Queensland University of Technology
Brisbane Australia

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INTRODUCTION

Diarrhoea in enterally tube fed (ETF) critically ill patients is a frequently experienced and multi factorial problem (Thorson et al, 2008). Although rarely associated with mortality, diarrhoea is distressing to patients, visitors and staff (Martin, 2007).

Enteral tube feeding is often debated as a main cause of diarrhoea (Lee and Auyeung, 2003; Ukleja, 2010). Approximately 46% to 77% of all critically ill patients will receive enteral nutrition (EN) during their intensive care unit (ICU) admission (McKenna et al, 2001; Lee and Auyeung, 2003; Gramlich et al, 2004; Whelan, et al., 2006; Whelan et al, 2007). The early commencement of EN is suggested to preserve the gut's immunological barrier, reduce bacterial translocation, reduce sepsis and multi organ failure and improve wound healing (Davies and Bellomo, 2004; Marshall and West, 2004; Artinian et al, 2006; Nguyen, et al., 2007; Lopez-Herce, et al., 2008; Lopez-Herce, 2009; McClave and Heyland, 2009; Ukleja, 2010).

Incidence of diarrhoea

The reported incidence of ETF diarrhoea is suggested to vary between 2% to 68% (Bengmark, 2002; McNaught, et al., 2005; Weisen, et al., 2006; Luft et al, 2008; Whelan et al, 2009). However, diarrhoea in ETF critically ill patients is more diverse with the reported incidence varying between 2% to 95% of all patients (Whelan et al, 2009). The variability of diarrhoea incidence depends on the diagnostic criteria and definitions used to identify and quantify diarrhoea (Lopez-Herce, 2009).

Causes of diarrhoea in the ETF patient

The causes of ETF related diarrhoea include physiological responses to critical illness, altered colonic responses to intragastric feeding, microbial contamination of the ETF formulae, sterile ETF formulae, constant flow administration of ETF formulas, low fibre ETF formulas, hypoalbuminaemia, disturbances to intestinal flora, increased exposure to antibiotics, and concurrent pharmacotherapy such as aperients, prokinetics and histamine-2 medications (Weisen et al, 2006; Ferrier and East, 2007; Sabol and Carlson, 2007; Whelan et al, 2007; Lopez-Herce, 2009; Btaiche et al, 2010). In addition, the diagnosis, severity of illness and co morbidities of patients can contribute to diarrhoea in critically ill patients (Thorson et al, 2008).

Diarrhoea management strategies

Inconsistent diarrhoea management practices are evident between different ICU's (Dorman et al, 2004; Ferrie and East, 2007). Strategies to manage ETF related diarrhoea include diarrhoea management algorithms, anti-diarrhoeal medications, electrolyte and fluid replacement, continuation of ETF, administering probiotics, prebiotics and synbiotics, and the administration of glycopeptides and metronidazole for infectious diarrhoea (Whelan et al, 2006; Lopez-Herce, 2009). It could be argued that the variations in bowel care management strategies in ICU lead to diarrhoea in critically ill patients.

It was noted that the reported incidence of ETF related diarrhoea in critically ill patients is well established in regards to interventional research such as administration of fibre containing ETF formulas and probiotics (Bleichner, et al, 1997; DeMao, et al.,

1998; Lee and Auyeung, 2003; Whelan, et al., 2006; Lopez-Herce, 2009). However, there remains a paucity of literature addressing the incidence and frequency of diarrhoea in ETF critically ill patients in relation to ETF formulae, diarrhoea incidence and duration, hypoalbuminaemia, infection, antibiotic therapy and concomitant pharmacotherapy within in a single centre tertiary referral ICU.

METHODS

A five month, retrospective, repeated measures cohort study was undertaken.

