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Clinico-Pathological Pattern and Early Post-Operative Complications of Gastro-Duodenal Perforations at Mulago Hospital Kampala- A Prospective Cohort Study.

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Background: ***Gastro-Duodenal Perforations are one of the commonest causes of mortality and morbidity in conditions that require emergency surgery. The main objective of this study was to determine the clinico-pathological pattern and evaluate factors for early post-operative complications of Gastro-duodenal perforations in Mulago.***

Methods: ***This was a prospective cohort study of patients with gastro-duodenal perforations managed by simple repair between September 2014 and April 2015 in Mulago was studied. Primary/ secondary outcomes were mortality and complications respectively. Data was managed using stata-12 and multivariate analysis using log-binomial regression model.***

Results*: A total of 65 patients were operated for Gastro-duodenal perforations in the study period. 86.2% were male (M: F 6.2:1). Median age was 35 years (range 16- 80 years). 93.9% had gastric perforations. Clinical diagnosis was predicted in 89.3%. H. pylori was present in 7.9%. Mortality was 18.5% and complications developed in 58.5%. Age above 35 and presence of co morbidity predicted mortality (CI 1.22- 21.12, p= 0.009) (CI 1.26- 8.82, p= 0.024) and early post-operative complications (CI 1.03- 2.44, p= 0.031) (CI 1.23- 2.44, p= 0.011) respectively.*

Conclusion: ***Gastroduodenal perforations remain a common surgical emergency in Mulago hospital affecting mainly young men below 35 years. Majority are gastric perforations. Mortality and early post-operative complications are high, and increase with age and presence of co morbidity.***

Keywords: gastro-duodenal perforations, perforated peptic ulcer disease, gastric perforations

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Introduction

A Gastro-Duodenal Perforation (GDP) is a potentially fatal surgical emergency and a formidable world health burden[1]. Globally, 250,000 people die from Peptic Ulcer Disease (PUD) each year, 70% of which are due to perforated disease[2]. The risk of developing a perforation in PUD is 2-14%[3]. Improved medical management has reduced elective surgery for PUD[4], but emergency surgery for complicated disease has increased[5]. The Global Burden of Diseases study (GBDS)[6] showed that surgical emergencies, majority of which are in Low and Middle Income Countries (LMIC), are insufficiently described and that perforated PUD is the commonest cause of death in conditions requiring emergency surgery[7]. The pattern of GDP has been reported to vary from one geographical area to another[8]. The complication rate after surgery for GDP is high ranging from 31.1% in Ghana to 45% in Nigeria[9,10]. Mortality is also high, the Peptic Ulcer Perforation (PULP) trial where patients in the intervention group were treated according to a multimodal and multidisciplinary evidence-based perioperative care protocol, reported mortality as high as 17% in the intervention group[11].

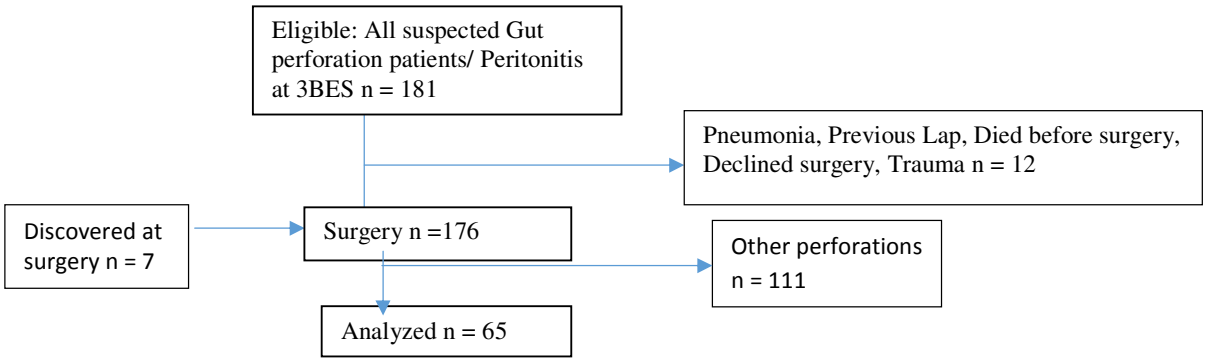
Prevalence of PUD and its complications parallels that of *H. pylori*[12]. Studies have shown a high prevalence of *H. pylori* in Uganda[13] with an increasing incidence of gastric cancer unlike other countries[14]. Some cases of GDP have been reported to be malignant[15]. In his study to determine the association between *H. pylori* infection and pathological changes of the gastric mucosa in different ethnic groups, Wabinga reported a high *H. pylori* prevalence in pre malignant states[16].

Histo-pathology especially on *H. pylori* has been missed in some GDP studies[8,9]. The purpose of this study therefore was to determine the clinico-pathological pattern and early post-operative complications of GDP in Mulago Hospital Uganda.

