EFFECTS OF DELAYED TREATMENT ON PERFORATED PEPTIC ULCERS AT KENYATTA NATIONAL HOSPITAL (KNH).

A DISSERTATION SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN SURGERY, UNIVERSITY OF NAIROBI.

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DECLARATION.

INVESTIGATOR.

This dissertation is my original work and has not, to the best of my knowledge, been presented for award of a degree in any other university.

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DEDICATION

I dedicate this book to my family especially to my wife Adelaide, who endured many hours without my attention and for her help in proof reading this work putting the commas and full stops where they needed to be, and to my son Derek. Both showed me their love, support, understanding and encouragement, which made the completion of this work possible.

ACKNOWLEDGEMENT.

May I extend my appreciation to my family for their perseverance during the entire period that this study was done.

I thank my supervisor Mr. Hassan Saidi for his patience, guidance and for his valuable support.

Finally I acknowledge the support of my colleagues who notified me of all the patients in their respective wards who satisfied the criteria for inclusion in this study.

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ABSTRACT

Background: Perforations complicate up to 5-10% of peptic ulcer diseases[1]. Mortality following peptic ulcer perforation can peak 29% [2, 3]. Of the factors that influence the outcome of peptic ulcer perforation, treatment delay is most important and modifiable. This study reviewed delay and how it affected outcome in patients treated for perforated peptic ulcers at the Kenyatta National Hospital.

Methods: Patient's files for the period January 2002 to December 2007 were reviewed and direct interviews carried out for patients seen from January to December 2008. Data sought included patient demographics, clinical presentation, time from symptom onset to presentation at casualty, time from presentation at casualty to surgical treatment and the treatment outcomes. The primary endpoint was mortality. Secondary endpoints included wound infection, wound dehiscence, length of hospital stay, discharge from hospital and associations between delay, age and gender. Data were entered using a structured data sheet /questionnaire. The effect of delay as a determinant of outcome was evaluated using univariate analysis.

Results: One hundred and ninety three patients were evaluated. File reviews were done for 151 patients treated between January 2002 and December 2007. Forty two patients were interviewed by the researcher during the period January to December 2008. Twenty four patients (12.4%) died. Sixty one patients (31.6%) developed complications post-operatively. Thirty patients were re-operated for the complications. No patient treated within 24 hours died. Complications rate was 0 %, 1.5% and 29.5% for patients treated within 24 hours, 24-48 hours and after 48 hours respectively. Delay >48 hours was significantly associated with increased mortality (*p value <0.001)*, morbidity (*p value <0.001*), and surgical site infections (*p value <0.001*). The mean length of hospital stay for patients with delay ≤48 hours and over 48 hours was 7.22 (± 1.9) and 19.7 days (± 19.1) respectively *(p<0.001)* There was however no significant association between delay of over 48 hours and site of perforation *(p= 0.116)*, and non infectious complications *(p = 0.566)*.

Conclusion: Delay of more than 48 hours is associated with high morbidity and mortality. Efforts should be made to reduce the amount of pre-treatment delay to less than forty eight hours.

INTRODUCTION.

Peptic ulcer perforation is the second most frequent abdominal emergency that requires surgery. Perforation occurs in 10% of patients with peptic ulcer disease.[1] Perforation is predominantly a surgical disease and surgery should proceed as soon as a patient is resuscitated. However, recent data indicates a worrying trend towards longer treatment delays when compared to earlier studies [1, 4]. In Norway for example, Svanes et al have shown a steady increase in treatment delay between the years 1935-1990, especially so for in-hospital delay [4].

Delays in treatment impact negatively on the outcome of perforation treatment especially when more than 12 hours are exceeded [5]. Delays of more than 24 hours increase surgical mortality seven-eight fold complication rate three fold and length of hospital stay two fold in the West [5].

The patterns and adverse effects of treatment delay have not been evaluated in Kenya. An understanding of this aspect is potentially relevant in guiding the treatment protocols at our institutions.

BACKGROUND KNOWLEDGE AND LITERATURE REVIEW.

Epidemiology

In the beginning of the 20th century, the prevalence of duodenal ulcers increased to several times that of gastric ulcers before starting to fall in the second half of the century [6, 7]. Between 1950s and 1980s, hospital admissions and mortality from peptic ulcers declined in Britain for most age groups [1, 8]. In contrast with this general trend, admissions for perforated peptic ulcer and mortality from duodenal ulcer increased among older women in the 1970s and 1980s [1, 8].

In the USA approximately four million people are affected by peptic ulcer disease with 500,000 new cases diagnosed yearly. Five thousand of these die each year due to complications [9].The incidence of perforated peptic ulcer disease in Western countries is 7-9 per 100,000 population per year [10]. Perforation is one of the most catastrophic complications of peptic ulcer [2]and occurs in approximately 5%-10% of peptic ulcer patients [1, 11, 12]. In Ethiopia, perforated peptic ulcer accounts for 3.4% of the adult emergency surgical procedures. The mean age is 32.6 years with a male to female prevalence of 7.2:1 [13].

Giddy at Kenyatta National Hospital (KNH) in Nairobi in 1979-1980 found an incidence of perforation of 22 persons per year. The male to female ratio was 21.5:1 while the largest group of patients was in the third and fourth decades of life [14].Jani, at the same institution reviewed 65 cases in the period from Jan 1980 to April 1985 and found fifty five of them to be duodenal perforations, ten gastric while two turned out to be adenocarcinomatous in nature. Ten patients died in the latter study [15].

Aetiology

Three different aetiologies underlie virtually all perforated ulcers: infection with *Helicobacter Pylori* [16, 17, 18,] use of non-steroidal anti-inflammatory drugs (NSAIDS) [12, 19]and massive acid hyper secretion secondary to gastrinoma.[20] The exact role of *H. pylori* in ulcer perforation is uncertain. In one study of acute peptic ulcer perforations for example, the infection was as common among patients as among hospital controls [21]. About 95% of patients with symptomatic duodenal ulcer are colonized with *H. pylori* as are 50% of those with perforated duodenal ulcers and 17% of those with bleeding duodenal ulcers [20, 22]. About 77% of patients with gastric ulcers are colonized. Thus not all patients are infected while those with the severest

disease resulting in complications exhibit a lower colonization rate than patients presenting with uncomplicated dyspepsia [21].