Study Aims and Research Questions

The aim of this study was to examine the causes of ETF diarrhoea in a single centre ICU. The research questions that guided this study include:

1. What is the incidence of ETF diarrhoea in the ICU?
2. Is the duration and incidence of diarrhoea related to the type of ETF administered?
3. Is the duration and incidence of diarrhoea related to the duration of ETF?
4. Do patients develop diarrhoea when the commencement of ETF is delayed?
5. Is diarrhoea incidence and duration influenced by age, gender and Acute Physiology and Chronic Health Evaluation (APACHE II) scores?
6. Does the duration of antibiotic therapy, aperients/prokinetic/sedation/paralysis administration affect the incidence and duration of diarrhoea?
7. Is diarrhoea related to hypoxia, hypoalbuminaemia, hypoglycaemia and elevated white blood cell counts?

Setting

The research setting was a twenty-two bed, single site, Level III ICU of a major teaching and tertiary referral, metropolitan hospital in Brisbane, Australia. A Level III Australian ICU is a tertiary referral unit that provides comprehensive critical care services for critically ill patients who require multi-system life support for indefinite periods of time. These ICUs also demonstrate a commitment to academic education and research (Joint Faculty of Intensive Care Medicine (JFICM), 2003).

Ethical Approval

Ethical approval was obtained from the local hospital and university human research ethics committees.

Participants

Participants were recruited using non-probability, retrospective sequential sampling of all emergency admission ICU patients who met the inclusion/exclusion criteria. Patients were eligible for inclusion if they: 1) were enterally tube fed via continuous infusion; 2) ≥18 years of age; and 3) were expected to have an ICU length of stay (LOS) >5 days. Participants were excluded from the study if they were: 1) immunocompromised; 2) suffered burns/hepatic failure; and 3) elective post operative patients. Consent was not obtained from participants as this study fulfilled the criteria of a quality assurance activity. Study participants were de-identified to a study number. A password protected enrolment log was maintained of study participants.

Data Collection

Data were collected retrospectively by review of medical records. A data collection tool was developed for this study (see Table 1). Data were collected to a maximum of fourteen days into the patients ICU admission or until the patient's discharge from ICU, whichever occurred first. It was deemed necessary to collect data for this length of time as diarrhoea is often not observed in the initial five to seven days of a patient's ICU admission. For this study, diarrhoea was defined as the 'abnormal passage of loose or liquid stools more than three times daily and/or a volume of stool greater than 200g/day during the patient's ICU admission' (Thomas et al, 2003).

No validated diarrhoea measurement tool was used in the ICU at the time of this study. Faecal output was recorded subjectively by nursing staff using the CareVue computer information management system. Faecal volume was recorded by nurses as small (<100ml), medium (100-200ml) and large (<200ml). Stool consistency was recorded as formed, semi-formed, loose, or watery. Data for this study was collected retrospectively at one point in time; therefore, education of nurses regarding the use of a faecal output measurement tool was not appropriate. The consistency of nursing documentation was unable to be checked due to the retrospective methodological design of this study. Faecal volume and consistency were then cross referenced by the researcher using the Bristol Stool Chart, which is a validated diarrhoea identification tool (Dorman et al, 2004).

Operational definitions used to guide this research include:

1. Diarrhoea: diarrhoea was either experience of not experience by the patient;
2. Diarrhoea episode: one event of diarrhoea experienced by a patient;

3. Diarrhoea duration: the number of days a patient experienced diarrhoea during their ICU admission;
4. Diarrhoea frequency: the total diarrhoea episodes experienced by a patient during their ICU admission;
5. Total diarrhoea days: the total number of days a patient experienced diarrhoea during their ICU admission.

Data Analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16. Descriptive statistics of patient demographics were performed using means and standard deviations (SD). Normality was assessed using Kolmogorov-Smirnov test. Univariate and bivariate correlations were assessed using the Pearson or Spearman Rho coefficient. Univariate associations were analysed using Chi square statistical test. A general linear model was used to explore univariate relationships. The Kruskal-Wallis test was performed to explore the variance between skewed continuous variables across groups. The Mann-Whitney U Test was used to explore non-parametric means. Generalised estimated equations (GEE) modelling was used to analyse the within subject variation across the repeated measures analysis. For all analyses, a $p < 0.05$ was considered statistically significant.

