies of upper gastrointestinal lesions by the double-contrast technique is approaches 90% (Mezoff and Balistreri 1995). However, in the case of children and especially in very severely ill newborns these studies are technically difficult to perform which renders them in practice unfeasible.

Upper gastrointestinal endoscopy of newborns has been a highly controversial issue; it has been claimed that this measure can cause more harm than good (Lowdon and Tidmore 1988, de Boissieu et al. 1994). The development of the new fiberoptic technique has made endoscopies possible also in newborns and even in VLBW infants (Ruuska 1994). This advance has made it possible to demonstrate that these infants have gastric lesions early during intensive care. Such

lesions may have an effect on mortality and morbidity, as is the case in adult patients treated in intensive care.

### **Prevention and treatment of stress-induced gastric lesions**

The key to the prevention and treatment of stress-induced gastric lesions lies in optimal intensive care. Lowering the level of stress is one of the main problems and it can sometimes be successfully resolved with good prenatal, antenatal and postnatal practice. After birth the most important steps in prevention are avoidance of hypovolaemia, immediate and adequate provision oxygen, prevention of infections and ensuring adequate analgesia and sedation. Especially in newborns treated in intensive care hypoxia and hypotension are the most critical problems in the immediate postnatal period. Despite all improvements in intensive care, stress-induced gastric lesion persists as a clinical entity and some patients need prophylactic therapy (Ben-Menahem et al. 1994, Tryba 1995, Cook et al. 1996, Tryba and Cook 1997, Lu et al. 1997).

Enteral nutrition is considered to cure and prevent gastric lesions also under stress (Pingleton and Hadzima 1983, Raff et al. 1997). In the case of newborns, however, it is not possible to start enteral nutrition early enough. Since in clinical practice, nutritionally significant enteral nutrition is usually commenced only several days postpartum, after the most critical phase of neonatal intensive care, the effect of the nutrition comes when most severe stress is already past. It is imperative that enteral nutrition be commenced at the earliest possible stage to support the healing processes (Dickson and Nour 1995, Troche et al. 1995).

In cases where prophylaxis is not used or the prophylactic manoeuvre fails, treatment of stress-induced gastric lesions should be started at the first symptoms, blood-stained aspirates from the nasogastric tube. In adult patients, various medications have been employed, while in newborns with haematemesis or melaena mostly H<sub>2</sub>-receptor blockers (Sarna et al. 1981, Agarwal et al. 1989) or antacids or both (Pelizzo et al. 1998) have been used. In the acute phases, when bleeding must be kept under control, iced saline lavage is commonly used. Significant loss of blood, especially with hypotension, must be compensated with blood transfusions. Sometimes stress-induced gastric lesions lead to gastric perforation and surgery is then the only possible treatment. In these circumstances mortality increases significantly, since such patients are already severely ill and cannot sustain the added stress of a major operation.

Drugs for the prevention of gastric lesions in adult patients are listed in Table 4.

Antacids neutralise gastric acid in large doses, but low doses can also be effective. The benefit may be related to the release of endogenous prostaglandins. By inducing production of prostaglandins antacids increase mucus and bicarbonate secretion, which is the protective mechanism of the gastric wall under stress. Findings here are mostly from experimental studies, whereas in human studies the efficacy of antacids has not been so clearly demonstrated. The onset of action of these drugs is not rapid enough for use as monotherapy (Cannon et al. 1987). In adult studies they have been employed as prophylactic treatment, with good results (Tryba 1991b). Since these drugs can only be administered enterally and this is often difficult soon after birth, their use is rare in neonatology.

Sucralfate is physicochemically an antacid, but it does not increase gastric pH (Eddleston et al. 1994). It has no effect on gastric acid secretion, but rather may contribute to healing by increasing mucosal blood flow and gastric mu-

cus and bicarbonate secretion. It also forms a protective cover over the gastric mucosa, thereby strengthening the mucus barrier (Kappstein et al. 1991). Sucralfate binds pepsin and bile acids at low and high pH values. It is effective in ulcer healing and is well tolerated also in children (Lopez-Herce et al. 1992). Again, the main problem is enteral administration.

The mechanism of action of prostaglandins is to increase the protective capacity of the gastric mucosa. Like sucralfate they stimulate mucus and bicarbonate secretion and improve mucosal blood flow, but have no effect on gastric acid secretion. Studies on these drugs during stress are scant. Misoprostole, one of the prostaglandins in clinical use, is effective in healing peptic ulcers in adults (Fiske 1988), but there have been no studies in children. It remains an open question whether the cytoprotective actions of prostaglandins are of clinical relevance in stress-induced gastric lesions.

Proton pump inhibitors (e.g. omeprazole), the newest drugs for peptic ulcers, are highly potent inhibitors of acid secretion. Studies are in progress on this drug in newborns and the side-effects in children have not yet been ascertained (Alliet et al. 1998). There are some studies of adult patients treated in intensive care in which the effectiveness of the drug in curing stress-induced gastric lesions has not been shown (Tryba and Cook 1997).

**Table 4. Different medications used to prevent stress-induced gastric lesions and their mechanism of effect.**

Medication	Mechanism of the drug	Effectiveness	References
Antacids	Neutralise gastric acid	Shown	Tryba 1991b
H <sub>2</sub> -blockers	Inhibition of acid secretion	Shown	Ben-Menachem et al. 1994, Halloran et al. 1994
Prostaglandins	Cytoprotective actions	not studied	van Essen et al. 1985, Fiske 1988
Proton-pump-inhibitors	Inhibit acid secretion	not studied	Alliet et al. 1998
Sucralfate	Enhance defensive factors	Shown	Tryba et al. 1991a Cannon et al.1987

