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Does Glutamine Supplementation Contribute to the Incidence of Diarrhea in Ventaltor Dependent Patients?

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DOES GLUTAMINE SUPPLEMENTATION CONTRIBUTE TO THE INCIDENCE OF DIARRHEA IN VENTALTOR DEPENDENT PATIENTS?

by

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ABSTRACT

Does glutamine supplementation contribute to the incidence of diarrhea in ventilator dependent patients?

by

Justin Johnson

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In this project we investigated the incidence of diarrhea and its possible causes in ventilator dependent patients in the intensive care unit (ICU) at McKay-Dee Hospital. Chronic diarrhea has been a long time problem in the ICU, but the etiology has never been fully explored. High dose antibiotic therapy has been thought to be a potential risk factor. Another proposed risk has been the use of glutamine, a conditionally essential amino acid contained in some enteral products. Glutamine is commonly used in feeding critically ill patients because of its immune enhancing properties.

Currently, we have not established a correlation between the use of glutamine and the incidence of diarrhea. Data obtained in this study, however, suggests that a correlation exists with high-dose antibiotic therapy.

Future application of this research could lead to standard protocols in treatment of diarrhea in the ICU. Such protocols might include all patients administered high dose antibiotic therapy be given a probiotic supplement to prevent diarrhea. Also, if further

evidence is found between glutamine supplementation and increased risk of diarrhea, discontinuing or reducing supplementation could be considered an alternative measure.

(22 pages)

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INTRODUCTION

This was a retrospective chart review conducted at McKay-Dee Hospital in Ogden, Utah during the period of January 2006 to December 2006 to determine risk factors for diarrhea. The intent of this study was to verify if glutamine supplementation is associated with diarrhea in ventilator dependent patients in the intensive care unit.

REVIEW OF LITERATURE

Diarrhea in the Intensive Care Unit

It has been estimated that about one-third of patients admitted to the intensive care unit (ICU) develop diarrhea during their hospitalization. The most common factors that have been attributed to diarrhea include the use of antibiotic therapy, enteral feedings, and *clostridium difficile* infection (1). Smith et al. (2) found that 63% of critically ill adult patients who required mechanical ventilation experienced diarrhea associated with enteral nutrition (2). It was concluded this was from improper administration of enteral products. Higher osmolarity and infusion rates of enteral products contributed to an increased incidence and longer duration of diarrhea (2). It has been estimated that 5% of reported diarrhea in ICU patients is attributed to mechanical ventilation (3).

Diarrhea can lead to further complications such as volume depletion and wound infection, which can considerably increase medical cost. Wu et al. (3) demonstrated that the average length of stay in the ICU with complications of diarrhea was 8 days (3). The estimated average cost per day of ICU care for the hospital is 6,000-7,000 dollars. In comparison, the length of stay was only 4 days for those without complications of diarrhea (3). This supports the rational that preventing diarrhea will decrease medical costs and ultimately provide optimal health care for the patient.

Antibiotic Associated Diarrhea

Antibiotic associated diarrhea occurs in up to 25% of patients receiving antibiotics. Diarrhea related to antibiotic use can occur after a single dose or may persist as long as 6 weeks after discontinuing antibiotic therapy. The most commonly diagnosed and potentially severe form of

antibiotic associated diarrhea is caused by *Clostridium difficile*, accounting for 15% to 25% of antibiotic associated diarrhea. The human digestive tract is host to a vast of microbes and harbors more than 500 identified species. Some of these bacteria are essential for health. To prevent bacterial invasion, the mucosa of the gastrointestinal tract functions as a barrier to numerous pathogens (4). Antibiotics alter the normal fecal flora, which predisposes the gut to colonization by potentially pathogenic microbes, such as *Clostridium difficile* (5).

One method to treat antibiotic associated diarrhea and *Clostridium difficile* infection is use of probiotics. Probiotics are live microbial food supplements or components of bacteria that affect the host by improving microbial balance, and have been used as a way of restoring beneficial intestinal microbes. The possible advantages of probiotics as therapeutic agents are that they can lower the dependence on antibiotic use, decrease antibiotic associated diarrhea, are relatively inexpensive, and are generally considered safe and well tolerated (5).

Currently, there are numerous forms of probiotics used in diarrhea prevention. One particular probiotic that has been researched extensively is *Saccharomyces boulardii.* There is evidence to support the use of *Saccharomyces boulardii* in the prevention of antibiotic associated diarrhea at a dose of 1 gram daily in hospitalized adults. Surawicz et al. (6) treated 180 hospitalized patients, who were administered antibiotics, with 1 gram of *Saccharomyces boulardii* daily or were administered a placebo (6). The patients continued treatment for 2 weeks after the last antibiotic dose was given. Of the 180 patients, 21.8% of placebo treated patients developed diarrhea, compared with 9.5% of patients treated with *Saccharomyces boulardii* (6).