RESULTS

Fifty patients were retrospectively audited over five months (January to May 2007). Patient demographic data are outlined in Table 2. The majority of patients (n = 39; 78%) developed diarrhoea. Diarrhoea was observed on 121 days (19%) of the 644

patient admission days. Single episodes of diarrhoea were observed 326 times (SD 7.3) over 449 ETF days (SD 3.3). Patients experienced 0 to 8 episodes of diarrhoea daily. However, the total single episodes of diarrhoea per patient admission varied between 0 to 29 episodes. Antibiotics, aperients, prokinetics and sedation were administered to most patients (Figure 1). Individual intestinal pro-motility and sedation medications administered to patients in this study are outlined in Figures 2 and 3.

No statistically significant difference between the patients' age and diarrhoea frequency (r = 0.003; p = 0.982) and diarrhoea duration (r = 0.122; p = 0.397) was observed. Gender did not influence diarrhoea (χ^2 = -0.188; p = 0.191), diarrhoea frequency (r = -0.207; p = 0.149) or diarrhoea duration (r = -0.183; p = 0.204) (Table 3). Higher APACHE II scores were associated with a higher frequency of diarrhoea (r = 0.334; p = 0.018) and a longer duration of diarrhoea (r = 0.372; p = 0.008). Patients who had a longer ICU LOS were more likely to develop diarrhoea (χ^2 = 0.535; p <0.01) and experience a longer duration of diarrhoea (χ^2 = 0.915; p < 0.001); however, statistical significance was not found between the ICU LOS and diarrhoea frequency (Table 3).

Enteral Nutrition and incidence of diarrhoea

All patients received ETF at some point during their ICU admission. Enteral tube feeding formulas consisted of Jevity Plus (n = 37; 74%), Jevity (n = 6; 12%), Nepro (n = 7; 14%) or another formulae (n = 0) at the start of ETF. Nine patients (18%) had their ETF formula changed (Jevity Plus n = 1; Jevity n = 1; Nepro n = 5; Other n = 1) during their ICU admission. The ETF formula was not associated with the development of diarrhoea (χ^2 = 2.540; p = 0.281). Additionally, no relationship was

observed between diarrhoea and the changing of the ETF formula (χ^2 = 3.096; p = 0.542). The duration (χ^2 = 3.469; p = 0.177) and frequency (χ^2 = 3.633; p = 0.163) of diarrhoea was not associated with the EFT formulae.

Total diarrhoea days (r = 0.422; p = 0.02) and diarrhoea frequency (r = 0.313; p = 0.027) increased when the patient was ETF for longer periods of time. Significant relationships were not found between diarrhoea (r = -0.152; p = 0.291), total diarrhoea days (r = 0.032; p = 0.825), diarrhoea frequency (r = -0.067; p = 0.646) and time delay from ICU admission to the commencement of ETF. Controlling for total ETF days did not demonstrate a relationship between the development of diarrhoea (r = -0.036; p = 0.806), total diarrhoea days (r = 0.240; p = 0.096) or diarrhoea frequency (r = 0.191; p = 0.189) with respect to the time delay from ICU admission to the start of ETF. Of particular interest though was that the duration of diarrhoea was linearly associated with the frequency of diarrhoea (χ^2 = 0.915; $p < 0.001$).

Medications administered

An increased duration of diarrhoea was associated with total antibiotic days (r = 0.300; p = 0.034) and sedation days (r = 0.363; p = 0.010). Patients who developed an infection (Md = 3; n = 33) compared to those patients who did not develop an infection (Md = 2; n = 17) were more likely to experience an increased duration of diarrhoea (U = 175; z = -2.200; p = 0.028; r = 0.31). The duration of diarrhoea was not associated with the duration of aperients (r = -0.033; p = 0.818), prokinetics (r = 0.135; p = 0.349) and neuromuscular blockade medications (r = 0.158; p = 0.274) days.