### **Histamine -H<sub>2</sub>- receptor antagonists**

H<sub>2</sub>-receptor antagonists (cimetidine, famotidine, ranitidine) are widely used in the prevention of stress ulcers and also in treating symptomatic lesions. The mechanism of action of these antagonists is inhibition of acid secretion from parietal cells and reduction of pepsin secretion and activity. They are highly effective in acute treatment and give rapid symptomatic relief. Several studies (Eddleston et al. 1989, de Angelis and Banchini 1989, Metz et al. 1993) have documented the effectiveness of histamine antagonists in the treatment of gastrointestinal bleeding in critical care patients. These same drugs are used for both prophylactic treatment and care in neonates treated in intensive care (Kelly et al. 1992, Fontana et al. 1993, Ng et al. 1993). As a group they have not been shown to be definitively more efficacious than those mentioned above, nor is any of the drugs within the group



superior to any other (Cannon et al. 1987, Lu et al. 1998). Cimetidine is the oldest H<sub>2</sub>-blocker and has most side-effects (Peura and Johnson 1985). Individual patients with different diseases requiring intensive care need varying doses of H<sub>2</sub>-blockers to raise the intraluminal gastric pH over 4 (Osteyee and Banner 1994).

An increased incidence of nosocomial infections has been connected with the histamine receptor antagonist use in patients treated in intensive care (Holzapfel et al. 1988). Adverse reactions such as gynaecomastia (Bosman et al. 1990), reversible liver damage (Hashimoto et al. 1994), headache, confusion (Cantu and Korek 1991) and bradycardia (Bush et al. 1987, Nahum 1993) have also been reported in infants. When these drugs block acid secretion and increase gastric pH they also improve gastric motility (Bortolotti et al. 1992), which is a desired effect in countering bile salt reflux. During recent years it has also been shown that ranitidine can act as a scavenger of oxygen radicals (Lapenna et al. 1994). Since these radicals are always produced in excess in conditions of hypoxia, asphyxia or ischaemia, this may also be a desirable effect. H<sub>2</sub>-blocker influence on gastric mucosal flow is controversial. Also in infants ranitidine treatment increases gastric pH and gastric bacterial colonisation rates may increase; this is not connected with the frequency of nosocomial infections in ranitidine-treated infants (Cothran et al. 1997).

## **Effectiveness of preventive medication of stress-induced gastric complications**

While prophylactic treatment with gastric acid-suppressing drugs may reduce the frequency of stress-induced gastrointestinal bleeding (Cook et al. 1994), it is controversial whether the overall mortality is reduced in critically ill patients (Tryba 1991a). Several meta-analyses have been made showing that all these drugs, histamine H<sub>2</sub>-receptor antagonists, sucralfate and antacids, appear to be equally effective in the prevention of stress ulceration (Lacroix et al. 1989, Tryba 1991a, Cook et al. 1991, Bortolotti et al. 1992). Their side-effects are mostly mild compared to the risk of bleeding from the upper gastrointestinal tract. Administration has been the most significant problem during treatment. Precise knowledge of the adequate dosages of all these medications is lacking in the case of infants, especially preterm VLBW infants. Side-effects of antacids, including both diarrhoea and constipation, have been shown depending on the type of antacid used. Aluminium-containing antacids may cause hypophosphataemia and hypocalcaemia, and may aggravate these problems inherent in prematurity (Mäki et al. 1987, Backström et al. 1996). The routine prophylaxis for stress-induced gastric lesions may have economic implications, but there have been few analyses of the cost-effectiveness of this therapy (McCoy et al. 1998). A recent study has shown that sucralfate is more cost-effective than cimetidine (Ben-Menachem et al. 1996).

## **AIMS OF THE STUDY**

1. To determine the frequency of stress-induced gastric lesions in newborn infants treated in a neonatal intensive care unit.
2. To identify the risk factors underlying stress-induced gastric lesions.
3. To evaluate whether prophylactic ranitidine is effective in the treatment of stress-induced gastric lesions in newborns
4. To optimise the dose of ranitidine for preterm and term newborns.

## SUBJECTS AND METHODS

### Patients

All infants included in studies **I-IV** were treated in the neonatal intensive care unit at the Department of Paediatrics, Tampere University Hospital. Most of them had respiratory problems, some required for surgery, some had infection problems. The clinical characteristics of the patients in the different studies are shown in Table 5. All of them were referred to the department on the first day of life, usually within the first few hours after birth. The infants in studies **I, III and IV** were prospectively evaluated, while study **II** includes retrospective material. The study data were compiled during the years 1990-1995.

All patients in studies **I, III, IV** and in the prospective part of study **II** were followed for four weeks or discharge. The history of the pregnancy was evaluated soon after birth. Study **II** had also a retrospective part for which the data were collected from the case records of the patients and their mothers. Items comprised mother's health during pregnancy, mode of delivery, Apgar scores, cord blood pH, birth weight, duration of mechanical ventilation, use of nasogastric tube, oral feeding, clinical problems, medication and where applicable causes of death.

Gastrointestinal problems were evaluated according to predetermined criteria. The clinical symptoms evaluated included bleeding from the gastrointestinal tract, vomiting or delayed gastric emptying. Gastrointestinal tract bleeding was defined as haematemesis, blood-stained aspirates from a nasogastric tube, gross blood in stools or melaena at any time during the four-week follow-up.

Analysis of risk factors for stress-induced gastric lesions was made using independent variables known to be risk factors from adult patients treated in intensive care. These variables are shown in Table 1 in study II. The study evaluated the risk factors by taking symptoms of gastrointestinal bleeding as the main outcome measure. In the prospective part the main outcome measure was abnormal gastric mucosa.

