Intravenous L-alanyl-L-glutamine: an adjuvant in the management of immunocompromised patients with invasive fungal rhinosinusitis

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Background
Invasive fungal rhinosinusitis is a potentially fatal infection in immunocompromised patients. Glutamine, a conditionally essential amino acid, is an energy source for rapidly dividing cells, particularly those of the immune system. This randomized, double-blind, placebo-controlled, two-group parallel study was designed to investigate intravenous L-alanyl-L-glutamine as an immune adjuvant in the management of patients with invasive fungal rhinosinusitis.

Patients and methods
Fourteen patients with invasive fungal rhinosinusitis undergoing endoscopic debridement and with postoperative admission to the ICU were included in this study. Group D ($n = 7$) received the standard protocol therapy and L-alanyl-L-glutamine 0.5 mg/kg/day infusion postoperatively for 10 days; group C ($n = 7$) received only the standard protocol therapy with the same volume and rate of saline postoperatively for 10 days as well. The primary outcome measure was patient response, either cure or persistence, whereas secondary outcome included length of ICU stay, ICU survival, hospital survival, and complications.

Results
In group D there was significant improvement in response rate as all five patients who survived in group D had a complete cure (100%), whereas in group C among the three patients who survived only one (33%) patient was completely cured. There was significant decrease in length of ICU stay ($P = 0.003$) and incidence of complications ($P = 0.03$) in group D compared with group C. The incidence of intracranial extension, renal impairment, and septic shock as well as ICU and hospital survival, was decreased in group D compared with group C but did not reach statistical significance.

Conclusion
Intravenous L-alanyl-L-glutamine 0.5 mg/kg/day infusion postoperatively for 10 days in patients with invasive fungal rhinosinusitis undergoing endoscopic debridement resulted in a better response accompanied with a decrease in ICU length of stay and complication rate.

Keywords:
complications, endoscopic debridement, hospital survival, ICU length of stay, ICU survival, intravenous L-alanyl-L-glutamine, invasive fungal rhinosinusitis

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Introduction

Invasive fungal rhinosinusitis is a potentially fatal infection in diabetic patients, in patients with immunocompromised status secondary to steroid therapy, chemotherapy, hematological disorders, and in transplant patients. The causative fungi usually originate from the classes zygomocytes (Mucor species) or Ascomycetes (Aspergillus species), causing severe infection [1]. Accurate diagnosis coupled with treatment of the underlying medical condition improves patient prognosis [1,2].

The patient's immune defense mechanism consists mainly of killing of mucorales by mononuclear and polymorphonuclear phagocytes by the generation of oxidative metabolites and the cationic peptides defensins [3–5]. Glutamine, a conditionally essential amino acid, has been found to play a major role in protecting cells against injury and serves as a metabolic substrate for enterocytes and immune cells supporting the immune system function, thus decreasing complications such as infection and mortality in surgical, trauma, and critical care patients [6,7]. Unfortunately, glutamine rapidly becomes deficient in hospitalized patients, including those with sepsis, trauma, or burns and those who have undergone surgery [7–10].

The aim of this study was to investigate intravenous L-alanyl-L-glutamine as an immune adjuvant in

the management of patients with invasive fungal rhinosinusitis.