Patients and Methods

This prospective cohort study was done at Mulago National Referral Hospital Uganda from September 2014 to April 2015. Sample size estimation was done using Open Epi Version 3.

Patients' flow chart



Patients with a pre-operative diagnosis of gut perforation were considered for eligibility. Patients with GDP confirmed at laparotomy were enrolled. Those with history of trauma were excluded. At surgery, GDP was closed by modified Graham's patch followed by peritoneal lavage. Biopsy of the perforation was done before closure

Tissue, preserved in 10% formal saline was embedded in paraffin-wax, before staining as part of tissue processing. Routine Haematoxillin and Eosin (H & E) and special Giemsa staining were employed for routine histology and demonstration of *H. pylori* respectively. Microscopy was done by one experienced pathologist. Post-operatively patients were managed from any one of the three general surgical wards until they were fit for discharge where treatment was according to ward protocol. Follow up was done daily until discharge. The primary outcome was mortality and the secondary outcomes were early post-operative complications. These included pneumonia, SSIs, burst abdomen, sepsis, re-laparotomy and others.

Epi Info7 with preset validity checks to minimize errors was used for data entry, and statistical analysis was done with stata 12. Relative risk (RR) with 95% confidence intervals for the occurrence of different exposures: age, co morbidity, late presentation, etc for the predetermined outcomes using Chi square and fisher's exact test were used to detect statistical significance at p value < 0.05. A step-wise removal method using log binomial regression model was used in the multivariate analysis because prevalence of the outcome of interest was greater than 10% which made logistic regression inappropriate.

Results

Out of 181 patients considered for the study, 65 with non-trauma- related GDP were enrolled for the study.

Table 1 Age Distribution

Age (Yrs)	**<20**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80+**
No	8	15	13	14	7	4	3	1
%	12.3	23.1	20	21.5	10.8	6.2	4.6	1.5

Table 2. Clinical Characteristics

Clinical feature	Number	Percentage
Age		
≤35	33	50.8
>35	32	49.2
Sex		
Male	56	86.2
Female	9	13.2
Dyspepsia/ PUD	29	44.6
Alcohol (n=59)	23	38.9
Smoking (n=59)	20	33.9
NSAIDs	19	29.2
Late presentation	58	89.2
Classical history	23	35.4
Pneumoperitonium (radiological) n = 53	53	81.5

Table 3. Histopathological Features

Site of Perforation	Number	Percentage
Gastric	61	93.9
Duodenal	4	6.1
Size of perforation		
<1cm	30)	46.2
1cm	11	16.9
>1cm	19	29.3
Number of perforations		
1	64	98.5
>1	1	1.5
Histology done		
Yes	38)	58.4
Histology results n= 38		
H. pylori positive	3	8.0
Features of PUD	29	76.3
Acute perforation	4	10.5
Metaplasia	6	15.8
Malignant features	1	2.6
Chronic parasitic infection	1	2.6
No evidence of GD tissue	2	5.2

Table 4 Early post-operative complications

Outcome	Number	Percentage
Died	12	18.5
Other complications		
Pneumonia	19	29.2
Surgical site infection	15	23.1
Re-operated	6	9.2
Burst abdomen	4	6.2
Prolonged ileus	4	6.2
Enterocutaneous fistula	3	4.6
Sepsis	2	3.1
Re admitted	1	1.5
Psychosis	1	1.5

Table 5. Factors for Complications: Multivariate Analysis

	Mortality					
Variable	**Died**	**Alive**	**Unadjusted RR (CI)**	**p-value**	**Adjusted**	**p-value**
Age	No	(%)			RR (CI)	
Old	10 (31.4)	22 (68.8)	5.16 (1.22- 21.72)			
Young	2 (6.02)	31 (93.9)	1	0.009	0.22 (0.05-0.93)	0.041
Co morbidity						
No	6 (12)	44 (88)	1			
Yes	6 (40)	9 (60)	3.33 (1.26- 8.82)	0.024	2.73 (1.09-6.87)	0.033
Presentation						
Early	1 (14.3)	6 (85.7)	1			
Late	11 (19)	47 (81)	1.33 (0.20- 8.80)	1.006	0.78 (0.12-5.23)	0.794
Sex						
Female	2 (22.2)	7 (77.8)	1			
Male	10 (17.9)	46 (82.1)	0.80 (0.21- 3.08)	0.667	0.76 (0.18-3.28)	0.717
Complications						
Age:	Yes	No				
Old	23 (71.9)	9 (28.1)	1.58 (1.03- 2.44)	0.031	2.92 (1.90-4.49)	0.052
Young	15 (45.5)	18 (54.5)	1			
Co morbidity						
No	25 (50)	25 (50)	1			
Yes	13 (86.7)	2 (13.3)	1.73 (1.23- 2.44)	0.011	6.18 (4.40-8.70)	0.027
Presentation						
Early	3 (42.9)	4 (57.1)	1			0.540
Late	35 (60.3)	23 (39.7)	1.41 (0.58- 3.40)	0.437	1.75 (0.72-8.70)	0.540
Sex						
Female	6 (66.7)	3 (33.3)	1			
Male	32 (57.1)	24 (42.9)	0.86 (0.51- 1.43)	0.724	0.88 (0.52-1.47)	0.876
Smoking*						
No	20 (51.3)	19 (48.7)	1			
Yes	13 (65)	7 (35)	1.27 (0.81- 1.98)	0.409	1.13 (0.72-1.76)	0.807