Current use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk for ulcer perforation 6-8 times, and seems to account for about a quarter of the events [19, 23, 24]. Perforated peptic ulcers are becoming common in older patients especially those with co-morbidities and are associated with a high incidence of recent consumption of NSAIDs [12, 19, 20].

NSAIDS can cause ulcers via stress erosion which is topical while chronic ulceration is directly related to the systemic effects e.g. prostaglandin synthesis inhibition [23, 24]. Prostaglandins play a protective role by inhibiting acid secretion, stimulating mucus and bicarbonate secretion and by stimulation of mucosal blood flow [20].

Ulcers of the stomach and duodenum are caused chiefly by the effects of hydrochloric acid, produced by the parietal cells of the stomach, and by lack of protection of the mucosa against this acid. Acid production is by far the most important factor as far as duodenal ulcer is concerned, but cannot be the only factor, since the severity of duodenal ulcers and their responses to therapy do not vary directly with the amount of gastric acid secreted.

Gastrinoma/Zollinger- Ellison syndrome is uncommon, occurring in 0.1 to 1.0% of all patients with peptic ulcer disease and in up to 20% of these

patients there is an association with multiple endocrine neoplasia 1(MEN 1)[20]. Duodenal ulcer patients have more parietal cells and chief cells increase in parallel.

Other important etiologic factors include smoking and alcohol ingestion. In Kenya, smoking and alcohol prevalence's of 39.3% and 39.3% [25] respectively have been documented compared to Smoking prevalence's of up to 84% - 86% in Western literature among patients with duodenal ulcer perforation.[21, 26.] Further, it has been suggested that smoking prevention is a far more effective tool in prevention of peptic ulcer perforation than *H. Pylori* eradication [19.]

Pathology & Clinical Manifestation.

Acute perforation may occur in both gastric and duodenal ulcers [27]. Perforated duodenal ulcers are reported to be sterile within the first 12 hours while perforated gastric ulcers are contaminated at the time of perforation [28]. The size of the perforation may vary greatly, from a diameter of only 2 to 3 mm to a hole of 2 to 5 cm across [2, 9]. The sites commonly associated with ulcers and perforation are the first portion of the duodenum, stomach antrum, gastro-esophageal junction in reflux disease, margins of a gastro-jejunostomy and in or adjacent to an ileal diverticulum.[20].

The diagnosis of an acute perforation of a duodenal ulcer is suggested by the sudden onset of severe epigastric pain followed by a variable degree of shock and often slight vomiting. In the untreated patient, the condition tends to improve after a few hours, to be followed shortly thereafter by increasing prostration, pain spreading throughout the abdomen, and cardiovascular collapse. Due to the acute nature of peptic ulcer perforation, the hour at which perforation occurred can be easily identified by the patient.

The patient looks sick, in pain, dehydrated and febrile. Physical examination typically reveals a board-like rigid abdomen, with tenderness most marked in the mid- or right epigastrium and reduced bowel sounds due to absence of peristalsis [14]. The temperature in the first few hours after perforation is

normal. This increases as peritonitis sets in. Paralytic ileus may be punctuated by vomiting and dehydration which are often the cause of shock.

Investigations

The patient's blood count shows leucocytosis and biochemical assays may depict serious electrolyte derangements including a metabolic acidosis. A plain abdominal X-ray radiograph shows pneumoperitoneum in 75% of patients with erect films of chest and abdomen revealing free air under the diaphragm (45%-53% in local studies) [14, 15]. A perforation may seal quickly and patients seek attention only after a localized intra- abdominal abscess develops. This can be detected by an abdominal ultrasound. In questionable cases, gastrografin (water soluble radio contrast material) can be injected through a nasogastric tube to determine whether or not there is a perforation. Laparascopy is a useful diagnostic tool and it offers an advantage in that it can be therapeutic in the same sitting. Some perforated ulcers may seal spontaneously and the patient will continue to improve. Exploratory laparotomy is often necessary to confirm the diagnosis in such scenarios [14, 29-32] where otherwise non operative treatment could be undertaken.

Treatment

The treatment of perforated peptic ulcer is still mainly surgical. Today, a surgeon faced with a perforated peptic ulcer disease has three procedures in his/her armamentarium to choose from;

- A simple closure of the perforation with a Graham patch [14, 15].
- Laparoscopic repair [33-39] or
- A definitive procedure designed to prevent future recurrences of ulcer disease.[22, 40].

Simple suture closure and a Graham patch is the preferred option for many surgeons.[14, 15, 41,]

Laparoscopic repairs have been used since 1990s in some institutions [33, 34, 35]. It offers advantages such as reduced size of the surgical wound and reduced wound infection, diminished post-operative pain, fewer post-operative complications, less intestinal manipulation, which should diminish post-operative ileus and the long-term risk of future adhesive obstructive complications; and the global costs derived from shorter hospital stay and an earlier return to daily activities and lower mortality rates [36, 37, 38]. The laparoscopic closure technique is contraindicated in patients in shock, and in those who have had delay in treatment of more than 24 hours [39].

Medical treatment is an important adjunct to surgery. The introduction of anti-secretor drugs in 1970s, proton pump inhibitors and use of antibiotics to eradicate Helicobacter pylori, have improved the outlook of peptic ulcer perforations treatment. The Graham patch repair has been associated with high recurrence rates of peptic ulcers [14, 41], but, with the adjunct use of proton pump inhibitors (PPI) and *Helicobacter pylori* eradication however, the recurrence rates are much lower obviating the need for definite surgery in perforations.

Some perforations seal spontaneously, covered in most cases by adjacent omentum. Such a finding has led some surgeons to advocate the non-operative treatment of what is believed to be an acutely perforated ulcer [14, 29, 30, 31, 32]. Such treatment comprises the use of nasogastric suction, antibiotics to eradicate *H. pylori*, management of fluid balance and electrolytes, proton pump inhibition, close monitoring of the haemodynamic status, and serial abdominal examinations. This approach has been shown to be safe and effective in a randomized controlled trial [42] .The approach is abandoned if the patient's condition appears to be deteriorating. The method is however associated with a longer hospital stay and often fails in patients over 70 years old [43]. The main indications for such treatment include patients with

recent coronary occlusion or those in whom the diagnosis has been delayed and in whom the ulcer has apparently sealed spontaneously [29, 32, and 43.]