Patients and methods

After obtaining approval from the institution medical board and written informed consent from the patients, 14 patients who met the inclusion criteria – namely, age more than 18 years, of either sex, with suspected invasive fungal rhinosinusitis and undergoing diagnostic nasal endoscopy, computed tomography (CT) scan of the nose and paranasal sinuses with local tissue biopsy of suspected tissues for diagnosis of invasive fungal sinusitis and type of fungus, and undergoing endoscopic debridement of the disease, with postoperative admission into the ICU between June 2010 and June 2014 – were assigned randomly using a computer program into one of two parallel groups (the control group, n = 7 patients, and the L-alanyl-L-glutamine group, n = 7 patients). Exclusion criteria included the presence of coagulopathy, hepatic impairment, renal impairment, cardiovascular dysfunction, neurological disease, intracranial extension, severe sepsis, and septic shock. Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society for Critical Care Medicine Consensus Conference on sepsis and organ failure [11]. Preoperative investigations were performed for all patients, including diagnostic nasal endoscopy, CT scan of the nose and paranasal sinuses, and paranasal smear study for fungus. All these patients underwent endoscopic debridement of the disease. Postoperative confirmation of the diagnosis was made by histopathology and by fungal culture with KOH. Patients were randomly assigned postoperatively after admission into the ICU using sequentially numbered opaque envelopes into one of two parallel groups: the study group (group D) and the control group (group C). The study group (group D) received the standard protocol therapy and L-alanyl-L-glutamine (Dipeptiven; Fresenius Kabi, Bad Homburg, Germany) 0.5 mg/kg/day infusion postoperatively for 10 days, and the control group (group C) received only the standard protocol therapy with the same volume and rate of saline postoperatively for 10 days as well.

All patients received a standard protocol of ICU management in Ain Shams University Hospitals. Patients were given intravenous fluid resuscitation, antimicrobials, antifungal therapy (amphotericin B 1 mg/kg over 6–8 weeks), stress ulcer prophylaxis (proton pump inhibitor), enteral nutrition, analgesic, antipyretics, and prophylactic low-molecular-weight heparin (enoxaparin). For all patients, routine laboratory tests were conducted, including complete blood picture, renal function tests (blood urea nitrogen and serum creatinine), and liver function tests (aspartate aminotransferase, alanine aminotransferase, serum albumin). Random blood glucose level was measured and maintained at around 150 mg/dl.

For all patients, general characteristics such as age, sex, and weight were recorded. Etiology of immunosuppression, severity of illness at admission using the acute physiological and chronic health evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) scores (recorded once daily) were recorded. Arterial blood gases and arterial lactate concentrations were also recorded once daily. Results of routine laboratory tests, liver function tests, renal function tests, blood cultures, and sinus swab were also recorded.

During the study period, careful neurological and cardiac examinations were conducted daily for all patients. Routine ECG, noninvasive blood pressure, arterial oxygen saturation (SpO_2), and hourly urine output were also monitored. Patients were mechanically ventilated if they met the criteria for mechanical ventilation and were weaned upon improvement according to protocols. Patient outcome was survival or death. In the survived patients, response was either cure (complete) or persistence (partial). Response was assessed by clinical and radiological improvement.

The primary outcome measure was patient response, either cure (complete) or persistence (partial), whereas secondary outcome included length of ICU stay, ICU survival, hospital survival, and possible complications such as intracranial extension in the form of mental changes (measured by GCS), seizures, stroke, or cavernous sinus thrombosis (by CT imaging), as well as renal impairment, hepatic impairment, need for mechanical ventilation, and septic shock.

Statistical analysis

Statistical analysis was performed using SPSS, version 15.0 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean (SD) for quantitative parametric measures, and comparisons were made using the independent t-test. Categorical data were expressed as both number and percentage and compared using the χ^2-test or the exact Fisher test. Quantitative nonparametric variables were reported as median and compared using the nonparametric Mann–Whitney U-test. A P value less than 0.05 was considered significant. A sample size was calculated with the assumption that a 20% change in response rate would be clinically relevant. On the basis of a statistical power of 0.8, a = 0.05, and b = 0.2, seven patients were suggested in each group.