Clinico-pathological pattern

There was a male predominance with 86.2% of the study participants being male (M:F 6.2:1). Age range was 16 to 80 years with a median of 35 years. Median duration of symptoms before surgery was 3 days (range 1-21days). Abdominal pain was reported by all patients. Classical history with initial epigastric and eventual generalized abdominal pain was reported by 35.4%.

Alcohol use was reported in 38.9% cases 33.9% reported smoking. NSAID use was elicited in 29.2%, 15.5% of whom were post-operative patients who had been operated for non-abdominal indications being managed by parenteral NSAIDs. 23.1% had other co morbidities: 44.6% had history of Dyspepsia/ PUD. The pre-operative diagnosis of either perforated gut or PUD perforation was missed in 7 patients mainly without radiography. Chest radiographs showed pneumoperitoneum in all cases where it was done.

Early post-operative complications

Mortality occurred in 18.5% and 58.5% had at least one post-operative complication. The commonest complication was pneumonia (23.1%). 83.3% of the deaths and 60.6% of those who developed complications were above 35 years. Age >35 (RR 5.16, CI (1.22- 21.12), p= 0.009) and presence of co-morbidity (RR 3.33 CI (1.26- 8.82), p= 0.024) were the major factors for mortality. The same factors: age > 35 (RR 1.58, CI (1.03- 2.44), p= 0.031) and comorbidity (RR 1.73, CI (1.23- 2.44), p= 0.011) predicted complications. These were still significant even after controlling for the other interactions and confounders. There was no difference noted in the treatment outcome between those who had history of dyspeptic symptoms and those who did not, Fisher's exact test: = 0.304; and in both the Smokers and Non Smokers (Fisher's exact test 0.279).

Discussion

The GDP disease pattern differs with different geographical locations. In Africa, patients commonly affected are those younger than 60 years. In this GDP study, the majority of the patients were below 40 years probably reflecting the young Ugandan population. This finding was closely similar to studies from Nigeria, Tanzania and Kenya[9,17,18] where mean ages were: 42.5, 32.4 and 35.4 years respectively. In contrast, a multicenter PULP study outside Africa[19] had mostly older patients with mean age of 60 years.

There was also a male predominance in this study (M: F = 6.2: 1). Most studies in Africa have showed a male preponderance and the highest was recorded by Nasio in Kenya where M: F sex ratio was 8.3: 1[17]. The male predominance may partially be explained by poor health seeking behavior of the African male compared to the female counterpart. However, a few studies have had female predominance[3].

Clinico-pathological pattern

The mean duration of symptoms was 4 days. Therefore, most patients had delayed/ late surgery. In Africa, late presentation (beyond 24hours) has been the norm. Afuwape[9] found that majority of the patients presented after 24 hours. Late presentation has been associated with poor outcomes[20]. Mulago, being a referral unit, late presentation may reflect delay in seeking health care, late detection and or late referral by the peripheral hospitals. However, late presentation in this study did not cater for institutional delays as some patients were not operated immediately.

Patients with previous history of dyspepsia or prior diagnosis of PUD in this study were 44.6% and majority had no such history. This finding is comparable to findings from previous work on the same topic[18] where 69% of the study population had no history of PUD. However, considering histology, 76.3% of the analyzed tissue had features of PUD probably reflecting the subclinical nature of PUD.

NSAID use in the current study was elicited in 29.2%. Alcohol use was noted in 35.4% of the study population and smoking was 30.7%. In his study, Chalya reported only 10.7% of prior NSAID use, and much higher rates of smoking and alcohol use (64.3% and 85.7% respectively). Thus, the NSAID use in the current study was relatively high. NSAIDs are popular because of their versatile effectiveness as analgesics, antipyretics, and as anti-inflammatory agents. The

pathogenesis of PUD caused by NSAIDs is mainly a consequence of systemic inhibition of GI mucosal cyclooxygenase (COX) activity. Even intravenous or intramuscular administration of NSAIDs can cause gastric or duodenal ulceration [21]. Findings of the current study may be suggestive of the tremendous contribution by NSAIDs in GDP causation. This hypothesis was supported by the three non GDP post-operative patients who developed GDP. Because these patients are not feeding and they have increased stress hormonal levels as part of metabolic response to surgery, NSAID use in these patients should be done with caution.