Treatment Complications

Perforated peptic ulcers have for long been associated with a significant morbidity (30–50%) and mortality (6–30%) [2, 3, 14, 21, 25, 33] In spite of modern advances in surgical, anesthetic and ancillary facilities, perforation still assumes life-threatening dimensions. A recent Danish study has shown that hospitalization and mortality from peptic ulcer complications have increased, especially among the elderly [44]. An earlier study (1979-80) at KNH documented a mortality rate of 11.1% [14]. In Ethiopia, 14 of 74 patients treated for perforated peptic ulcers died in hospital [13].

A posterior perforation of an ulcer may occur in 15-20% of patients. This erodes the gastro duodenal artery and may cause brisk hemorrhage [20]. Wound infections, anastomotic leaks, or recurrence of bleeding are recognized early complications of perforated peptic ulcer disease after operative management. Late complications, such as dumping syndrome especially in patients who have had vagotomy and drainage procedures, post-vagotomy diarrhea, and alkaline reflux, have been reported mostly in adults but can also occur in children [20.]

Gastric outlet obstruction develops in less than 5% of patients with duodenal ulcer. This may be due to pyloric channel ulcers or duodenal ulcers which cause oedema or scarring. It may cause incapacitating crampy abdominal pain or intractable vomiting with resultant malnutrition.[20] Duodeno-pleural fistula is another, but very, uncommon complication of peptic ulcer perforation and usually follows empyema after a sub-diaphragmatic abscess rupture [45].

Treatment delay is an important determinant of prognosis of ulcer perforation [5, 12]. The risk of post-operative death and complications is closely related to duration of perforation [12, 25, 46, 47]. These adverse effects are more prevalent when the delay exceeds 12 hours [5, 12]. Delays of more than 24 hours increase mortality 7-8 fold, complication rate 3 fold, and length of hospital stay 2 fold in the West [5]. Treatment delay seems to have increased during the last few decades and is higher among women and the elderly [19, 48]. Nzarubara [49] stratified perforated peptic ulcer patients into two groups: (a) The previously fit patients who had relatively mild physiological compromise imposed on previously healthy organ system and who could withstand the operative stress of a definitive procedure and (b) a second category that included patients who were critically ill, who poorly tolerated any operation and hence poor surgical risks and outcome. Treatment delay

was the single most important determining factor in differentiating between the two groups above.

Early presentation of patients to surgical care facilities may reduce morbidity and mortality in cases of peptic ulcer perforation. [13, 14]

STUDY JUSTIFICATION

Perforated peptic ulcers are associated with significant morbidity (30–50%) and mortality (6–30%) [2, 3, 14, 21, 25, 33]. Previous studies on gastro duodenal perforations at Kenyatta National Hospital analyzed the clinical presentation, clinical findings and management of patients with perforated peptic ulcers but not the factors that determined outcome [14, 15, 25]. The main risk factor for increased morbidity and mortality in general setting has been described as delay in treatment of more than 24 hours [5, 25, 50] however; some papers have expressed conflicting ideas about the effect of delay in treatment on outcomes [51-54].

Little is known about delay as a determinant of outcome of perforated peptic ulcer disease (PUD) in KNH. It is clear that risk stratification of patients with perforated peptic ulcers [49] should facilitate their management and improve survival rates. Unlike other prognostic factors e.g. co morbid illnesses, presence of preoperative shock, preoperative ASA class, age etc treatment delay can be modified to improve survival outcome. Knowledge of how this factor affects outcome will enable us to offer quick surgical treatment to the affected patients and advise patients on the importance of early presentation to hospital in order to reduce poor outcome

BROAD OBJECTIVE.

To establish the pattern and adverse effects of delayed treatment in patients with perforated peptic ulcers (PPU) at Kenyatta National Hospital.

SPECIFIC OBJECTIVES

1) To analyze the patterns of delays in treatment of PPU patients.
2) To determine the effects of delayed treatment/presentation on morbidity, length of hospital stay, and mortality for patients with PPU.
3) To assess the association between delay in treatment and gender and/or age.

PATIENTS AND METHODS

Study Design

A six year (2002-2007) retrospective and a one year (2008) prospective descriptive study.

Setting

Kenyatta National Hospital (KNH), a 2,000 bed teaching and national referral hospital in Nairobi -Kenya.

Inclusion Criteria

Inclusion criteria were all patients treated surgically with a clinical diagnosis of PPU and who at operation the diagnosis was confirmed between Jan 2002 and Dec 2008.

Exclusion Criteria

- Retrospective patients whose files were missing or the information sought was missing and or incomplete.
- Patients with perforations due to malignancy.

Ethical Considerations

Permission to do the research was sought and granted from KNH-ERC. (see appendix 3)

Data Collection

This descriptive study involved consecutive selection of patients treated surgically for perforated peptic ulcer disease at KNH between Jan 2002-Dec 2008. The information sought included patient characteristics, treatment delays, treatment complications and length of hospital stay.

Treatment delay encompassed both pre-hospital and intra-hospital delay. Pre-hospital delay was the time in hours from onset of pain to presentation at the hospital's casualty department. Intra-hospital delay was defined as the time in hours from arrival at casualty to operative treatment.

The information sought was collected by means of a structured data sheet (see appendix) by one reviewer (the author) and the details entered into a computer database followed by analysis using SPSS program version 11.5. The total delay time was used to stratify the patients into three delay groups: <24 hours, 24-48 hours and over 48 hours.

For descriptive purposes, data were presented as means with standard deviation for continuous variables or as absolute and relative frequencies for qualitative variables. The Student t test was used for the comparison of continuous variables e.g. mean delay in hours for outcome categories and mean length of stay in days. Categorical and binary variables were tested by Fisher's exact test/chi square test e.g. comparison of proportion of

complications for delay categories. A P value of <0.05 was accepted as significant.