**Table 5. Clinical characteristics of the infants in studies I-IV.**

	<b>Study I</b>	<b>Study II a</b>	<b>Study II b</b>	<b>Study III</b>	<b>Study IV</b>
	<b>prospective</b>	<b>retrospective</b>	<b>prospective</b>	<b>randomised</b>	<b>randomised</b>
Total number of patients	17	100	89	48	16
Male/female	11/6	55/45	52/47	29/24	10/6
Mean gestational age (weeks)	30	35	32	32	33
Range	(23-41)	(25-43)	(23-42)	(24-41)	(28-42)
Mean birth weight (g)	1230	2512	2013	1832	2660
Range	(570-4180)	(785-4340)	(570-4550)	(620-4550)	(1000-4360)
Under mechanical ventilation (n)	14	64	89	48	16
Intracranial haemorrhage (n)	5	4	12	12	3
Proven or suspected infection (n)	10	42	32	15	8
Need of surgery (n)	1	8	6	3	4
Deaths during follow-up (n)	1	5	4	7	0

## **Gastrosopies and biopsy samples**

Gastroscopy was performed in study I using the prototype upper gastrointestinal “baby endoscope” XGIF 5.2, and elsewhere (II b, III) with GIF-N30, Olympus Optical, Tokyo, Japan. These instruments were specially designed for endoscopic procedures in pre- and full-term newborns. Gastroscopy was always performed with careful constant observation of oxygen saturation, heart rate and blood pressure. Most of the infants were treated with phenobarbital and/or morphine as routine pain relief for clinical purposes in intensive care. Multiple biopsies were taken from pre-determined sites for histological diagnosis and bacteriologic evaluation (I, III): one to three from the gastric mucosa and one from the lower third of the oesophagus. The biopsies were taken from oesophageal and gastric mucosa if there were no contraindications such as risk of bleeding (a thromboplastin time of <40% or a platelet count of  $<50 \times 10^9/L$ ). Visual findings were classified during the procedure into four groups: normal, mucosal friability, erythema or gross blood and erosions or ulcers. Any abnormalities in the oesophagus were evaluated.

The biopsy specimens (I, III) were formalin-fixed and paraffin-embedded and stained with haematoxylin-eosin. In addition, alcian blue periodic acid Schiff and modified Giemsa stains were used to demonstrate fungi and bacteria. Biopsy specimens were also obtained for bacterial culture. The histology of the gastric mucosa was classified into four groups: normal, haemorrhage without inflammation, gastritis and erosions or ulcers. The pathologist was blinded as to the medication of the patients when evaluating the biopsy specimens.

## **Intraluminal gastric pH monitoring**

Continuous long-term 24 hour gastric pH monitoring was carried out using a Digi-trapper Gold II (Synetics Medical, Stockholm, Sweden) pH monitor with one-channel registration and monocrystant antimony pH probe (91-0011 Monocrystant Antimony pH Catheter, Synetics Medical, Stockholm, Sweden). The pH measuring methodology is given in full in study **IV**, section Methods.

## **Treatment**

One of the H<sub>2</sub>-blockers, ranitidine, was chosen as the study drug, and was used in all studies. In studies **I**, **II** and **III** the dosage was 4-5 mg/kg intravenously or orally. In study **I** and in the prospective part of study **II** ranitidine was prescribed by the neonatologist on duty if the infant manifested symptoms of bleeding or if the endoscopic finding in the gastric mucosa was visually characterised as severe. In the retrospective part of study **II** ranitidine had been used if there were symptoms of bleeding. In study **III** the effectiveness of ranitidine treatment in preventing stress-induced gastric mucosal lesions was prospectively evaluated. Ranitidine treatment was given or not given to the patients in random order as described in study **III**, section Materials and Methods. In study **IV** ranitidine treatment was given to all infants enrolled in the study, who were randomised into three groups according to the ranitidine dose: either 0.5 mg/kg, 1.0 mg/kg or 1.5 mg/kg body weight. The methodology of the treatment is given in detail in study **IV**, section Methods.

## **Statistical analysis**

The statistical analysis included Fisher's exact test (I-III), Student's t-test (I-III), chi-square tests and test for linear trend in bivariate analysis (III). Multivariate analysis was carried out using logistic regression modelling (II-III). We also calculated odds ratios when the results were significant. The 95% confidence intervals for means were calculated when appropriate (I-IV). Analysis of variance was also used (IV). The equality of variances was tested using Levene's test, and Brown-Forsythe approximation was applied when necessary (IV). We used the data management system of the University of Tampere.

## **Ethics**

The parents received both oral and written information on the study and informed consent was obtained from the parents of the subjects studied. Special care was focused on gentle handling of the infants. Upper gastrointestinal endoscopy was performed by two physicians, a paediatric gastroenterology endoscopist and a neonatologist. One physician regulated the tip bending while the other passed the endoscope through the oropharynx into the stomach; both examiners had visual control through the main and side optics. A nurse monitored blood pressure, heart rate, oxygen saturation by pulse oximeter, and the general condition of the infant at 1-minute intervals (Bendig 1991). The infants were also connected to an electrocardiographic monitor. The parents were also allowed to withdraw the child from the study before gastroscopy. None, however, chose to do so.



The study was approved by the Ethical Committee of Tampere University Hospital. The studies were conducted according to good clinical practice and in keeping with the declaration of Helsinki.

## RESULTS

### Frequency of stress-induced gastric lesions in newborns treated in intensive care

In the retrospective part of study II twenty mechanically ventilated infants (20%) evinced one or more clinical signs of gastrointestinal bleeding. The distribution of the signs is shown in greater detail in Table 6.

**Table 6. Signs of gastrointestinal bleeding in 100 consecutive infants treated in neonatal intensive care unit.**

Sign of bleeding	No mechanical ventilation N=36	Mechanically ventilated N=64
Blood-stained nasogastric aspirates	0	9
Haematemesis	0	8
Gross blood in stools or melaena	0	10
All symptomatic infants	0	20

Upper gastrointestinal endoscopy showed stress-induced gastric lesions to be markedly prevalent during the first week of life in infants treated in intensive care (I-III). The frequency in study I was 88%; thus 15/17 of infants had

gastric lesions at the first endoscopy and 4 out of 7 still had lesions at the control endoscopy. In study III 80% (20/25) of the patients had lesions if they had not received ranitidine, in contrast to 39% (9/23) if ranitidine treatment had been given. Prospective evaluation of mechanically ventilated patients revealed a frequency of 53% of conspicuous (gastritis or ulcers) stress-induced gastric lesions (II). The result of histology in each study correlated well with visual evaluation. The upper gastrointestinal findings are shown in detail in Tables 7 and 8. Gastritis with cystic gland was seen in 5/17 (29%) of the patients (study I, Figure 1).