Similarly, an increase in diarrhoea frequency was associated with total antibiotic days (r = 0.320; p = 0.023) and total sedation (r = 0.362; p = 0.010) days. Patients who developed an infection (Md = 7; n = 33) experienced an increased frequency of diarrhoea compared to those patients who did not experience an infection (Md = 1; n = 17) (U = 162; z = -2.444; p = 0.015; r = 0.35). The frequency of diarrhoea demonstrated no relationship with the duration of aperients (r = -0.099; p = 0.493), prokinetics (r = 0.101; p = 0.486), and neuromuscular blockade medications (r = 0.203; p = 0.157) days.

Physiological variables

This study applied GEE modelling for repeated measures of physiological data to describe the within subject variability that could not be explained using a repeated measures ANOVA test. Table 4 demonstrates that all binary and covariate physiological variables used in this study are significant. Positive associations were found between the dependent variable of diarrhoea and all explanatory variables of total ETF days, glucose, albumin, white cell counts.

Infectious diarrhoea (*Aeromonas hydrophilia* spp) was observed in the first of two stool cultures in one patient. The stool cultures were collected on days four and seven of the patient's ICU admission. *Aeromonas* spp infections have previously been associated with gastroenteritis in children; however, the role of this bacteria in relation to infection remains unclear and caution related to the cause of diarrhoea in this patient was applied (Forbes, Sahm & Weissfeld; 2007). No other infectious causes of diarrhoea such as *Clostridium difficile*, *Salmonella* or *Shigella* were cultured.

DISCUSSION

The key result of this retrospective clinical chart audit is that the high frequency of diarrhoea in ETF critically ill patients (n=39; 78%) is not attributed to one causal factor. Rather, many factors influence the frequency and duration of diarrhoea in critically ill patients. This high frequency of diarrhoea supports the findings of similar studies and suggests that diarrhoea is common in the ICU environment (Bengmark, 2002; Lebak, 2003; Ferrie and East 2007).

No general consensus of diarrhoea definition is used in the clinical setting (Lebak et al, 2003; Whelan et al, 2003; Martin, 2007; Sabol and Carlson, 2007). Although a stringent definition of diarrhoea was used by this study, a similar definition was not used by clinicians in the ICU where the study was undertaken. Diarrhoea definitions that rely on clinical judgement in the absence of standardised criteria are fraught with complications (Lebak et al, 2003) and should be avoided. In the absence of a standardised diarrhoea definition, a taxonomy of definitions embracing stool frequency, consistency, duration and weight is suggested (Lebak et al, 2003). Diarrhoea prevalence is lower when stringent, measurable diarrhoea definitions are used (Lee and Auyeung, 2003; Whelan et al, 2003; Whelan et al, 2008). The higher prevalence of diarrhoea may have been influenced by the definition and diagnostic qualities of diarrhoea used in this study.

Enteral nutrition has been previously associated as a risk factor for diarrhoea (Thorson et al, 2008; Whelan et al, 2009). Some risk factors related to enteral nutrition were controlled for in this study. The ETF formula was delivered via a closed sterile

system. The ETF formula and administration flow sets were changed every 24 hours. All patients were fed via continuous infusion. Diarrhoea related to bolus feeding was therefore minimised. There was no report of infectious diarrhoea in this study.

In this study, the type or osmolality of the ETF formula was not found to affect the frequency or duration of diarrhoea. These findings are supported by seminal research conducted by Pesola et al (1990) who demonstrated that the osmolality of ETF formulas did not increase in the incidence of diarrhoea is healthy volunteers (n = 5) and ward (n = 10) and ICU patients (n = 24). Diarrhoea developed in only three ICU patients in Pesola's study (1990); however, these patients had an average albumin level of 2.8 g/dl. This diarrhoea finding was not statistically significant (Pesola et al, 1990). Similar to Pesola's study (1990), an average hypoalbuminaemia of <30g/L was reported in 34% (n=17) of patients in the clinical chart audit undertaken for this study. Statistical significance was also not observed in the clinical chart audit.

