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ORIGINAL ARTICLE

Predictor of mortality in children with typhoid intestinal perforation in a Tertiary Hospital in Nigeria

Abdulrasheed A. Nasir · Lukman O. Abdur-Rahman · James O. Adeniran

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Abstract
Purpose Typhoid intestinal perforation (TIP) exerts a great toll both on the patients and the surgeons in resource poor countries. Factors that predict mortality in patients with TIP remain controversial. The study aims to determine factors that predict mortality in a Nigerian tertiary facility and to offer strategies for improvement.
Materials and methods We conducted a retrospective analysis of data of 153 children who underwent surgery for TIP at a Tertiary Hospital in Nigeria over a period of 8 years (January 2002 to December 2009). Data collected included patient demographics, presentation, haemoglobin level (Hgb), presentation–operation interval, type of surgical procedure, nature of peritoneal collection, the number of perforations and duration of surgery. Postoperative complications, duration of hospital stay and outcome were also examined.
Results There were 99 (64.7%) boys and 54 (35.3%) girls aged 3–15 years, mean (SD) = 9.4 (±3.6) years. There were 105 single perforations and 46 multiple perforations (range 1–32). The surgical procedure was simple 2-layer closure in 128 (83.7%) and segmental resection in 9 (5.9%) children. The mortality was 16 (10.4%). The mean (SD) age of children who survived and those who died was 9.3 (±3.6) years and 10.1 (±4.0) years, respectively; $p = 0.446$, the mean duration of symptom in children who survived and those who died was 10.3 (±4.9) days and 12.3 (±5.6) days; $p = 0.164$, and the mean interval between presentation and operation in those who died and those who survived was 29.3 (±25) h and 28.4 (±13.4) h; $p = 0.896$. Temperature ≥ 38.5°C ($p = 0.040$), anastomotic leak ($p = 0.029$) and faecal fistula ($p = 0.000$) were significantly associated with mortality. Age <5 years ($p = 0.675$), male gender ($p = 0.845$), presentation-operation interval ≥24 h ($p = 0.940$), Hgb less than 8 g/dL ($p = 0.058$), faeculent peritoneal collection ($p = 0.757$), number of perforations ($p = 0.518$) and the surgical technique ($p = 0.375$) were not related to mortality. Logistic regression analysis showed that only postoperative faecal fistula ($p = 0.001$; OR = 13.7) independently predicted mortality.
Conclusion Development of postoperative fecal fistula significantly predicted mortality. Prioritizing the prevention of typhoid fever than its treatment and attention to surgical details may significantly reduce mortality of TIP in children in this setting.

Keywords Typhoid intestinal perforation · Mortality · Mortality predictor · Children · Prevention

A. A. Nasir (✉) · L. O. Abdur-Rahman · J. O. Adeniran
Department of Surgery, University of Ilorin Teaching Hospital, Ilorin, Nigeria
e-mail: draanasir@yahoo.com

Introduction

Typhoid intestinal perforation (TIP) remains the most serious complications of typhoid fever. It exerts a great toll both on patients and surgeons in resource poor countries, where most of the burden of the disease occur due to poor sanitary conditions [1]. Operative management clearly afforded a survival advantage in the care of patients with TIP [2]. Mortality rates in patients with perforation who undergo operative intervention have been reported as 4.5–75% [2–7]. The outcome of surgical management of patient with typhoid perforation is affected by multiple factors [7, 8]. To date, factors that accurately predict mortality in patients with TIP remain controversial. This

study aims to determine factors that predict mortality in Ilorin and to offer strategies for improvement.

Materials and methods

One hundred and seventy-eight children underwent surgery for TIP at University of Ilorin Teaching Hospital, Ilorin, from January 2002 to December 2009.