**Table 7. Visual findings in gastric mucosa and ranitidine medication of infants treated in neonatal intensive care.**

	Study I		Study II b		Study III Controls		Study III Ranitidine treated	
	N	%	N	%	N	%	N	%
Normal gastric mucosa	2	12	18	20	5	20	14	60
Abnormal gastric mucosa	15	88	71	80	20	80	9	40
Mucosal friability	3	18	23	26	4	16	7	30
Erythema, gross blood	7	41	29	33	8	32	2	10
Erosions/ulcers	5	29	19	21	8	32	0	0
<i>Number of patients receiving ranitidine treatment before gastroscopy</i>	0	0	0	0	0	0	23	100
<i>Number of patients receiving ranitidine treatment after gastroscopy</i>	8	47	26	29	8	32	0	0

**Table 8. Gastric mucosal histological findings in infants treated in neonatal intensive care unit.**

Histological findings	Study I		Study II b		Study III Controls		Study III Ranitidine treated	
	N	%	N	%	N	%	N	%
Normal	1	7	12	16	4	16	13	57
Abnormal	13	93	68	84	21	84	10	43
Haemorrhage	4	29	23	19	5	20	5	22
Gastritis	4	29	32	41	11	44	5	22
Erosions/ulcers	5	36	13	17	5	20	0	0

Almost 40 % of the infants also evinced oesophageal changes. However, the biopsy material was not sufficient for evaluation in all the cases (110 biopsies evaluated /150 taken altogether).

### **Risk factors for stress-induced gastric lesions in newborns**

In the retrospective analysis (Study II a) the main risk factor underlying stress-induced gastric lesions in 100 consecutive preterm and full term infants treated in neonatal intensive care was mechanical ventilation (odds ratio (OR)=4.06, 95% confidence interval (CI) 1.21-12.3). There were no other statistically significant risk factors in this study group.

Further analysis was made in 89 gastroscopied and mechanically ventilated infants to determine risk factors for endoscopically visual gastric lesions (II b). Analysis by logistic regression modelling using certain variables listed in Table 1 in study II b revealed three other factors with statistical significance. These were abnormal delivery (OR=5.1, 95% CI 1.2-17.9) or delayed delivery (OR=1.2, 95% CI 1.2-1.9) and hypotension after birth (OR=4.2, 95% CI 1.5-13.2). No other factors reached statistical significance.

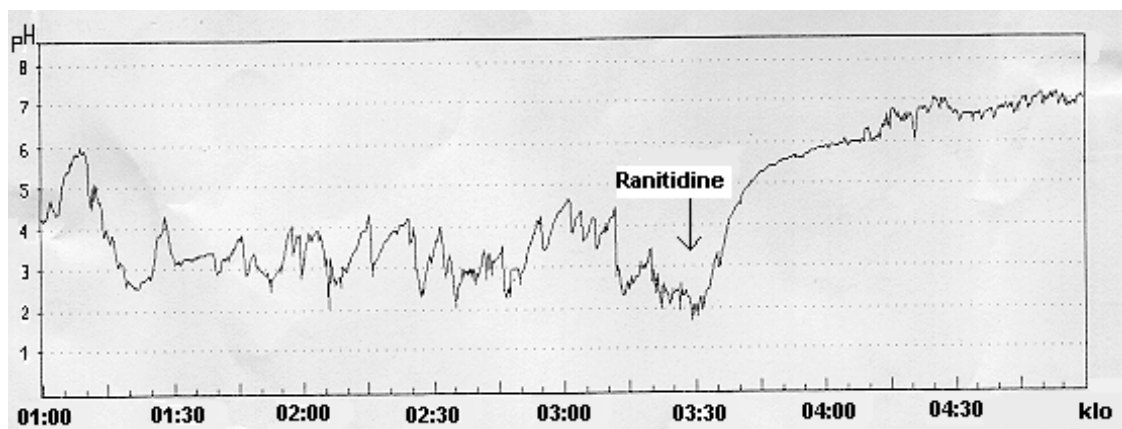
In study III surfactant treatment for infant respiratory distress syndrome reduced the risk of stress-induced gastric mucosal lesions (OR=12.1; 95% CI 1.27-115), whereas other variables (birth weight, gestational age, Apgar scores, cord blood pH and duration of intubation) had no significant effect.

### **Ranitidine treatment and stress-induced gastric lesions in newborns**

In the first two studies (I and II) the decision on ranitidine treatment was individual and clinical, i.e. it depended on the severity of the endoscopic findings. Follow-up gastroscopies showed normalisation or improvement in most cases.

Figure 1 in study III shows clearly that ranitidine effectively prevents gastric lesions. The increased risk of gastric mucosal lesions in infants not receiving prophylactic ranitidine was 41.7 (95% confidence interval 5.62-302). There were no ulcers or erosions in the gastric mucosa of infants receiving brief four-day prophylactic ranitidine treatment (Table 6) as compared to 8/25 in infants not treated. The frequency of lesions reduced by up to half (80% vs. 39%) with ranitidine.

To optimise the ranitidine treatment long-term gastric pH monitoring was used (IV). Ranitidine treatment increased gastric pH in all infants in a dose-dependent manner. Figure 2 shows an example of a long-term pH curve of one preterm infant (born at 28 gestational weeks with a birth weight of 1000 g) and the effect of ranitidine on gastric pH. The higher the dose, the faster and more long-lasting was the effect (Table 2 in study IV). Figure 1 in study IV shows that both gestational age and ranitidine dose had a significant impact on the maintenance of gastric pH. Preterm infants needed lower doses than term infants. Judging from individual gastric pH curves and the mean time gastric pH remained over four in preterm and term infants after receiving three different doses of ranitidine, it may be estimated that the required optimal ranitidine dose for preterm infants is 0.5 mg/kg/body weight twice a day and that for term infants 1.5 mg/kg body weight three times a day.