The associations between delay and age/sex were also analyzed by the Fisher's exact test/chi square tests as appropriate e.g. comparison of the proportion of females in the delay groups.

RESULTS.

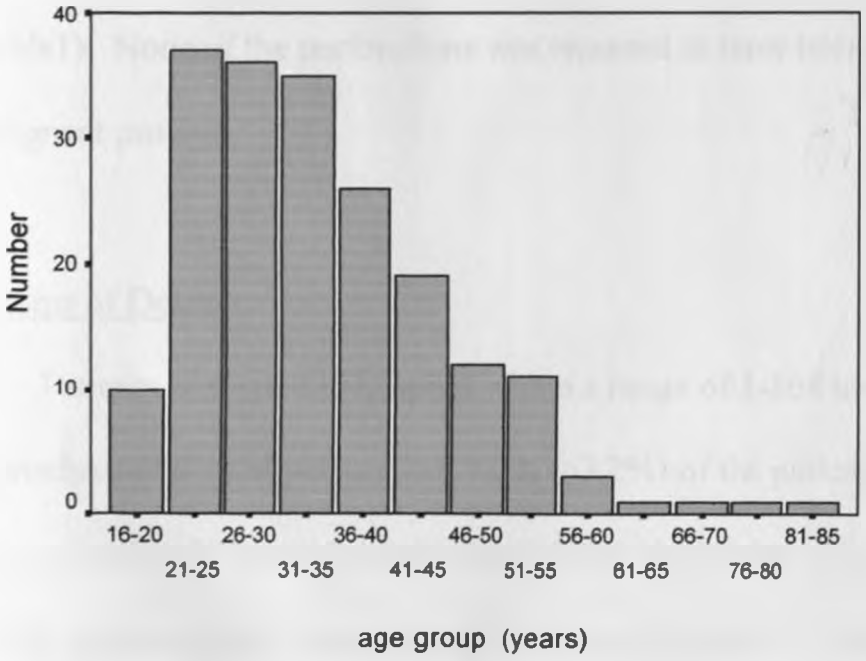
One hundred and ninety three (193) patients were recruited during the study period. One hundred and fifty one (151) patients had their records reviewed (2002-2007) while forty two patients were directly interviewed by the researcher (January 2008 to December 2008). An annual incidence of 27.5 patients per year was recorded in this study period. Of the total 193 patients, 175 (90.7%) were males while 18 (9.3%) were female (Gender ratio was 10:1, Table 1).

Table 1: Characteristics of peptic ulcer perforations at KNH

Characteristics	Number of Patients	%
Gender		
Male	**175**	**90.7**
Female	**18**	**9.3**
Age		
<40 years	**144**	**74.6**
>40years	**49**	**25.4**
Site of perforation		
Anterior duodenal	**151**	**78.2**
Posterior duodenal	**2**	**1.1**
Gastric	**40**	**20.7**
Nature of perforation		
Acute(benign)	**61**	**31.6**
Chronic(benign)	**38**	**19.7**
Not specified	**94**	**48.7**
Pre-treatment Delay (hrs)		
<12 hours	**1**	**0.5**
12-24 hours	**21**	**10.9**
24-48 hours	**98**	**50.8**
>48 hours	**73**	**37.8**

The patient's ages ranged from 16 to 84 years. The mean age for women was 35.78 (± 15.9) years while that for men was 34.35 (± 10.8) years. Younger patients were predominantly affected (Fig. 1); patients younger than 40 years (especially in the third and fourth decades) accounted for 74.6% of all cases while those above forty years of age formed 25.4%.

Fig. 1 Age disriution for perforated ulcer patient



The duodenum was the most common site of perforation accounting for 77.2% of all the patients treated. Forty (40) patients had gastric perforations representing 21.7% of total number of patients. No posterior gastric perforation was seen in any patient while two (2) posterior duodenal perforations were witnessed (Table 1). The mean ages for gastric and duodenal perforations were 34.67 and 34.07 years respectively (p=0.541).

Majority of patients had acute benign perforation (31.6%) at histology as a further 19.7% were reported as perforations due to benign chronic peptic ulcerations. Histopathology reports were missing in 48.7% of patients (Table1). None of the perforations was reported to have been caused by a malignant process.

Patterns of Delay

Patients presented to hospital within a range of 1-168 hours from approximated time of perforation. Most (63.2%) of the patients presented to hospital within 24 hours from the start of their symptoms (Fig 2). The mean time to presentation to hospital was 36.3 hours (median 23 hours). Males generally presented to hospital earlier than their female counterparts by a difference of up to eighteen hours (34.3 hours *vs.* 52.5 hours). This

difference was statistically significant *(p value 0.012)*. The intra hospital delays were similar for the genders.

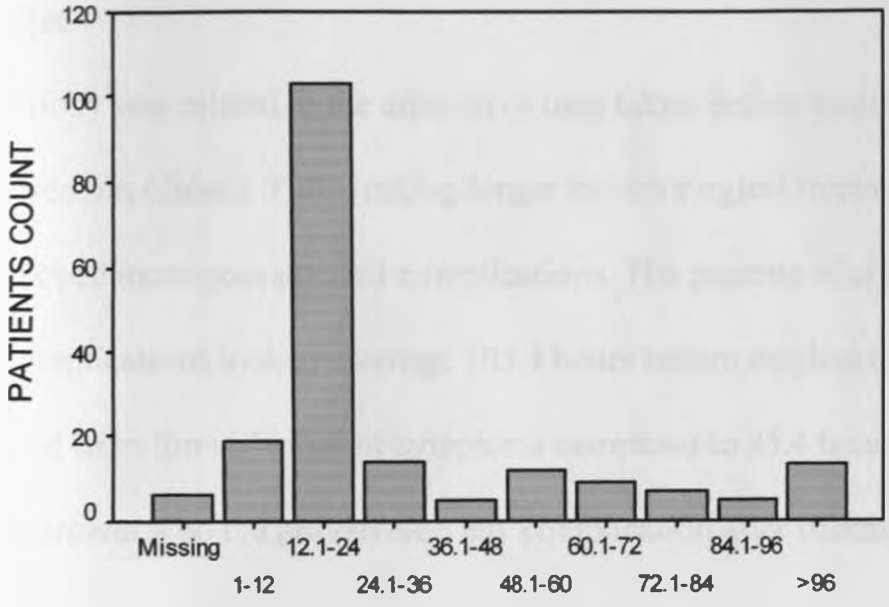
The total time from onset of symptoms to treatment ranged from a minimum of two hours to a maximum of 240 hours with a mean total time to treatment of 58.03 hours.