The diagnosis of typhoid intestinal perforation was based on clinical and intraoperative findings. All the patients who had TIP were treated as a surgical emergency. Preoperatively all the patients had prompt and adequate fluid-electrolyte and acid–base balancing and preoperative administration of broad spectrum antimicrobial agents (cefuroxime or ciprofloxacin and metronidazole), nasogastric tube decompression. Anemia was corrected with blood transfusion. Single perforations were trimmed and closed in two layers. Multiple perforations that were far apart were closed separately. The bowel was resected, if the perforations were close together. Perforations in the caecum or right side of colon were managed with right hemicolectomy. The peritoneum was generously lavaged with warm saline. The abdominal incision was closed with nylon (polyamide) No 1 suture and interrupted nylon 2–0 mattress suture applied to skin. Gentamicin was added for all patients postoperatively for 72 h. On the basis of clinical relevance and a review of the literature, the following potential risk factors were evaluated: age (<5 years), gender, presentation–operation interval, duration of symptoms, high fever (≥38.5°C), anemia (hemoglobin level <8 g/dl, preoperative hypokalemia, malnutrition, multiple perforation (≥2 perforation), type of surgical procedure, duration of surgery, burst abdomen, anastomotic leak, and fecal fistula. Data were adequate for retrospective analysis in 153 children.

Statistical analysis

Data were analyzed with SPSS 16.0. For univariate analyses, a Chi-squared or Fisher's exact test was used for categorical variables and a Student's t test for continuous variables. Multivariate analysis using logistic regression model was performed to determine predictors of mortality. Candidate variables with a p value less than 0.1 were entered for logistic regression analysis. The differences were taken as significant only if the p value is <0.05 and the odds ratio is >1.

Results

There were 99 (64.7%) boys and 54 (35.3%) girls aged 3–15 years, mean (SD) 9.4 (3.6) years and M:F was 2:1 (Table 1). The mortality was 16 (10.4%). The mean (SD) age of children who survived and those who died was 9.3 (3.6) days and 10.1 (4.0) days respectively, $p = 0.446$. The mean duration of symptoms in children who survived and those who died was10.3 (4.9) and 12.3 (5.6), $p = 0.164$.

One hundred and thirty-five patients presented within 2 weeks of onset of illness with a mortality of 8.9% (12 out of 135 patients), and 13 presented after 2 weeks with 7.7% mortality (1 out of 13 patients). This did not appear to significantly influence mortality ($p = 0.884$). Sixty-five patients presented with temperature ≥38.5°C with mortality of 15.4% and 78 presented with temperature less than 38.5°C with mortality of 5.1% ($p = 0.040$). Young age, sex, duration of symptoms prior to presentation, nutrition status, hypokalemia and degree of anemia were not significantly associated with mortality (Table 2).

Forty-eight percent of patients were operated within 24 h with a mortality of 10.1%, while 52% patients were operated after 24 h with a mortality rate of 10.5% ($p = 0.940$). The mean (SD) interval between presentation and operation in those who died and those who survived was 29.3 (25) h and 28.4 (13.4) h; $p = 0.896$.

The mortality in the 105 patients with single perforations was 9.5% and the mortality in the 46 patients with multiple perforations was 13%, $p = 0.518$. The surgical procedure was simple closure in 128 (84.8%) patients, segmental resection in 11 (7.3%), right hemicolectomy 10

Table 1 Characteristic of study population

Variable	Survivors	Non-survivors	p Value	95% CI
Age years (mean ± SD)	9.3 ± 3.6	10.1 ± 4.0	0.446	−31.6 to −13.98
Age group				
0–4	14	2	0.518	
5–9	72	6		
10–15	51	8		
Gender (M/F)	89/48	10/6	0.845	
Duration of symptoms in days (mean SD)	10.27 ± 4.9	12.31 ± 5.6	0.164	−4.9 to 0.84
Duration of surgery (mean ± SD)	92.2 ± 27.8	94.2 ± 18.6	0.813	−18.27 to 14.37

Table 2 Univariate analysis of clinical parameters in relation to mortality

Variables	Survivors	Non-survivors	*p* value
Age			
<5 years	14	2	0.675
≥5 years	123	14	
Temperature ≥ 38.5°C			
Yes	55	10	0.040
No	74	4	
Preoperative Hb < 8 g/dl			
Yes	29	7	0.058
No	102	9	
Preoperative hypokalaemia			
Yes	18	3	0.469
No	109	11	
Nutritional status			
Normal	88	7	0.099
Malnutrition	29	6	
Interval between presentation and operation			
<24 h	62	7	0.940
≥24 h	68	8	
Number of perforations			
Single	95	10	0.518
Multiple	40	6	
Type of surgery			
Simple closure	116	12	0.375
Wedge resection	2	0	
Segmental resection	9	2	
Right hemicolectomy	8	2	
Burst abdomen			
Yes	6	1	0.546
No	131	15	
Faecal fistula			
Yes	6	6	0.0001
No	130	10	
Anastomotic leak			
Yes	1	2	0.029
No	136	14	