There is no support for prophylactic probiotic treatment to prevent an initial infection of *Clostridium difficile*, but *Saccharomyces boulardii* can be used to decrease its recurrences (4). Future application of this research could lead to standard protocols in treatment of diarrhea in the

ICU. Such protocols might include all patients administered high dose antibiotic therapy be given a probiotic supplement to prevent antibiotic-associated diarrhea.

Glutamine

Infection often occurs among critically ill patients. Infection contributes to increased morbidity, mortality, and healthcare costs. Several therapies that may reverse immunosuppression have been identified. One such therapy is glutamine supplementation and is often added to enteral and parenteral products (7).

Over the past 20 years, glutamine has been reported to help maintain acid-base balance, act as a primary fuel source for rapidly dividing cells, preserve integrity of gastrointestinal mucosa, act as a substrate for purines and pyrimidines bases, synthesize glutathione and arginine, and function as a key substrate for gluconeogensis (8).

Human studies have shown that glutamine supplementation can help decrease infection, gram-negative bacteremia, nitrogen losses, and ventilator days, resulting in a decrease in hospital length of stay and total healthcare cost (9). In a randomized, controlled clinical trial in ICU patients, of which 71% were septic, glutamine supplementation resulted in a 24% decrease in mortality (10). The positive effect of glutamine on morbidity related to infection was also validated by a meta-analysis comparing the use of glutamine supplementation in surgical and critically ill patients. There were 14 randomized trails included in this study that evaluated the effect of glutamine versus standard care on clinical outcomes (11). The results showed a reduced length of hospital days (on average a decrease of 2.6 days). In surgical patients glutamine supplementation was associated with few infectious complications but no effect on mortality was found. In critically ill patients glutamine supplementation was associated with a reduction in infectious complications and improved morality rate (11).

Glutamine is the most abundant amino acid in the body. It comprises 60% of the total free amino acid pool. Much of the nitrogen transport from the skeletal to the visceral tissues is via glutamine (8). Under normal physiologic conditions, glutamine is synthesized from glutamate and glutamic acid by glutamate-ammonia ligase and is therefore considered nonessential. However, it has been suggested that glutamine may become a conditionally essential amino acid for patients in a catabolic state (11).

During periods of increased metabolic stress, glutamine is released freely from skeletal muscle and intracellular glutamine concentrations fall by more than 50% (11). As a result, during periods of catabolism glutamine synthesis cannot meet physiologic needs. Dietary protein via oral or enteral routes provides only maintenance levels of glutamine. Furst et al. (12) stated that during periods of stress, 15 to 35 grams of supplemented glutamine may be needed to preserve muscle glutamine stores, maintain gut integrity, provide fuel for cells with rapid turnover, and improve overall nitrogen balance (12).

The mechanism that explains the role of glutamines benefit during critical illness is related to its interaction with arginine. One theory suggests that glutamine increases arginine synthesis in the kidneys. Arginine aids in wound healing and is the precursor to nitric oxide. Nitric oxide regulates blood flow through vital organs and is particularly critical during stress. Thus, glutamine may be important in regulating blood flow by serving as a precursor to arginine (13).

Recent evidence suggests that glutamine can induce heat shock proteins. Heat shock proteins are a class of cellular chaperone proteins that support appropriate protein folding during ribosomal translation. These proteins prevent poorly folded intracellular proteins. Supplementation with glutamine increases production of heat shock proteins, enhancing cellular

ability to protect against stress (8, 9). It has been found that individuals deficient in glutamine manifest changes in gut morphology including increased membrane permeability resulting in bacterial translocation, malabsorption, and diarrhea.

Dosing parameters for oral and enteral glutamine have varied widely over the years. Current research has generally used 0.5 grams of glutamine per kilogram of actual body weight. This level is thought to be sufficient to provide for the increase in glutamine required during metabolic stress. Doses lower than 0.285 grams per kilogram of actual body weight has been found to convey no benefit over standard feedings. It is also recommended that glutamine dosing should be divided throughout the day to increase contact with enterocytes (8).

Glutamine Supplementation and Diarrhea

Recently, glutamine supplementation has been investigated to determine its relationship to the incidence of diarrhea in the ICU. However, prior studies have not established a consistent association between incidence of diarrhea and glutamine supplementation. One reason for this is the very limited amount of research conducted in this area. In fact, there is no research published to date that specifically has focused on this relationship. Until more research is gathered, debate will continue on the association between glutamine supplementation and diarrhea. Some studies have been conducted to determine the efficacy and safety of glutamine supplementation. It has been reported that no adverse effects of glutamine have been observed when administered doses of 50-60 grams of glutamine per day (14). However, there is evidence that protein intake, greater than 200 grams per day, might be toxic. Furthermore, a consumption of more than about 40% of daily energy intake from protein sources can result in nausea and diarrhea (14). Because glutamine is metabolized to glutamate and ammonia, both of which have known neurological

effects, psychological and behavioral status should be monitored while on high doses of glutamine (14).