Seventy four percent (74.5%) of the patients were operated on within twenty four hours of hospitalization. The rest were delayed due to several reasons including delayed diagnosis, initial admission to the medical ward (2.5%), instances where patients were too ill and needed prolonged "stabilization" before undergoing surgery- 11 patients. In others the reason for intra-hospital delay beyond 24 hours could not be established.

Table 2: Reasons for intrahospital delay.

Reason	Patient number	percentage
Patient too ill	11	6
Initial admission to non Surgical ward.	5	2.5
Unknown	33	17

Figure 2. PREHOSPITAL TIME GROUPS.



Morbidity

Sixty one patients (31.6%) developed complications after treatment. The commonest complication was surgical site infections in 49 patients (25.8%).These surgical site infections included intestinal leak, wound dehiscence, wound sepsis, deep seated infections like peri hepatic and intra abdominal abscesses, peritonitis etc. Other complications noted in these postoperative patients included intestinal obstruction in two patients; acute renal failure was observed in four patients who died, two patients had poor reversal from anesthesia and were admitted to the intensive care unit.

Paralytic ileus was present in one patient and pneumonia presented in another.

Morbidity was related to the amount of time taken before surgical intervention (delay). Those taking longer before surgical treatments developed more post surgical complications. The patients who were affected by complications took an average 105.4 hours before surgical treatment was offered from time of onset of symptoms compared to 35.4 hours in their counterparts who did not develop any complication after treatment *(p <0.001).*

When the patients were dichotomized to those with pre treatment delay of less than 24 hours only 22 patients qualified and of these twenty two, there was no recorded post op complication. For those whose symptoms lasted more than 24 hours before operation 60/164 patients had post surgical complications while 104 had no post operative morbidity *($p < 0.001$).* Delays of less than 48 hours were associated with morbidity in only three of one hundred and thirteen patients (2.6%). This changed significantly when the delay increased to over 48 hours with 57 of 73 patients (78.0%) recording morbidity post surgery *(p value <0.001) (Table 3).*

Table 3. Association of delay and morbidity/mortality

	Delay ≤48 Hrs	Delay >48 Hrs	P Value	OR (95% C/I)
Morbidity				
yes	**3**	**57**	**< 0.001**	**4.441**
no	**110**	**16**		**(2.877-6.855)**
Gender				
Male	**107**	**61**	**0.012**	**0.323**
Female	**6**	**12**		**(0.127-0.823)**
Mortality				
Yes	**0**	**23**	**<0.001***	**1.460**
No	**113**	**50**		**(1.250-1.706)**
Surgical site infections yes				
no	**3**	**46**	**<0.001***	**2.632**
	109	**25**		**(1.948-3.556)**
Non infectious complications				
Yes	**0**	**15**	**0.566***	**1.357**
no	**3**	**42**		**(1.162-1.585)**
Perforation site				
Duodenal				
gastric	**93**	**53**	**0.116**	**0.646**
	20	**20**		**(0.3741.115)**

* Fischer's exact test. OR- Odds ratio, C/I Confidence Interval

There was also a statistically significant *(p value< 0.001)* effect of delay over 48 hours on surgical site infections. Those who delayed more than 48 hours were 2.6 times more likely to develop surgical site infections

compared to those who presented earlier. Three patients (3/112) who presented within 48 hours suffered surgical site infections compared to their counterparts (46/71 patients). Non infectious post surgical complications were identified only in patients who had delayed more than 48 hours. This was however not statistically significant.

Associated factors analyzed for their effect on morbidity included patient age, sex and perforation site. The female gender was associated with morbidity in a statistically significant way (Table 4). Whereas less than a third of the males (29.1%) developed complications, more than a half of the females (55.5%) had morbidities.

There was a relatively higher rate of complications in the gastric (40%) compared to duodenal perforations (27.7%) but this did not achieve statistical significance. The site of perforation (gastric or duodenal) had no effect on complications (Table 4). The average age of patients with complications was however significantly higher than those who did not 36.79 (± 14.03) years versus 33.42 (± 9.824) years, *($P < 0.001$)*.

Length of hospital stay.

The time taken from onset of symptoms to presentation in hospital had an impact on total length of hospital stay in days. The length of hospital stay ranged from 2-136 days while the average stay was 12.08 days.

Patients with delay of ≤48 hours had a mean hospital stay of 7.22 days compared to 19.7 days for those receiving treatment after 48 hours *($p <$ 0.001)*. Males stayed for a mean of 11.8 days while their female counterparts took 14.4 days in hospital *($P < 0.001$)*.

Table 4. Perforation site, gender and age versus morbidity

	Morbidity present	**Morbidity absent**	**P value**	**OR (95%C/I)**
Site of perforation				
Duodenal	**45**	**108**	**0.200**	**1.176**
Gastric	**16**	**24**		**(0.895-1.546)**
Sex				
Male	**51**	**124**	**0.022**	**1.594**
Female	**10**	**8**		**(0.943-2.696)**
Age				
≤40 years	**42**	**102**	**0.211**	**1.157**
>40 years	**19**	**30**		**(0.904-1.480)**

Table 5: shows how various factors affected mortality.