Several other diarrhoea risk factors have been identified in other studies and include APACHE II scores, longer ICU LOS, infection, bolus ETF, previous total parenteral nutrition (TPN), hypoalbuminaemia, fever or hypothermia (Heyland, 2000; Barbut and Meynard, 2002; Marshall and West, 2004; Thorson et al, 2008; Lopez-Herce, 2009). In this study, the presence of numerous risk factors including time delay to initial bowel activity, total ETF days, total antibiotic days, total prokinetic days, and ICU LOS influenced the frequency and duration of diarrhoea in critically ill patients.

Infection has been previously identified as a risk factor for diarrhoea in ETF critically ill patients. This study re-affirmed the significant relationships between infection and diarrhoea incidence and duration. However, caution must be exercised in regards to these relationships as the presence of infection in critical illness may also be influenced by higher severity of illness scores, antibiotic use and increased ICU LOS.

High severity of illness scores including APACHE II scores was associated with an increased frequency and duration of diarrhoea. Critically ill patients who are more acutely ill may experience a hyper metabolic stress response, altered gut pathophysiology such as increased intestinal lumen permeability, electrolyte imbalances, and altered immune responses (Ferrie and East, 2007; Thorson et al, 2008).

The significant relationships found between diarrhoea, duration of ETF, glucose control, albumin and white cell counts have been inconsistently reported elsewhere. These findings require further examination in studies with larger sample sizes.

STRENGTHS AND LIMITATIONS

This study was a retrospective, single centre cohort clinical chart audit and as such the findings may not be generalisable. However, the longitudinal approach adopted and the extent of data collected and analysed has not been embraced in previous studies reviewed. A major strength of this study was that only emergency admission critically ill patients who were ETF were included and elective surgical patients or patients transferred to the ICU from a ward or another hospital were excluded. These criteria enabled clear identification of diarrhoea relationships in critically ill patients.

The single centre setting may be seen as both a strength and weakness. The limitation of the single centre is that study findings may not be generalised to the wider ICU community. Conversely, the strength of this approach is that bias between patient characteristics and local unit clinical protocols has not influenced the study findings. A notable limitation of this study was 1) no diarrhoea measurement tool was used by the ICU; therefore, clinicians based their subjective assessment of faecal stool output on professional opinion; and 2) the researcher retrospectively applied a faecal stool output measurement tool to the patient's faecal output which was recorded in the patient's medical record. Subjective assessment of faecal stool output has been associated with inaccurate stool quantification. The higher incidence of diarrhoea observed in this study may be in part, related to the subjective nature of stool assessment. The final limitation of this study is the study's oversight to examine the relationships between aerobic intestinal microflora, enteral nutrition and diarrhoea in critically ill patients.

RECOMMENDATIONS

The results of this study reinforce that diarrhoea in ETF critically ill patients is caused by many factors. Recommendations for clinical practice and future research arising from this study include 1) re-examine ETF related diarrhoea risk factors in all subsets of critically ill patients; 2) develop and validate a faecal output measurement tool that is appropriate for use in critically ill patients; 3) implement a diarrhoea measurement tool to quantify faecal output; and 4) conduct prospective exploratory research that examines the relationships between aerobic intestinal microflora, enteral nutrition and diarrhoea in critically ill patients.

CONCLUSION

This paper has presented findings related to diarrhoea risk factors and the prevalence of diarrhoea in a single centre ICU. The findings suggest that diarrhoea in ETF critically ill patients has many causes; however, the degree of involvement of these diarrhoea risk factors varies between critically ill patients. The differences in diarrhoea risk factors may in part be related to the inconsistent approaches to defining diarrhoea. Few studies have examined aerobic bacteria, enteral nutrition and diarrhoea relationships in critically ill patients. This paucity of knowledge requires future research.

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