It is of interest that dosing parameters for oral and enteral glutamine have varied widely over the years. Current research has generally used 0.5 grams of glutamine per kilogram of actual body weight. This level is thought to be sufficient to provide for the increase in glutamine required during metabolic stress. Doses lower than 0.285 grams per kilogram of actual body weight has been found to convey no benefit over standard feedings. It is also recommended that glutamine dosing should be divided throughout the day to increase contact with enterocytes (8).

Glutamine supplementation enhances sodium and water reabsorption, and therefore contributes to a decrease in diarrhea symptoms. It has been reported that patients with inflammatory bowel disease experience decreased gastrointestinal symptoms and improved quality of life when glutamine supplementation is given long-term (8). Bushen et al. (15) conducted a study to determine the effects of glutamine therapy on diarrhea incidence in patients with acquired immune deficiency syndrome (AIDS) (15). Subjects that received a high-dose of glutamine had improved gastrointestinal symptoms. As a result, it was concluded that glutamine was effective in decreasing diarrhea in patients with AIDS undergoing antiretroviral drug treatment (15). In addition, Byrne et al. (16) found that 6 adult patients with short-bowl syndrome that were given a combination of growth hormone, oral or intravenous glutamine, and a high-fiber diet, had increased water, nitrogen, sodium and energy absorption and decreased stool weights compared to baseline (16).

The proposed mechanism of the role of glutamine supplementation in diminishing symptoms of diarrhea could be explained by the effect glutamine has on increasing plasma concentrations of taurine. Taurine is an intracellular osmolyte that can regulate cell volume and

therefore has a major influence on fluid homeostasis. It is plausible that glutamine may reduce symptoms of diarrhea due to its impact on taurine availability (13).

RESEARCH OBJECTIVE

The objective of this study was to establish a relationship between glutamine supplementation and diarrhea in ventilator dependent patients in the intensive care unit. Therefore, the hypothesis that was tested is that glutamine supplementation does not increase risk for diarrhea in ventilator dependent patients in the intensive care unit.

MATERIALS AND METHODS

Data Collection

This study was a retrospective chart review conducted at McKay-Dee Hospital in Ogden, Utah from January 2006 to December 2006 to determine risk factors for diarrhea. All study participants (n=126) were admitted to the intensive care unit and placed on mechanical ventilator assistance. This specific population was selected due to their known immunocompromised status and the increased likelihood of being administered glutamine as a result (17). There were three participants that were excluded from the study because they had a colostomy.

Potential variables assessed in this study were collected from the medical charting system used at McKay-Dee Hospital. Potential variables included, but were not limited to stool output, rectal tube use, glutamine supplementation, Beneprotein® supplementation, antibiotic therapy, use of bowel stimulants, colonic lavage therapy, and blood detected in stools. Based upon this information, independent variables were identified that could potentially affect the occurrence of diarrhea. Specific variables selected for analysis were glutamine supplementation, Beneprotein® supplementation, and antibiotic therapy.

Statistical Analyses

Contingency tables were calculated and chi-square analysis was used to compare the expected contingency table to the observed contingency table. Logistic regression analysis and modeling techniques were used to determine the associations between glutamine supplementation and incidence of diarrhea. Initially odds ratios were used to evaluate the incidence of diarrhea. The Breslow-Day test was used to assess the homogeneity of the odds ratios.

The dependent variable in the models was average stool output which had two values, diarrhea (average stool output of 2 stools or more per day)=1 and no diarrhea (average stool output less 2 stools per day)= 0. The dependent variable was binary (0 or 1). The independent variables were discrete in nature instead of continuous.

Because of the discrete nature of the data, the data was logit transformed and logistic regression analysis was used. The logistic regression model used in this study was:

$$\text{Ln}\{Y=[\text{Prob}(\text{diarrhea}=1)]/[\text{Prob}(\text{no diarrhea}=0)]\}=B0+B1*X1+B2*X2+\ldots..+Bx*Xn$$

The X's were the independent variables. The B's were the logistic regression coefficients. Their estimates were represented by b's. The B's represent the original unknown parameter, while b was its estimate.

The left-hand side of this relationship is known as the logit transformation of a probability. It is also called the log-odds ratio. The odds ratio gives the linear relationship between the dependent variable and the independent variable.

All statistical analyses were conducted with SAS statistical software program (SAS System Version 8.02).

RESULTS

Table 1.