	Mortality occurred before discharge	No mortality reported	P value	OR (95%C/I)
Site of perforation				
Duodenal	**16**	**137**	**0.103**	**1.119**
gastric	**8**	**32**		**(0.950-1.319)**
Sex				
Male	**18**	**157**	**0.005**	**1.346**
female	**6**	**12**		**(0.967-1.873)**
Surgical site infection				**0.740**
yes	**15**	**34**	**<0.001**	**(0.612-0.896)**
no	**9**	**135**		
Non infection complication				
yes	**10**	**6**	**0.027**	**0.544**
no	**14**	**31**		**(0.281-1.056)**
Age ≤40years				
>40 years	**15**	**129**	**0.145**	**1.097**
	9	**40**		**(0.950-1.267)**
Delay				
≤24 hours	**0**	**22**	**0.045***	**1.163**
>24hours	**23**	**141**		**(1.093-1.237)**
Delay				
≤48hours	**0**	**113**	**<0.001***	**1.460**
>48hours	**23**	**50**		**(1.250-1.706)**
Re intervention				
yes	**13**	**17**	**<0.001**	**11.624**
no	**10**	**152**		**(4.429-30.504)**

* Fischer's exact test.

Mortality

Twenty four patients died in hospital before discharge representing 12.4% of all patients treated.

Delay was also an important determinant of mortality. Patients who presented to hospital and were operated within 24 hours of the start of their symptoms recorded no death as compared to those operated > 24 hours where 23 of 164 patients died (*p= 0.045).*

Likewise when the patients were dichotomized to those who were treated before 48 hours and those treated after 48 hours the results for mortality mirrored those of morbidity- i.e. no mortality for those treated less than 48 hours with all mortality occurring to those treated after 48 hours i.e. 23 of 73 patients (30.1%) *p value <0.001* (table 5).

Mortality was higher (9.6%) in patients below 40 years of age compared to those above (5.4%) but this was not significant (table 5). The site of perforation did not significantly influence mortality although there were more deaths in gastric perforations (20%) relative to duodenal perforations (10.4%). The difference was not statistically significant.

More significantly, eighteen of 175 (10.2%) male patients died in hospital as compared to 6 of 18 (33.3%) female patients *(p =0.005)*

Patients who were re operated also had significantly worse mortality outcomes ($p < 0.001$)

Surgical site infections, re-intervention, gender

Table 6 showing how various factors determined surgical site infections.

	Surgical site infection = yes	Surgical site infection = no	P value.	OR (95% C/I)
Age ≤40	36	108	0.832	1.021(0.842-1.238)
>40	13	36		
Sex male	42	133	0.167	1.244 (0.852-1.815)
female	7	11		
Nature of perforation				
Acute	13	48	0.666	N/A
chronic	11	27		
none	24	68		
Site of perforation				
duodenal	36	117	0.246	1.133(0.898-1.429)
gastric	13	27		
Simple patch repair	47	141	0.583	1.125(0.503-2.515)
definitive	1	2		
Delay <48hours	3	110	<0.001	2.632(1.948-3.556)
>48hours	46	27		

Forty nine patients recorded a surgical site infection (table 6). The age, sex of patients, site of perforation or the surgical treatment modality used did not have any significant effect on the occurrence of a surgical site infection

(table 6). The presence of a surgical site infection was commonly associated with a re intervention/reoperative procedure in the immediate post operative period *p value< 0.001*(table 7). Those patients who were operated less than 48 hours since their symptoms started had fewer surgical site infections compared to those operated after 48 hours from the time their symptoms started. *P value<0.001*

Other variables that determined whether or not a patient underwent re-intervention included the female gender *(P = 0.04)*, delay more than 48 hours *(p < 0.001)* and presence of a complication *(p < 0.001)* (Table 7). Age and site of perforation did not determine re-interventions.

Table 7.

	Re intervention = yes	Re intervention =no	P value	OR (95% C/I)
Sex male	**23**	**151**	**0.004**	**1.420**
Female	**7**	**11**		**(0.978-2.062)**
Age				
< 40 years	**20**	**124**	**0.251**	**1.088**
>40 years	**10**	**38**		**(0.928-1.276)**
Delay				**1.674**
<48 hours	**0**	**113**	**<0.001***	**(1.385-2.024)**
>48 hours	**29**	**43**		
Morbidity				
yes	**30**	**30**	**<0.001***	**0.500**
no	**0**	**132**		**(0.388-0.644)**
Wound dehiscence				
Yes	**8**	**1**	**<0.001**	**0.126**
No	**22**	**161**		**(0.020-0.802)**
Non septic complications				
yes	**3**	**12**	**0.008**	**2.000**
No	**27**	**18**		**(1.290-3.100)**
Site of perforation				
Duodenal	**23**	**130**	**0.654**	**1.036**
Gastric	**7**	**32**		**(0.881-1.217)**

*Fischer's exact test.

There were statistically significant differences in both sexes with women more likely to undergo a re operation (38.9%) compared to their male

counterparts (13.2%) $p = 0.004$. Likewise they suffered more post surgical complications and mortality *p values 0.022* and *0.005 respectively*. There was a statistically significant difference in delay between sexes (*p value 0.012.)*. There were no significant differences between sexes in terms of the site of perforation, treatment offered and nature of perforation. Similarly there was no difference in sexes with specific complications such as wound sepsis and dehiscence.

Simple repair and Graham patch formed the mainstay of treatment for patients with peptic ulcer perforations (190 of 193). Only three patients had a definitive repair done for their perforation. No patient had a laparoscopic surgical repair done for their perforated peptic ulcer.

DISCUSSION.

This study has documented the impact of delay in the surgical treatment of peptic ulcer perforations at the Kenyatta National Hospital in Kenya. Peptic ulcer disease is present in up to 10% of the general population. Perforation complicates 5-10% of peptic ulcer [1]. The morbidity and mortality associated with perforation in PUD approach 30-50% and 6%-31% [2, 3, 50, 52, 54] respectively. Several factors have been associated with increased morbidity and mortality in patients with perforated peptic ulcers. These factors include presence of co morbidity, presence of shock, age of patient, ASA class, and delay in treatment [4, 5]. Delay in treatment is most important because it is modifiable.

The annual incidence of perforated ulcers has risen from 22.5 in the earlier study 1979-80 [14] to 27.5 in this study. This could be explained by increase in population of Nairobi over the last thirty years. There was however a high number of patients (forty two) witnessed in the prospective arm of this study. The latter admission rate is likely closer to the true incidence. Presumably inaccuracies in record keeping have masked a more robust documentation of increasing prevalence of the disease in the retrospective arm. Several studies in Africa have documented increasing burden of perforated peptic ulcer disease [55].