Results

Fourteen patients with suspected invasive fungal rhinosinusitis undergoing endoscopic debridement and postoperative ICU admission were included in this study. There was a male predominance of 64%; the mean age of the patients was 57 (11) years, weight was 78 (12) kg, median APACHE II score was 20, SOFA score on admission was 8, and mean ICU length of stay was 17 (5) days. In all, 64% of the study group were diabetic: 28% were only diabetic and 36% had diabetes in addition to another immunosuppressive condition. In the study group 57% of patients were presented with nasal blockade, 57% with endoscopic finding of purulent secretion in the middle meatus, and 64% had eroded lamina papyracea as a radiological finding (Fig. 1). In 79% of patients there was unilateral involvement of the sinus, whereas 79% showed ethmoid, 50% showed maxillary, 29% showed sphenoid, and 21% showed frontal sinus involvement. Mucormycosis was diagnosed in 79% of cases, whereas Aspergillus was diagnosed in 21% of cases.

The study group consisted of seven patients in the intravenous l-alanyl-l-glutamine group (group D) and seven patients in the control group (group C). There was no significant difference within the groups regarding the patient characteristics (Table 1). The clinical presentation was not significantly different between groups, although 57% of patients in group D presented with facial pain and headache, and 71% of patients in group C presented with nasal blockade (Table 2). Both endoscopic examination and radiological findings showed no statistically significant difference between groups (Tables 3 and 4).

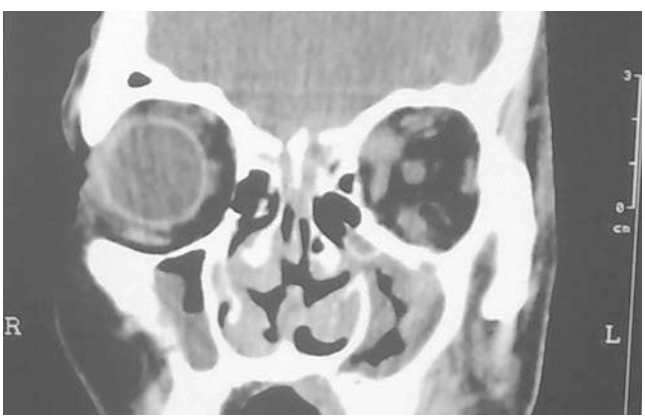
There was unilateral sinus involvement in five (71%) cases in group D and in six (86%) patients in group C, whereas bilateral sinus involvement was present in two (29%) cases in group D and in one (14%) case in group C, with no statistically significant difference between groups ($P = 0.5$). Ethmoid sinus was involved in six (86%) cases in group D and in five (71%) cases in group C ($P = 0.5$); maxillary sinus was involved in three (43%) cases in group D and in four (57%) cases in group C ($P = 0.6$) (Fig. 2); sphenoid sinus was involved in three (43%) cases in group D and in only one (14%) case in group C ($P = 0.2$); and the frontal sinus was involved in two (29%) cases in group D and in only one (14%) case in group C ($P = 0.6$). Sinus involvement showed no statistically significant difference between

Table 1 Patient characteristics

Patients characteristics	Group D ($n = 7$)	Group C ($n = 7$)	Significance ($P < 0.05$)
Age (years)	56 (10)	57 (13)	0.9
Sex [*n* (%)]			
Male	5 (71)	4 (57)	0.6
Female	2 (29)	3 (43)	
Weight (kg)	75 (13)	80 (10)	0.5
APACHE II score	20	22	0.2
SOFA score	7	8	0.9
Aetiology of immunosuppression [*n* (%)]			0.9
Diabetes	2 (29)	2 (29)	
Hematological malignancy	1 (14)	1 (14)	
Steroid therapy	1 (14)	1 (14)	
Chemotherapy	0 (0)	1 (14)	
Diabetes in combination to other immunosuppressive status	3 (43)	2 (29)	