Total days of antibiotic therapy	Less than 10 days of glutamine use		10 or more days of glutamine use		Total
	Average of less than 2 stools/day	Average of 2 or more stools/day	Average of less than 2 stools/day	Average of 2 or more stools/day	
0-15	25	5	4	2	36
16-30	9	7	11	2	29
31-45	5	1	7	1	14
> 46	1	3	5	3	12
Total	40	16	27	8	91

Table 1 depicts if stool output depends on glutamine use and if this effect is modified by antibiotic therapy. The marginal odds-ratio is 0.74, which may indicate that glutamine is inversely related to stool output.

Table 2.

Total days of antibiotic therapy	Stratum-wide odds-ratio
0-15	2.5
16-30	0.23
31-45	0.71
> 46	0.2

Yet, it appears that antibiotic therapy could be a potential confounding factor because antibiotic therapy appears to affect the average stool output per day according to table 2. However, there are small cell counts in the last 2 strata, which may have impacted the results.

There appears to be an association between antibiotic therapy and glutamine use, but there appears to be no association between glutamine use and stool output.

The Breslow-Day test assessed the homogeneity of the odd-ratios and the result was $B^2 = 4.1781$, with a p-value of 0.2449. Therefore, there is no significant difference among odds-ratios and the small cell counts in the last 2 strata are most likely the cause of the association and the differences are due to chance

DISCUSSION

Although further research is warranted, this study supports the hypothesis that glutamine use does not increase risk for diarrhea.

These findings also support previous research that antibiotic therapy may be related to frequency of stool output. As reported by Katz, antibiotic associated diarrhea occurs in up to 25% of patients receiving antibiotics (5).

Of greater importance to future research is the fact that this study showed that glutamine use does not appear to increase risk for diarrhea and in fact, may appear to have a protective effect. The proposed mechanism of the role of glutamine supplementation in diminishing symptoms of diarrhea could be explained by the effect glutamine has on increasing plasma concentrations of taurine. Taurine is an intracellular osmolyte that can regulate cell volume and therefore has a major influence on fluid homeostasis. It is plausible that glutamine may reduce symptoms of diarrhea due to its impact on taurine availability (13).

Our findings are in accordance with that of prior research in that there have been no reported adverse side effects of glutamine supplementation (14). However, this was a correlation study and cannot be used to unequivocally state that glutamine use is not related to diarrhea and may exhibit a protective effect against stool output. Furthermore, there were potential variables such as tube feed rate, sorbitol use, and recent gastrointestinal surgeries that may impact stool output that were not obtained. One limitation of this study is the small sample size. Statistical significance may have been achieved with a larger sample size. Consequently, continuation of this study should be considered to possibly obtain a stronger association.

SUMMARY

Recently, glutamine supplementation has been investigated to determine its relationship to the incidence of diarrhea in the ICU. However, prior studies have not established a consistent association between incidence of diarrhea and glutamine supplementation. The focus of this study was to perform a statistical analysis on various data collected form the medical charting system at McKay-Dee Hospital in ventilator dependent patients to determine whether there was an association between glutamine supplementation and diarrhea. Although further research is warranted, this study supports the hypothesis that glutamine use does not increase risk for diarrhea.

Findings from this study support previous research that antibiotic therapy may be related to frequency of stool output. There are many benefits of glutamine supplementation in critically ill patients. One in particular is that glutamine may exhibit a protective effect against diarrhea. Wu et al. (4) demonstrated that the average length of stay in the ICU with complications of diarrhea was 8 days (4). In comparison, the length of stay was only 4 days for those without complications of diarrhea (4). This supports the rational that preventing diarrhea will decrease medical costs and ultimately provide optimal health care for the patient. The results and conclusions derived from the data may eventually lead to standard protocols in treatment of diarrhea in the ICU.

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Author's Biography

Justin Johnson was born and raised in a small Midwestern town in Nebraska. At the age of sixteen he moved to Logan, Utah were he would later graduate from Logan High School. Upon completion of high school Justin attended Rick's college on a baseball scholarship. He attended Rick's college for two years before transferring to Utah State University. Justin entered Utah State University as a Nutrition and Food Science major, and would late add the emphasis of coordinated dietetics. He continued to play baseball on the Utah State University Club Baseball team. In 2005, Justin was selected to the NCBA All-American Team as a center fielder. Justin's academic accomplishments include; being on the Deans list during most of his academic career at Utah State University, academic scholarship awards, and being part of the honor program, which will allow him to graduate with honors.

When Justin graduates in May 2007, he plans to move to Salt Lake City, Utah where he will work as a Nutrition Support Dietitian at the new Intermountain Medical Center in Murray, Utah. After working for a few years, Justin wants to attend the University of Utah's Physician Assistant program were he will earn a masters degree.