This condition has long been related to levels of stress [56].There were more men than women affected by perforation (gender ratio 10:1). Other studies have documented ratios ranging from 7.2: [13] to 21.5:1 [14].

The reason for more male involvement over their female counterparts has not been elucidated but it has been suggested that the female hormone- estrogen- may be responsible [46]. In the West more elderly females in the 5th and 6th decades are involved compared to our predominantly young males [1, 8, 15, 25]. This could be due to the distribution of the risk factors where the Kenyan young male is more likely unemployed, smoking cigarettes and taking alcohol [25] with a family he can't provide financially for. These problems are the ones that the elderly female in the Western world face i.e. smoking as depicted by a parallel increase in lung cancer in the west, drinking alcohol, retirement, reduced income, postmenopausal and lonely since the children are grown up and have moved away from home. Patients younger than forty years comprised (74.6%) of the afflicted population, a pattern replicated in other regional studies [13, 14, 25].

There were more duodenal perforations compared to gastric perforations. This is expected since the duodenum is the first portion of the gastrointestinal tract that gets in contact with acid after secretion in the

stomach. This has been shown consistently in other studies [5, 13, 14, 25, 15]. Duodenal secretions are sterile in the first 12 hours while gastric perforations are infected at perforation [5, 28]. As the time of delay increases infection sets-in in duodenal perforations and worsens in gastric perforations causing much of the complications being observed i.e. more surgical site infections, high probability of developing shock due to septicemia and acute renal failure and increased chances of death. Following this argument one expects more morbidity and mortality from gastric perforations compared to duodenal perforations [5].

Our results above suggest seemingly poorer outcomes with gastric perforations where post surgical complications involved 40% of patients in the gastric perforations as compared to 27.7% in duodenal perforations. Also there appeared to be more deaths in gastric perforation (20% of patients) relative to duodenal perforations (10.4% of patients). This pattern has been witnessed in other literature [5, 57].

The age of the patient had no bearing on the post surgical complications. This was surprising since other studies have shown that advanced age is associated with poor outcome [5, 48]. However, as majority of our patients were young, the effect of age with its attendant co morbidities, did not manifest. Our results also contrast the observation that perforated gastric

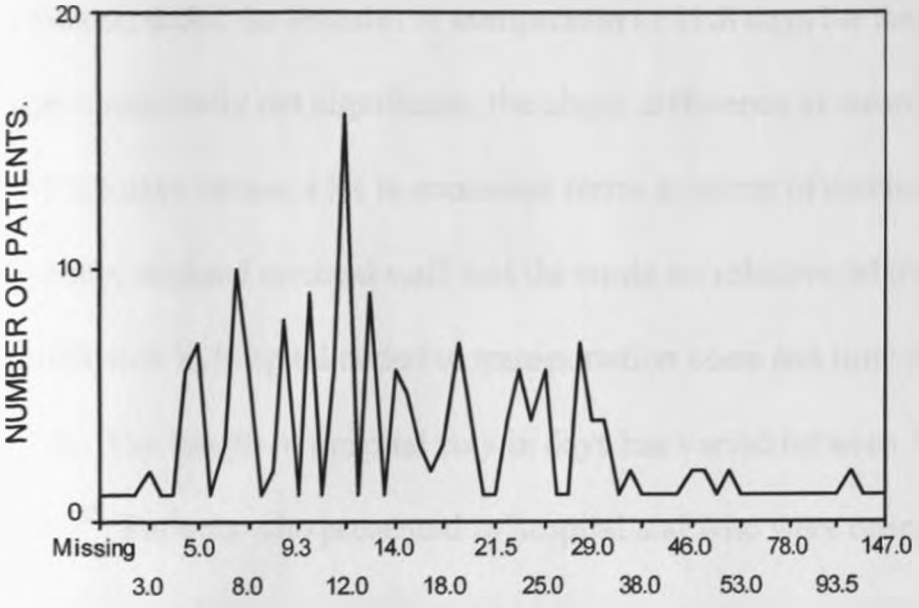
ulcer patients are usually a decade older. The mean age for the perforated duodenal ulcer patients in this study was 34.07 years compared to 34.67 years for those with gastric perforations.

There was a statistically significant delay in presentation to hospital between the sexes with males presenting on average 18 hours earlier than their female counterparts. The reason for this may be socio economic where women have to await decision as to whether or where they will attend hospital from their husbands. Women have been economically disempowered at the household, community and national levels [58]. They have limited access to capital, education, training and health care. The men are more economically empowered compared to the women (poverty rate among women 46% compared to 30% among men) [58] and so they take effective measures regarding their health.

The mean time to presentation to hospital was 36.3 hours (median 23 hours). In the developed world delay in treatment is defined as the time from perforation to operation [5]. Twelve hours is the cut off point where patients presenting later than this have significant increase in morbidity and mortality [5]. This cut off point cannot be achieved in our scenario where only one patient would have certified this criteria representing 0.5% of the total. Most of the patients (63.2%) however, presented to hospital within the first twenty

four hours. Twenty two (22) patients were operated on within twenty four hours from the start of symptoms representing 11.8% of the total. The significant delay in presentation to hospital can largely be blamed on poor infrastructure i.e. roads and means of transport [58] and the fact that the amount of delay is an indication of development of the area where the study was done [56]. Majority of patients (74.5%) were operated within twenty four hours after presenting to hospital (mean 21.7 hours) However if the outliers are eliminated, the mean delay falls to twelve hours (fig 3). This is impressive considering that the patients had delayed in presenting to hospital and thus more likely physiologically unstable and in shock and sepsis. Much of the precious time may have been utilized in optimizing the patients before surgical treatment.

FIG 3. INTRAHOSPITAL DELAY



Post surgical complications and mortality were directly related to delay- the total amount of time that it took from onset of symptoms to the time a patient was treated. Delay was more marked in the pre hospital segment compared to intra hospital delay. Morbidity was worse in females who presented relatively later to hospital compared to the men. For instance, whereas 10 of 18 women (55.5%) had a complication of one nature or another, men had a rate of 51 of 175 (29.1%). The same scenario is repeated when mortality is considered where 33.3% of females died compared 10.2% for males.