**Figure 2.** An example of the long-term gastric pH curve and the influence of ranitidine on it in a preterm girl born at 28 weeks of gestational age, weighing 1000 g.

## DISCUSSION

The origin of the present study was the conception that newborns treated in intensive care may have severe gastric lesions due to stress to the same extent as has been previously demonstrated in adults and older children (Lacroix et al. 1992, Tryba and Cook 1997). We also perceived a threat in routine clinical handling of preterm infants under stress, where treatment of gastrointestinal lesions was started late, only after gross bleeding gave a sign of the lesions. In adult patients prevention and effective treatment have been shown to reduce both morbidity and mortality (Cook et al. 1996). A wide variety of gastrointestinal problems complicates the treatment of infants in neonatal intensive care (Ricour 1989). Stress-related gastric lesions may be connected with these, and effective prophylaxis and treatment of stress on the one hand and cure of gastric lesions on the other may improve survival of critically ill neonates.

The progressive attitude prevailing in the paediatric gastroenterology unit in Tampere University Hospital and collaboration with Olympus, Tokyo, Japan made it possible for a prototype neonatal gastroscope to be created and first used in this hospital (I). In this pioneering pilot study we demonstrated that gastric lesions are indeed frequent, occurring in up to 88% of critically ill neonates under stress. Technical improvements have made it possible not only to visually inspect the gastric mucosa, but also to obtain biopsy specimens for histological evaluation. Histological examination can confirm the pathological nature of lesions seen on inspection, and often the microscope reveals more severe changes than the eye.

## **Gastroscopy**

The availability of the new baby gastroscope, first the prototype, subsequently Olympus GIF-N30, has made gastroscopy possible also in the case of VLBW infants. It has been shown that endoscopies are necessary in evaluating the reason for gastrointestinal bleedings. There are reports of retrospective evaluations of gastroscopy findings in infants under one year of age (Rintala and Lindahl 1992). However, desaturations and other problems arising when performing gastroscopies on infants have also been described (Casteel et al. 1990). The present study showed that upper gastrointestinal endoscopy can be performed safely and without extra stress even in the most premature infants. Careful continuous monitoring of oxygen saturation, pulse rate and blood pressure revealed no significant signs of complications in these babies. Transient tachycardia was frequently observed while passing the oesophagus, but no cardiac arrhythmia or significant desaturation was observed. According to clinical experience, such mild changes also occur when inserting a nasogastric tube. In the NICU of Tampere University Hospital the clinical routines include repeat ultrasonography of the central nervous system on days 1, 3 and 7 postpartum, and weekly thereafter. This means that ultrasound was performed twice before gastroscopy and several times thereafter. No pathological changes could be associated with the endoscopy procedure, as shown in studies I and III.

It is well known that stress-induced gastric lesions are painless and that clinical symptoms, i.e. bleeding, are seen late (Sarna et al. 1981, Peura and Johnson 1985). This makes it essential to evolve improved methods of detecting such lesions in good time (de Boisseau et al. 1994). In practice, as shown in the present study, gastroscopy is the method of choice in evaluating the gastric mu-

cosa in children, now also in sick preterm infants. However, wide experience with endoscopy, preferable in paediatric patients, is imperative if the intervention is to proceed safely.

### **Visual and histological evaluation**

An experienced endoscopist can easily differentiate the typical changes caused by a nasogastric tube from other abnormalities (Tryba 1994). This was also the conclusion in the present study. The lesions described here, i.e. friability, erythema and ulcers, were most probably not induced by a nasogastric tube since the like were also seen in patients not fitted with a nasogastric tube (III).

There are no previous reports on gastric biopsies in preterm infants treated in intensive care. Here it was shown that biopsies can be safely taken from the gastric mucosa; no severe bleeding or perforations were observed in 154 newborn infants treated in our neonatal intensive unit. However, by measuring thromboplastin time and platelet count we ensured before biopsy that any increased risk of bleeding was excluded. Technically, the most difficult site to biopsy in these infants was the oesophagus, where samples often either could not be obtained or were too small for histological evaluation. For this reason oesophageal lesions were not included in the calculations on stress lesions in this study. This is unfortunate, since it has been shown that these particular lesions bleed early on (Wilmer et al. 1999).



The pathologist evaluated all biopsy specimens blinded, i.e. she had no knowledge of the treatment group the patients belonged to. Figure 1 in study III shows a clear correlation between clinical description and the pathologist's diagnosis. It was observed here that there were only a few inflammatory cells to be seen in stress-induced gastric lesions in contrast to what is found in gastritis in general. Our results are in concordance with those of autopsy studies (Holgersen 1981). Hence the usual gastritis classification could not be applied in the present study (Misiewicz 1990). Interestingly, cystic glands were seen in connection with gastritis, especially in preterm infants under stress. This is a novel finding, not previously described in the literature, except as a premalignant condition in adult patients (Honore et al. 1979) or in connection with severe inflammation in children (Niv and Turani 1994). The clinical significance of this finding is unclear. Upon repeat endoscopy and biopsy these changes were no longer seen.

### **Frequency and severity of the gastric lesions and symptoms**

The present study revealed stress related gastric lesions to be common in critically ill neonates, occurring in eight out of ten patients. Moreover, more than half of these lesions were classified as severe. The frequency of mucosal changes of varying severity has been determined neither in older children nor in infants.

The mucosal lesions progress gradually and ultimately clinical signs of bleeding appear (Marrone and Silen 1984). This involves overt or occult bleeding, a symptom which has been described mainly in adult patients in intensive care. In contrast to the case of adult patients, occult bleeding does not mean the same in the VLBW infant, where every millilitre of blood is vital; in an infant weighing 500 g,

5 ml bleeding means that 10% of blood volume is lost. Therefore any sign of bleeding such as blood in nasogastric tube aspirate calls for immediate medical attention. In the present series up to 20% of the patients evinced symptoms of upper gastrointestinal bleeding. This percentage is the same as that described in adult patients (Peterson 1994).