(6.6%) and wedge resection in two (1.5%) children. The mortality rates for individual procedures were: right hemicolectomy 20%, segmental resection 18.2%, simple closure, 9.4% and wedge resection 0%, $p = 0.375$. Two (66.7%) out of three patients who had anastomotic leak died ($p = 0.029$) and 6 (50%) out of 12 patients with postoperative fecal fistula died ($p = 0.0001$).

Twenty (13%) patients were re-operated. Reoperation was done to repair various degree of wound disruption in 12, drainage of intra-abdominal abscess in 2, anastomotic leak in 3 (initial procedure was right hemicolectomy 1, simple closure 1 and segmental resection 1), fecal fistula in 2 (initial procedure was simple closure), and adhesiolysis for intestinal obstruction in 1 patient.

Table 3 Multivariate logistic regression analysis of factors that predict mortality

Variables	OR	95% CI	*p* value
Malnutrition	0.697	0.109, 4.48	0.703
Anaemia	0.591	0.127, 2.757	0.503
Temperature ≥ 38.0°C	2.491	0.515, 12.061	0.257
Anastomotic leak	2.722	0.103, 72.194	0.549
Faecal fistula	35.724	4.681, 272.625	0.001

OR odd ratio, *CI* confidence interval

Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 3.3$, d.f. = 5, $p = 0.65$

Logistic regression analysis showed that postoperative faecal fistula [$p = 0.001$; OR = 35.72, 95% confidence interval (4.681–272.625)] was the only independent risk factor predicting the mortality (Table 3). The mean duration of hospital stay for survivors was 21 days with a range of 8–67 days.

Discussion

The overall mortality of 10.4% in this study is comparable to previously published studies. Adeniran et al. [4] from the same center reported a mortality of 7.3%, Saxe [2] 16%, Beniwa [9] 10.5% and Edino [7] 15.5%. This report shows a significantly lower mortality rate compared to 39% reported by Ameh [5] in Zaria, 22.8% by Uba [10] in Jos and 75% by Osifo [6] in Benin, Nigeria. Lower mortality rate of 4.5–4.8% was reported in series from Turkey [3, 11]. This was probably as a result of improved socioeconomic infrastructures in that part of the developed world. In a report of 42 patients by Onen et al. [11] from Turkey, only two patients died of overwhelming sepsis. Parenteral nutrition was available for 22 patients, none of them died. Mortality was significantly associated with temperature ≥ 38.5°C, anastomotic leak and faecal fistula. These factors are either a reflection of degree of septicemia or lead to worsen septicemia. High temperature usually signifies overwhelming septicemia that can lead to sepsis syndrome, multiple organ dysfunction and death. Our findings are similar to a previous report that found significant association between high temperature and mortality in patients with intra-abdominal sepsis [12]. Development of faecal fistula is usually due to leak of repair, reperforation or perforation from another ulcer. All the fecal fistulae in this series were due to leak of repair. This usually has a significant impact on mortality [8, 9]. Fistulation may further contaminate the peritoneal cavity and jeopardized the clinical state of patient who is recovering from initial septicemia. Faecal fistula was the only factor that

accurately predicts mortality ($p = 0.001$, OR = 35.724) in this study. This has replicated previous clinical evidence in published case series [8, 9, 13]. The faecal fistula rate of 12 (7.8%) in this study is favorably comparable with 7.8% reported by Kamacharya [14], 7.6% by Edino [7] and 6.3% by Usang et al. [15]. The primary goal of surgery is the elimination of peritoneal soilage and endotoxemia. Our approaches to the management of patients with postoperative fecal fistula was copious saline lavage and fashion an ileostomy all aimed at halting the peritoneum contamination. Patient with low output fistula and no distal obstruction may do well with nonoperative management with oral or intravenous hyperalimentation. Anastomotic leak is one of the significant complications of surgery for typhoid perforation. Two (67%) of 3 patients who developed anastomotic leak in this study died. All the patients with anastomotic leak were re-operated and had ileostomy constructed to halt contamination. Death resulted from overwhelming sepsis, from peritoneal soilage and abdominal sepsis. Anastomotic leak and fecal fistula may lead to intra-abdominal sepsis which has been reported to be associated with microvascular dysfunction, as well as the impairment of cellular metabolism resulting in organ failure and subsequent death [16]. It is therefore pertinent that this sequence is aborted early by attention to the treatment of septic focus.