The length of hospital stay adds to this observation where a mean of 14.4 days was recorded for females in comparison to 11.8 days for the males. Though statistically not significant, the above difference in mean hospital stay of 2.6 days means a lot in economic terms in terms of medical bills, bed occupancy, strained medical staff and the strain on relatives who have to visit their sick in hospital added to transportation costs and time away from work etc. The length of hospital stay in days has varied between 11 days and 15 days [25]. Patients who presented to hospital and who were operated before their symptoms had lasted 24 hours had no post surgical complication/ morbidity and likewise no mortality was reported. However when the patients were dichotomized to those who received treatment within 48 hours and those after 48 hours the results were statistically significant in that in those under 48 hours group had complications in only 3 of 113 as compared to 57 of 73 in the over 48 hours group. In the same scenario deaths occurred only in those who received treatment after 48 hours. It seems reasonable that delay in our set up should be adjusted upwards with a cut off at 48 hours since at 24 hours delay no morbidity and mortality were observed, and in delays of $\leq$48 hours only 3 patients had complications and no mortality. Morbidity and mortality increased exponentially after 48 hours delay in treatment.

Twenty four patients (12.4%) died after treatment. In this region, mortality rates of 11.1%-18.9% [13, 14] have been reported while internationally mortality from this condition represents a percentage range from 6-31% [2, 3, 50, 52, 54].Our results therefore seem to fall within this limit. Mortality was high in those under forty years compared to those over forty years. This is at variance with other publishers who had more mortality in the elderly but this could be explained, as highlighted earlier, by the fact that the majority of our patients were younger than theirs [52].

The treatment modality offered to our patients was mainly simple Graham patch repair in 98.4%. Of 193 patients only 3 patients had definitive surgery that involved pyloric exclusion in one patient after multiple re perforation recurrences, the other 2 patients had vagotomy and drainage. None of our patients got laparoscopic treatment for their ailment. With the current advances in medical management of peptic ulcers, most surgeons would agree that the need for doing the much more difficult and technically demanding definitive treatment for perforated ulcers is not necessary [12, 15, 48.] On the other hand most of our patients present and are operated on beyond twenty four hours from the start of symptoms which means more peritoneal contamination hampering use of laparoscopic surgery for them. The

recommendation is that this treatment can be offered when there's no overt peritonitis in the early hours after perforation [39].

Sixty one (61 of 193) patients representing 31.9% of the patients had histology done from the ulcer reported as acute benign ulcers in nature while 38 of 193 representing 19.9% of patients were reported as benign chronic ulcers. In almost half of the patients (48.2%) histopathologic reports were not confirmed. This is a trend which shouldn't be encouraged. Some studies have shown several of their patients' gastric perforations are due to malignancy in 1%-16.7% [15, 59] This vital information would dramatically change the management of the patient from Graham patch to gastrectomy and lymph node dissection and from acid suppressing therapy to chemoradiotherapy. Therefore surgeons should be encouraged to submit adequate samples for histology.

This study had limitations. Although it was possible to determine intra hospital time delay accurately to the minute, the pre admission delay time may not be as accurate especially in the retrospective chart reviews. Difficulty in retrieval of information for the retrospective arm of the study was also common.

CONCLUSIONS.

This study has shown the relationship between delay and outcome where the more the delay the poorer the outcome in terms of increased post surgical complications, increased mortality, and increased length of hospital stay. Most of the delay is pre hospital. Females are more likely to present late consequently have poor outcomes. Delay as defined in literature from the developed world with a cutoff point at twelve hours may not be easily achieved in our set up where majority of our patients present already after twelve hours have lapsed. The more reasonable cutoff point in our set up should be 24 to 48 hours which is the period beyond which complications increase exponentially. There are more duodenal perforations than gastric perforations and the later may be associated with poorer outcome compared to the former.

RECOMMENDATIONS.

Patients should be encouraged to present to hospital earlier. Surgeons should be encouraged to take specimen for histology whenever a perforation is encountered.

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Appendix 2

DATA SHEET.

STUDY NUMBER……..

1. Age----------
2. Sex (1) male (2) female.
3. Site of perforation (1) anterior duodenal (2)posterior duodenal

   (3) gastric
4. Time from start of symptoms to presentation to hospital in hours

   _____
5. Prehospital time groups

   (1) 0-24hrs (2) 24-48 hrs (3) 48-72 hrs (4) 72-96 hrs. (5) >96 hrs.
6. Time from presentation in hospital to operation in hours _____
7. Intra-hospital time groups

   (1) 0-24hrs (2) 24-48 hrs (3) 48-72 hrs (4) 72-96 hrs. (5) >96 hrs
8. Treatment (1) simple patch repair (2) definitive repair

NB; definitive repair refers to one of the various forms of vagotomy and drainage operative procedures

9. Nature of perforation/histology as reported by the pathologists

(1) acute (2) chronic

10.General complications in the immediate post operative period.

(1) yes (2) no

11. Wound sepsis (1)yes (2)no

12. Wound dehiscence (1) yes (2) no

13. Re-intervention (1) yes (2) no

14.Other complications (1) yes (2) no

15.State other complications

.....

16. Mortality occurring in hospital before discharge of post operative patient. (1) yes (2) no

17.Length of hospital stay in days (till the day a decision to discharge the patient is made) ____

Appendix 3: Ethical approval

KENYATTA NATIONAL HOSPITAL
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Ref: KNH/UON-ERC/ A/28

8th August 2008

Dr Abner Nasio Nasio
Dept of Surgery
School of Medicine
University of Nairobi

Dear Dr Nasio

RESEARCH PROPOSAL: "EFFECTS OF DELAYED TREATMENT OF PERFORATED PEPTIC ULCERS AT KENYATTA N. HOSPITAL" (P78/04/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 8th August 2008 – 5th August 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K.M.Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Surgery, UON
Supervisor Dr. Dr Said Hassan, Dept of Human Anatomy, UON