Blood transfusions have been used to evaluate the severity of bleeding (Chan et al. 1995). However, repeated blood samples are necessary for clinical follow-up of the state of the preterm patient, and therefore critically ill neonates need frequent transfusions. Extra transfusions are also given whenever the red blood cell volume drops below a pre-set 40%, to ensure adequate tissue oxygenation in conjunction with mechanical ventilation. It is thus impossible to analyse overt and occult bleeding on the basis of the number of transfusions or red cell volume. In the present study it seemed that infants with gastric lesions needed more transfusions than those without these lesions (II and III).

According to the literature the prevalence of gastric lesions in adults treated in intensive care varies up to 100%. The time of evaluation influences the percentage of occurrence: the lesions appear up to 72 hours from the beginning of stress, whereafter a spontaneous healing process starts provided the stress is also alleviated (Lucas et al. 1971). In the present series the gastroscopies were performed from 72 hours to 144 hours of age. At this point some of the infants were already stable and without marked stress. Severe mucosal lesions in the prospective study (II) still occurred in over 50% of the patients.

## **Evaluation of risk factors**

Previous adult studies have identified a number of factors entailing a risk of gastrointestinal bleeding (Cook et al. 1994). These include mechanical ventilation, hypotension, coagulopathy and intracranial processes, all of which are among the most frequent objects of urgent medical attention in modern neonatology. The retrospective analysis in study II identified mechanical ventilation as the main and only risk factor. That other risk factors could not be brought out with statistical significance may be due to the fact that when a critically ill premature infant also has problems with respiration. This in itself would mean that mechanical ventilation as a risk factor cloaks all other possible sources of threat in this material.

The prospective study (II) again brought on the fact delivery causes stress to the newborn. Abnormal delivery, i.e. caesarean section, forceps or prolonged delivery seem to increase the risk of gastric lesions in mechanically ventilated infants treated in intensive care. Hypotension would likewise appear to constitute further important risk factor for stress-induced gastric lesions. This is in concordance with findings in adult studies (Geus and Lamers 1990). In the pathogenesis of stress-induced gastric lesions reduced circulation in the splanchnic region is one important component (Casado-Flores et. al. 1998).

All factors tending to lower the level of stress make for a reduction in the risk of stress-induced gastric lesions. Corticosteroids given to the mother reduce the risk of infant respiratory distress syndrome and thereby the need for mechanical ventilation. Surfactant therapy for respiratory distress syndrome has been a turning-point in modern neonatology; today even the smallest preterm infants have a chance to survive (Kari et al. 1994). Infusion of surfactant into the lungs results in some overspill into the gastrointestinal tract, which may improve the gastric

mucosal barrier as a defensive factor (Hills 1996). Interestingly, surfactant could be shown in this study to have a protective effect since it reduced the risk of gastric mucosal lesions significantly.

Factors leading to critical developments include infections, anomalies, cardiac problems, many kinds of medication, metabolic diseases etc. (Tryba 1994). Analysis of the role of all of these would have involved a much larger patient population, which in our unit would have meant years of study and the additional problems arising with the rapidity of change in medical technology and new treatments in neonatal care. One obvious solution would have been a multicentre study, but then there should also have been experienced paediatric endoscopists available in other hospitals.

Newborns, especially preterms, have an immature haemostatic system (Mautone et al. 1997) and this is routinely treated with vitamin K; frequently also frozen plasma is given. We chose not to evaluate coagulopathy as a separate risk factor, since it would have been laborious to disentangle the effects of these preventive measures.

Although intracranial pathological processes, including intracranial haemorrhage, constitute one of the most important factors increasing the risk of gastrointestinal bleeding during intensive care (Lu et al. 1997), we found no connection here with intraventricular haemorrhage and stress-induced gastric lesions in the newborns studies. This may be due to the low number of cases of intracranial haemorrhage in this study.

## **Optimisation of treatment of stress-induced gastric lesions**

In the randomised, controlled study ranitidine prevented stress-induced gastric mucosal lesions without significant side-effects in newborns. The findings show clearly that prophylactic use of the drug is effective. The neonates not receiving the prophylactic drug had a 40-fold increased risk of gastric mucosal lesions.

Ranitidine was used on clinical grounds with good results and the healing process was verified by gastroscopy (I). The drug was chosen, because its use is well documented also in children and infants (Rosenthal and Miller 1988, Wiest et al. 1989, Lopez-Herce et al. 1992, Fontana et al. 1993, Kelly 1994). The choice was also in part based on our own previous clinical experience with the drug. Ranitidine can be administered parenterally, which is an advantage. The enteral route in preterms is not to be recommended during the first days of life, and it is at this point that the drug would be most needed. Enteral nutrition started early would again be inducive of normal development of the gastrointestinal tract (Berseth 1992), and enteral feeding might even prevent gastric ulceration. It is, however, customary to provide nutrition parenterally during the first days of life in the NICU. Ranitidine improves gastric motility and gastric emptying (Hall and Washabau 1999). Enteral feeding, again, if it were possible to give, would of itself serve to enhance gastric pH.

The current policy is to prevent lesions before any severe complications such as haemorrhage or perforation occur (Cook et al. 1996). Despite the wide use of prophylaxis there is no consensus as to how long the treatment should last. There are no studies addressing this specific question (Tryba 1999). The period of prophylactic ranitidine administration in this study was set as short as was considered possible. Brief treatment is beneficial; its prolongation is associated with

an increased risk of side-effects (Tryba 1989) such as interaction with other medications (Roy et al. 1988), liver toxicity (Ament et al. 1994), cerebral toxicity, haemodynamic instability, renal complications, haematologic abnormalities (thrombocytopenia, granulocytopenia, pancytopenia), and immunologic effects (Crill and Hak 1999). Ranitidine treatment and increased gastric pH have also been associated with nosocomial pneumonia in patients treated in intensive care (Noseworthy and Cook 1994). Stomach acidity is an important barrier against infection, but is also needed for the normal development of intestinal enzymatic activity (Hamosh 1994). All these considerations underline the desirability of minimising the dose and duration of ranitidine treatment and of targeting the preventive treatment to well-defined risk groups only. The present short four-day ranitidine treatment did not increase the risk of bacterial colonisation in the newborns treated, nor did ranitidine prophylaxis increase the numbers of suspected or proven bacteraemias. No other side-effects were associated with the use of ranitidine in the present study.