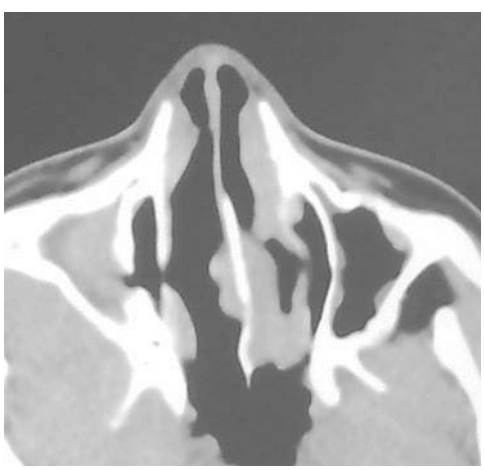
Data are presented as mean (SD) for age and weight, as frequency and percentage for sex and etiology of immunosuppression, and as median for APACHE II score and the SOFA score; APACHE II score, acute physiological and chronic health evaluation II score; SOFA score, sequential organ failure assessment score. Group D = L-alanyl-L-glutamine group; group C = control group; *$P < 0.05$, significant difference between groups.

Figure 1



Coronal computed tomography PNS soft-tissue window showing erosion of the left lamina papyracea with fungus extending into the orbit with septal perforation and left maxillary sinus affection.

Figure 2



Axial computed tomography PNS showing unilateral maxillary affection by fungus.

groups (Fig. 3). Mucormycosis was diagnosed in 86% of patients in group D versus 71% in group C, with no significant difference between groups ($P = 0.5$) (Fig. 4).

In group D there was significant improvement in response rate compared with group C, as all five patients who survived in group D had a complete cure (100%), whereas in group C among the three patients who survived only one (33%) patient was completely cured, whereas the other two (67%) patients were partially cured. There was a significant decrease in length of ICU stay ($P = 0.003$) and incidence of complications ($P = 0.03$) in group D compared with group C. The incidence of intracranial extension, renal impairment, need for mechanical ventilation, and septic shock, as well as ICU and hospital survival, was decreased in group D compared with group C but did not reach statistical significance. There was no case of hepatic impairment in the study groups (Table 5).

Discussion

In this study we investigated the effect of intravenous L-alanyl-L-glutamine 0.5 mg/kg/day infusion given postoperatively for 10 days in patients with suspected invasive fungal rhinosinusitis who were undergoing endoscopic debridement. Better response was seen as all five patients who survived in group D had a complete cure, whereas only one patient in the control group was completely cured.

In our study group there was a male predominance of 64%; the mean age was 57 (11) years and 64% were diabetic; the causative fungus was Mucormycosis in 79% of patients. Moghadami and colleagues in

Table 2 Clinical presentation

Clinical presentations	Group D ($n = 7$)	Group C ($n = 7$)	Significance ($P < 0.05$)
Facial pain and headache	4 (57)	3 (43)	0.6
Nasal blockade	3 (43)	5 (71)	0.3
Palatal involvement	3 (43)	2 (29)	0.6
Ophthalmic manifestations	1 (14)	1 (14)	1

Data are presented as frequency and percentage; Group D = L-alanyl-L-glutamine group; group C = control group; *$P < 0.05$, significant difference between groups.

Table 3 Endoscopic presentation

Endoscopic presentations	Group D ($n = 7$)	Group C ($n = 7$)	Significance ($P < 0.05$)
Purulent secretion in the middle meatus	5 (71)	3 (43)	0.3
Blackish crustation	3 (43)	2 (29)	0.6
Polypoidal changes	3 (43)	1 (14)	0.2
Cheesy debris	3 (43)	1 (14)	0.2
Deviated nasal septum	2 (29)	3 (43)	0.6
Boggy uncinate process	1 (14)	2 (29)	0.5
Septal perforation	1 (14)	1 (14)	1

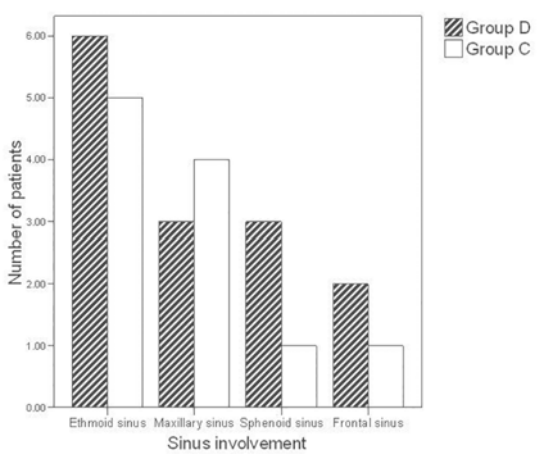
Data are presented as frequency and percentage; Group D = L-alanyl-L-glutamine group; group C = control group; *$P < 0.05$, significant difference between groups.