Peritonitis was clinically elicited in 93.9% of patients. These findings are in keeping with those from other studies[20]. Pneumo-peritonium by plain radiography was demonstrated in 84.6% of patients either by CXR or erect Abdominal X-ray (AXR). This was slightly better detection than in other studies where 65.8% had pneumo-peritonium[18]. In fact the remaining proportion of patients were those for whom either the investigative modality was not available or patient had a clear indication for surgery. Pneumo-peritonium is a good indicator of perforation anywhere along the bowel loop. It actually gives loss of hepatic dullness a sign that is rarely looked for (<5% in this study) probably due to generalized tenderness. USS picked free fluid within the peritoneal cavity in all the 55 patients in whom it was done. The diagnosis of either Gut perforation or PUD perforation was only missed in 10.7% cases. Thus, GDP should be ruled out in every patient with peritonitis. Plain radiographs are useful whenever available to confirm diagnosis and aid planning of surgery. They can also help exclude chest infections for proper planning of anesthesia.

There was predominance of gastric over duodenal perforations in the GDPS. The dominant site of perforation varies from one study to another. Similar to the GDPS, gastric perforations have dominated in Nigeria and Ghana[9,10]. In contrast, Duodenal outweighed gastric perforations in Kenya and Tanzania studies [17,18]. Ojuka, Ekwaro and Kakande[22] in Nsambya Hospital Uganda found a higher prevalence of duodenal than gastric perforations in patients with peritonitis. The reason for this inconsistence even in the same country is not clear. However, duodenal ulcers have been more associated with *H. pylori* than gastric ulcers and this may partially account for the low prevalence of *H. pylori* in the GDPS (7.9%). In contrast, other studies have found higher rates of *H. pylori* in GDP/PUD[2,23]. *H. pylori* prevalence in Uganda in non GDP patients was demonstrated to be high[24]. Oling et al[25] reported *H. pylori* prevalence of 36% in dyspeptic non-perforated patients referred for endoscopy, a prevalence far higher than what we found in the current study. However, *H. pylori* may not be a big contributor in perforations[26]. In a similar line, from their work, Zelickson et al[26] did not detect *H. pylori* in 60% of the patients. Mucosal erosion (where bacilli resides), prior antibiotic use, increased pH may all be contributory to this low prevalence.

A total of 58.5% patients had tissue available for histology and no tissue for the remaining patients due to technical issues in theatre. 15.8% of patients had intestinal metaplasia. This has rarely been reported in other studies. These patients probably contribute to that group of patients who require follow up with endoscopy and biopsy especially in resource limited settings. Malignancy was detected in 2.6% of patients. This was Squamous cell carcinoma (SCC) of the duodenum. Although rare, primary SCC has been reported in case series[27]. Adenocarcinoma is a more common entity. This malignancy was either primary or metastatic in the duodenum. These findings indicate the relevance of histology in both gastric and duodenal perforations.

Early post-operative complications

Mortality in the GDPS was 18.5% and other early post-operative complications occurred in 58.5%. This mortality was high compared to that (10.6%) generally observed in LMICs[6]. The highest mortality, (22.1%) was registered by Ohene et al[10]. The high complication rate was also within the range observed by other studies especially in Africa[9]. The PULP study[4], which

instituted a peri-operative care protocol in one group of patients, demonstrated that mortality could be reduced from 37% to 17% in the intervention group. Therefore, it is clear in all the studies that GDP is associated with high mortality and morbidity.

In the current study, age >35 and presence of co-morbidity were the major predictors of mortality and early post-operative complications (RR 5.16, CI 1.22- 21.12, p= 0.009) (Adjusted RR 3.33 CI 1.26- 8.82, p= 0.024) and (RR 1.58, CI 1.03- 2.44, p= 0.031) (Adjusted RR 1.73, CI 1.23- 2.44, p= 0.011) respectively. This was similar to previous research findings elsewhere[2]. These factors are non- modifiable, however, they can be used in both stratification of patients for intervention and prognostication of outcome. Effect of late presentation, that is, late surgery and other variables did not significantly affect outcome possibly due to small observations in one arm.

Limitations

There was non-uniformity of care to the patients as in pre-operative fluid resuscitation, anesthesia, technique of perforation repair and post-operative medications. These differences might have affected the results.

Recommendations

To address the high mortality, further studies into the factors for GDP and outcomes of its surgery are necessary with a peri-operative care protocol to standardize and unify the peri-operative care are required. A prognostic scoring system that has worked elsewhere may be used in stratification of patients[4, 28].

Conclusion

GDP remains a common surgical problem with high mortality and post-operative complications and strategies to reduce mortality are necessary.

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