During the first day of life gastric pH decreases to below 4 in most term and preterm neonates, from being alkaline during gestation because of amniotic fluid. In this study 6 of the 22 (30%) neonates had gastric pH over 4 during the first 24 hours of life, and they did not receive any medication for prevention of stress-induced gastric lesions. All six infants were premature. The reason why gastric pH did not decrease was not evaluated in this study. The study design did not include gastric pH after the first day of life in these infants and studies are obviously needed to clarify the importance of this matter. It is, also obviously important to assess gastric pH before initiating any antacid prophylactic treatment.

It is customary to derive the paediatric dosing of any new drugs from adult doses, and based on adult studies in the first place. This has been the case with ranitidine treatment in newborns. The recommended dose for intravenous administration has varied from 1 mg up to 5 mg/kg body weight per day. To determine

the optimal dose here we used long-term gastric pH monitoring, which also made possible the timing of the bolus (Sutphen and Dillard 1989). It clearly emerged that preterm infants need a significantly lower dose of ranitidine than full-term (**IV**); its metabolism appears to be much slower in preterm infants.

In conclusion, complete respiratory and haemodynamic control of infants would be the means to avoid stress-induced gastric lesions. Also one should anticipate the stress. When this is not feasible, prophylactic ranitidine may be used to prevent these lesions in preterm and term infants treated in neonatal intensive care. This applies especially in the case of mechanically ventilated newborns. Gastroscopy is safety to perform if symptoms or signs of bleeding occur.

## **SUMMARY**

Neonatal medicine has succeeded in effecting remarkable improvements compared to even a decade ago. Babies born at 26 weeks of gestation now have a better than even chance to survive. Adult patients treated in intensive care are known to evince severe symptoms from the gastrointestinal tract due to stress. Also in newborns in intensive care life-threatening gastrointestinal bleeding and perforation have been described. As to who is who is prone these lesions, how severe they are and how and with what they should be treated, little has hitherto been established. The present study concentrated on these issues.

Improvement in fiberoptic gastroendoscopes has made it possible technically to perform upper gastrointestinal endoscopies and to evaluate the gastric mucosa before symptoms occur in newborns, even in VLBW infants. All infants here tolerated the endoscopy procedure well. Using this procedure we revealed that gastric mucosal lesions are highly prevalent, over 80%, also in neonates in intensive care, before any symptoms or signs occurred.

Mechanical ventilation is the main, single risk factor underlying these gastric mucosal lesions, and is also an indicator of severity of the illness of the preterm infants. Our prospective study also showed that abnormal and delayed delivery increase the risk of gastric lesions. After birth it would seem that hypotension is likewise one of the risk factors, as indeed described in adult patients in intensive care. However, the improvements in recent neonatology such as surfactant treatment reduce stress and stress-induced gastric lesions.

Ranitidine as prophylactic medication during the first, most stressful days significantly reduces the frequency of gastric mucosal lesions in NICU patients requiring mechanical ventilation. The four-week follow-up suggested that



there may be a relationship between early gastric mucosal lesions and late-occurring gastrointestinal problems, and with ranitidine these can be avoided.

With long-term intraluminal gastric pH monitoring it was easy to determine gastric acidity in newborns, and this was used to evaluate the optimal dose of ranitidine required to increase gastric pH when treating critically ill preterm and term neonates. The optimal dose varied by gestational age, term newborns needing higher doses more frequently than preterms: according to this study 0.5 mg/kg twice a day sufficed for preterm infants, while term infants need 1.5 mg/kg three times to keep the gastric pH over 4.

These studies showed that fiberoptic endoscopy can be safely performed when needed to evaluate upper gastrointestinal changes in neonates. Stress-induced gastric lesions are highly prevalent in infants treated in neonatal intensive care, mechanical ventilation as an indicator of respiratory failure being the main source of risk. With optimal-dose ranitidine treatment these stress-induced gastric lesions can be avoided without side-effects and with decreasing frequency of late-occurring gastrointestinal problems.

## FINNISH SUMMARY

Jo pitkään on tiedetty, että tehohoidossa oleville potilaille voi tulla tehohoidon sivuvaikutuksena mahasuolikanavan vaurioita. Lapsilla ja myös aivan vastasyntyneillä on kuvattu tehohoitoon liittyviä vakavia mahasuolikanavan verenvuotoja. Vastasyntyneiden lasten tehohoito on kehittynyt nopeasti viime vuosina, ja nyt pystytään hoitamaan sekä hyvin pieniä keskusia että muutenkin vaikeasti sairaita vastasyntyneitä paljon tehokkaammin kuin aiemmin. Hoidon tehostuminen lisää vastasyntyneiden lasten altistumista stressille, joka puolestaan saattaa johtaa herkästi mahasuolikanavan vaurioitumiseen.

Tämän tutkimuksen tarkoituksena oli selvittää kuinka tavallisia mahasuolikanavan vauriot ovat ennenaikaisina ja täysiaikaisina syntyneillä lapsilla tehohoidon aikana. Tarkoituksena oli myös selvittää, onko erityisiä riskiryhmiä, joiden todennäköisyys saada näitä vaurioita olisi suurempi kuin muilla. Samalla pyrittiin löytämään mahdollisuuksia ennaltaehkäisevään hoitoon. Vastasyntyneet ovat erityisen herkkiä kaikille lääkkeiden sivuvaikutuksille. Kirjallisuudesta ei löydy annos-suositusta pienten keskosten mahasuolikanavan limakalvovaurioiden lääkehoitoon, joten tutkimuksessa määritettiin sopiva annos tälle ikäryhmälle.