Table 4 Radiological findings

Radiological findings	Group D ($n = 7$)	Group C ($n = 7$)	Significance ($P < 0.05$)
Deviated nasal septum	4 (57)	2 (29)	0.3
Septal perforation	1 (14)	1 (14)	1
Eroded lamina papyracea	5 (71)	4 (57)	0.6
Eroded ethmoidal septae	2 (29)	3 (43)	0.6
Orbital involvement	1 (14)	1 (14)	1
Hyperdense shadow	3 (43)	2 (29)	0.6

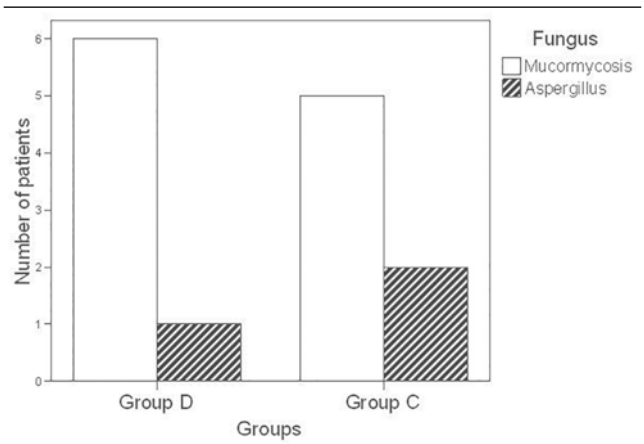
Data are presented as frequency and percentage;
Group D = L-alanyl-L-glutamine group; group C = control group;
*$P < 0.05$, significant difference between groups.

Figure 3



Bar chart for sinus involvement among groups. *$P < 0.05$, significant difference between groups. Group D = L-alanyl-L-glutamine group; group C = control group.

Figure 4



Bar chart for causative fungi among groups. *$P < 0.05$, significant difference between groups. Group D = L-alanyl-L-glutamine group; group C = control group.

Table 5 Outcome parameters

Outcome parameters	Group D (n = 7)	Group C (n = 7)	Significance (P < 0.05)
ICU survival [n (%)]	5 (71)	3 (43)	0.3
Length of ICU stay [mean (SD)]	14 (3)	20 (3)	0.003*
Need for mechanical ventilation [n (%)]	2 (29)	4 (57)	0.3
Hospital survival [n (%)]	5 (71)	2 (29)	0.1
Complications [n (%)]	2 (29)	6 (86)	0.03*
Intracranial extension	2 (30)	3 (43)	0.6
Renal impairment	0 (0)	2 (29)	0.1
Hepatic impairment	0	0	0
Septic shock	0	1	0.3

Data are presented as mean (SD) for length of ICU stay, and as frequency and percentage for ICU survival, hospital survival, need for mechanical ventilation, and complications; Group D = L-alanyl-L-glutamine group; group C = control group; *P < 0.05, significant difference between groups.

a multicenter study found diabetes mellitus as the most common predisposing factor for invasive fungal sinusitis. However, their study group consisted of 58.4% women, of a mean age of 40 years; 44% were diabetic and the most common causative fungus was Aspergillus fumigates [12]. Their study is in contrast to ours and to a study by Chopra *et al.* [1], in which 67% of patients were male, 64% were of the age group 36–70 years, and 56% of the causative fungi were Mucormycosis. Both Aspergillus and Mucor are the main causative fungi in invasive rhinosinusitis; however, the prevalence is highly variable depending on the geographic regions [13,14].