Multiple perforations have been reported to be associated with severe peritoneal contamination and high morbidity and mortality [7–9, 17, 18]. Multiple perforations is not significantly associated with mortality in this study. Six (13%) of 46 patients with multiple perforation compare with 10 (9.5%) of 105 patient with single perforation died in this case series with no significant statistical difference. This is consistent with the clinical evidence in published case series [11, 19]. We have also reported our previous experience in the management of patient with multiple perforations (8–32 perforations) with good outcome [20, 21]. Although, the reason for the high number of perforations in the children is not known, aggressive resuscitation and attention to surgical detail would result in better outcome irrespective of number of perforations.

Surgical intervention in patients with typhoid intestinal perforation offers the best chance of survival [2, 11]. The optimal surgical procedure has been a matter of dispute. Randomised controlled trial comparing different surgical procedures are, however, scanty. Ameh et al. [22] in a retrospective review of 64 patients compared simple closure, wedge excision and resection, and anastomosis. He concluded that segmental resection and anastomosis offer the best option for patients with TIP. Shah [23] also supported this view. However, our experience in this study has shown that the type of operation performed is unrelated to mortality. This is consistent with other published case series [2, 7, 8]. The choice of the procedure undertaken to deal with the perforation should be individualized, dictated by the number of perforations and the state of the adjacent bowel. Excision of perforated edge and simple closure suffices in most instances and it is the quickest procedure, gives good results and is cost effective. Intestinal resection with anastomosis is, however, indicated in multiple perforations, gangrenous bowel or severely diseased terminal ileum, but extensive procedures under prolonged anesthesia should not be done to avoid fatal outcome [2, 7]. Ileostomy appears to be an effective procedure, particularly in patients with severe abdominal contamination and postoperative fecal fistula. The effect of age on mortality in TIP remains speculative. The mortality in TIP in children less than 5 years is reported to be high [18, 24, 25]. This view has not been supported by our findings in that age less than 5 years is not significantly associated with increased mortality. Two (12.5%) of 16 under 5 children died while 14 (10.2%) of older children died. Six of our patients were 3 years old, only one died. This report is similar to the other reports [7, 9, 12, 19] that show that young age did not appear to influence mortality. These reported differences may be due to different case-mix and differing co-existing pathologies in the study population. In this study, as in others [2, 3] the mortality was unrelated to the sex, preoperative hypokalemia, duration of perforation, preoperative Hb < 8 g/dl and timing of surgical intervention (p value > 0.05).

Compromised nutritional status has been postulated to possibly play a role in the poor prognosis of the patient with typhoid ileal perforation [10], but this theory has not been proven [17]. The nutrition status was not different between the dead patients and the survivor in our study. TIP is endemic in developing countries where socioeconomic infrastructure is lacking and there is always a background malnutrition. The malnutrition is, however, worsened by Zenkar's hyaline muscle degeneration and proteolytic effects of the septicemia which is common in most TIP patients. This should not however lead to underestimation of the role of parenteral nutrition in the treatment of TIP as this has been shown to improve the outcome [11].

This study was limited by all the deficits of a retrospective review. There remain many unanswered questions in the appropriate surgical management and factors that predict mortality of typhoid intestinal perforated. A multicenter-based randomize controlled study would be necessary.

Conclusion

TIP still remains a significant cause of mortality in developing countries irrespective of the number of perforations

and type of operative procedure performed. Mortality is significantly affected by the development of postoperative fecal fistula. Debridement and simple repair of perforation in two layers was the choice of treatment for TIP. Segmental resection and primary anastomosis should be considered selectively in patients with multiple perforations and an unhealthy gut. Ileostomy as a secondary procedure should be considered once fecal fistula develops, in order to avoid peritoneal contamination. Prioritizing the prevention of typhoid fever than its treatment and attention to surgical details may significantly reduce mortality following TIP.

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