Tutkimuksen ensimmäisessä osassa tehtiin ylämaha-suolikanavan tähystys 17:lle tehohoidossa olevalle vastasyntyneelle. Näistä lapsista 15:llä todettiin eriasteisia mahan limakalvovaurioita. Nämä vastasyntyneet saivat hoidoksi ranitidiinia, jos vauriot näyttivät vaikea-asteisilta. Uudessa tähystystutkimuksessa todettiin vaurioiden kaikilla lapsilla vähentyneen, joillakin jopa hävinneen kokonaan.

Mahaverenvuotoon liittyvien oireiden esiintyvyys selvitettiin 100 tehohoitoon joutuneen vastasyntyneen joukossa. Hengityskonehoito oli ainoa merkittävä riskitekijä. Tutkimuksen etenevässä osassa pyrittiin selvittämään muita

riskitekijöitä. Kaikki raskauteen ja synnytykseen liittyvät tilanteet voivat lisätä mahan limakalvovaurioiden riskiä. Tässä tutkimuksessa synnytyksen pitkittyminen ja poikkeava synnytystapa lisäsivät merkittävästi limakalvovaurioiden esiintyvyyttä. Lääkitystä vaativa verenpaineen lasku syntymän jälkeen oli myös merkittävä riskitekijä.

Tutkittavaksi lääkkeeksi valittiin ranitidiini, koska siitä on paljon käytökemusta ja se on aikaisemmin osoitettu tehokkaaksi ja turvalliseksi myös vastasyntyneillä. Ranitidiini vähensi tehokkaasti mahan limakalvovaurioita. Lääke mahdollisesti vähentää myös mahanvetovaikeuksia, mikä on tavallinen keskoshoidon ongelma. Tutkimuksemme perusteella pienet keskokset tarvitsevat täysiaikaisiin vastasyntyneisiin verrattuna ranitidiinia harvemmin ja pienempinä annoksina.

Tämä tutkimus osoittaa, että tehohoitoa tarvitsevilla keskosilla ja täysiaikaisilla vastasyntyneillä on ylämaha-suolikanavan vaurioita aivan kuten aikuisillakin tehohoitopotilailla. Merkittävin yksittäinen riskitekijä vastasyntyneillä lapsilla on hengityskonehoito. Jo lyhytkestoinen ennaltaehkäisevä ranitidiinihoito vähentää limakalvovaurioita, mutta annostelussa on huomioitava vastasyntyneen ennenaikaisuus.

## ACKNOWLEDGEMENTS

This study was carried out at the Department of Paediatrics, Tampere University Hospital and the Department of Paediatrics, Medical School, University of Tampere.

*First and foremost I wish to express my thanks to Professor Markku Mäki, who first picked me as a student on his own study project and thereafter offered me the possibility to do my own scientific work; with his endless optimism and faith he succeeded in inducing me complete this thesis.*

*I wish to thank Emeritus Professor Jarmo Visakorpi for encouragement and interest during this undertaking and for giving me the opportunity to become a neonatologist.*

*I am grateful to the Head of the Paediatric Clinic, Professor Mikael Knip, for his support during the last years. I also thank Professor Timo Vesikari for his support from my first research efforts until now.*

*My sincere thanks are due to the official referees of this study, Docent Pentti Kero and Docent Jorma Kokkonen, for their positive criticism during the preparation of the final manuscript of this thesis.*

*I am grateful to my co-authors Docent Sami Ikonen, Martti Janas, MD, Riitta Karikoski, MD, and Docent Tarja Ruuska for their collaboration. Especially I thank Professor Pekka Laippala, PhD, for his patience and skill with statistical analyses.*

*I am forever grateful to Minna Kaila, MD, colleague and friend, without whose support this work would not be finished today. My dear friends and colleagues Marja-Terttu Saha, MD, and Päivi Luukkainen, MD, and Outi Saarenpää-Heikkilä, MD, have shared good and bad days both in the course of this work and in everyday life. Liisa Tomminen, MD, has been a faithful friend - long phone calls providing the opportunity to evaluate critically all possibilities at work and in this study.*

*I am indebted to the staff at the Department of Clinical Physiology for their help. Special thanks are due to Marita Laurila, RN, and Marja Pelkonen, RN. I also thank*

*my colleague Visa Lautamatti, MD for his support and collaboration, and acknowledge the contribution of Riitta Koivunen, RN, at Maternity Unit Nr 3b in team-work and organising skill.*

*The assistance of the nursing staff of the neonatal intensive care unit is also gratefully acknowledged and I am indebted to the nursing staff of the paediatric intensive care unit for all their encouragement during these years.*

*The English language of the manuscript and the original papers was revised by Robert MacGilleon, MA, whom I sincerely thank.*

*Warm thanks go to the personnel of the Department of Medical Records and to the personnel of the Medical Library in Tampere University Hospital.*

*I wish to thank all senior and junior colleagues at the Department of Paediatrics for their support and sympathy in the process of this work.*

*Last but not least I wish to thank my beloved husband Markku, whose amazing patience has carried me through life during these years with joy and sorrows. I am also grateful to our sons Kimmo, Timo and Aki, who have tolerated all the inconvenience arising from my work. They have made sure that after coming home I have an opportunity to put aside all thought of work. They have also survived among the mountains of paper and dust and have eagerly awaited these results. In particular thank both older sons for their capability with the computer, helping me to bring this thesis to its conclusion.*

*Permission from the copyright owners of the original articles to reproduce the original contributions of this thesis is gratefully acknowledged.*

*This study was financially supported by grants from the Foundation for Paediatric Research and the Medical Research Fund of Tampere University Hospital.*

*Tampere, November, 1st, 1999*

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