Although uncommon, invasive fungal rhinosinusitis is still commonly seen in immunocompromised patients such as those with diabetes [1]. The Mucor spores settle on the mucosa of the nose and paranasal sinuses and penetrate the tissues with angioinvasion, causing thrombosis, ischemic infarction, and hemorrhagic necrosis; they also spread to nearby structures such as soft tissue of the cheek and orbit. Moreover, intracranial extension may be fatal, even with treatment. Thus, managing the underlying medical problem together with medical treatment, as well as surgical debridement, may confer a better prognosis. Medical treatment of fungal rhinosinusitis is conventionally achieved with amphotericin B, but is often prolonged and complicated by adverse effects [1]. In our study, patients in both groups received amphotericin B coupled with debridement of infected devitalized tissues.

We used the APACHE II score and, on admission, the SOFA score to assess the severity of illness on ICU admission and its possible prognosis as both scores are well validated in sepsis and in critically ill patients [15,16]. In our study clinically susceptible patients underwent diagnostic nasal endoscopy, CT scan of the nose and paranasal sinuses, local biopsy with histopathological study and culture for fungus, as well as endoscopic debridement of the disease; postoperative confirmation of the diagnosis was made by histopathology and by fungal culture with KOH, in accordance with other studies [1,2]. Debridement of infected tissues was done for all patients as the fungus is known to thrive in necrotic tissues [1].

As the underlying medical condition was found to be an important factor in the prognosis of invasive rhinosinusitis [1,2,17], treatment of the underlying medical condition and improvement of the immune system function as an adjuvant to antifungal therapy and surgical debridement may improve the response to treatment and prognosis of patients with invasive fungal sinusitis. We are not aware of any randomized controlled trials using intravenous L-alanyl-L-glutamine 0.5 mg/kg/day postoperatively as an adjuvant to both medical and surgical treatment in invasive fungal rhinosinusitis to improve the response to treatment. Response to treatment was assessed by clinical and radiological improvement [1].

Glutamine has important roles in maintaining the acid–base balance, in nitrogen transport, and in muscle mass and function, and serves as an energy source for rapidly dividing cells, especially the immune system. However, glutamine becomes rapidly deficient in cases of severe metabolic stress, and both synthesis and release are unable to meet the demands. Decreased serum glutamine has been associated with immune dysfunction in experimental studies as well as with mortality and morbidity in the form of infectious complications in septic patients [18–27].

In our study the intravenous infusion of L-alanyl-L-glutamine was accompanied by a decrease in both ICU length of stay and complication rate. The incidence of intracranial extension, renal impairment, need for mechanical ventilation, and septic shock, as well as ICU and hospital survival, was decreased in group D compared with group C but did not reach statistical significance. This may be due to the beneficial effect of L-alanyl-L-glutamine on the immune function [6,7]. Several trials using glutamine-supplemented parenteral nutrition have been associated with improved nitrogen balance, mood, enhanced immune cell function, reduced infectious complications, and improved outcome [21–27]. Also glutamine has been studied in the prevention of chemotherapy and radiation-induced toxicity and has been shown to reduce the incidence of gastrointestinal, neurologic, and possibly cardiac complications of cancer therapy [28]. Moreover, in a study by Allen *et al.* [29], glutamine was shown to reduce fungal infection in critically ill patients randomized to a glutamine-containing parenteral diet.

The current study has potential limitations. Although it is a prospective, placebo-controlled study in patients with invasive fungal rhinosinusitis, it is a small, single-center study and lacked measurement of nitrogen balance, interleukin, and cytokine. Further studies are warranted with measurement of nitrogen balance, interleukin, and cytokine.

Conclusion

Intravenous L-alanyl-L-glutamine 0.5 mg/kg/day infusion postoperatively for 10 days in patients with invasive fungal rhinosinusitis undergoing endoscopic debridement resulted in a better response, accompanied by a decrease in ICU length of stay and complication rate.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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