Clinical Outcome Study of Critically-ill Septic Egyptian Patients given Taurine Supplemented Enteral Nutrition

Thesis

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List of abbreviations

ACCP	**American College of Chest Physicians**
ADE	**Adverse drug events**
AIDS	**Auto immune deficiency syndrome**
APACHE	**Acute Physiology and Chronic Health Evaluation**
ARDS	**Acute respiratory distress syndrome**
BP	**Bodily pain**
CARS	**Compensatory Anti-inflammatory Response**
CD	**Cluster of differentiation**
CRP	**C-reactive protein**
DAMPs	**Danger-associated molecular patterns**
dC	**Delta change**
ED	**Emergency department**
ELISA	**Enzyme-linked immunosorbent assay**
EN	**Enteral nutrition**
ESR	**Erythrocyte Sedimentation rate**
GH	**General health**
HR	**Heart rate**
HRQOL	**Health related quality of life**
ICNARC	**Intensive Care National Audit and Research Center**
ICUs	**Intensive care units**
(IFN)-ɣ	**Interferon gamma**
IL	**Interleukin**
IL-6	**Interleukin-6**
IL-10	**Interleukin-10**
iNOS	**Nitric oxide synthase**
INR	**International normalized ratio**
Mac-1	**Macrophage -1 antigen**
MAP	**Mean arterial pressure**
MH	**Mental health**
NF-Kβ	**Activated nuclear factor kappa-light-chain-enhancer of activated B cells**
NO	**Nitric Oxide**
NO2	**Nitrogen dioxide**
OSL	**Observed safe level**
PaCO2	**Partial pressure of arterial carbon dioxide**
PAMPs	**Pathogen-associated molecular patterns**
PCT	**Procalcitonin**
PEG	**Percutaneous endoscopic gastrostomy**
PF	**Physical functioning**
PMN	**Polymorphonuclear**
PN	**Parenteral nutrition**
PRRs	**Pattern recognition receptors**
PT	**Prothrombin time**
QOL	**Quality of life**

List of abbreviations

RE	**Role emotional**
ROS	**Reactive oxygen species**
RP	**Role Physical**
RR	**Respiratory rate**
SBP	**Systolic blood pressure**
SCCM	**Society of Critical Care Medicine**
SD	**Standard Deviation**
SF	**Social Functioning**
SF-36	**Short form health survey-36**
SIRS	**The systemic inflammatory response syndrome**
SOFA	**Sequential organ failure assessment**
SS/SS	**Severe Sepsis / Septic Shock**
Tau	**Taurine**
TLC	**Total leukocyte count**
TLR	**Toll-like receptors**
TNF-α	**Tumor necrosis factor alpha**
VT	**Vitality**
WBC	**White blood cell**

Abstract

Background: Sepsis is a significant public health concern and is the main cause of death in surgical intensive care units (ICUs). Patients with sepsis have features consistent with immunosuppression. Taurine is rapidly emerging as one of the more interesting amines which has been reported to have immune-modulatory effect through its action on cytokines.

Purpose: To determine the effect of using immune-enhancing enteral nutritional feed containing Taurine compared to Standard enteral nutritional feed on clinical outcomes of ICU septic population.

Methods: This was a prospective, randomized, controlled study. The study included adult patients who were diagnosed with sepsis and stayed for more than 24 hours in the ICU while exclusion criteria were patients who received anti-inflammatory drugs or corticosteroids before admission and patients suffering from immunosuppressive illness. A total of 45 patients were randomly divided into 3 groups: Group 1: (n=15) received Standard Enteral Nutrition feed for two weeks, Group 2 (n=15) received Immune-Enhancing Enteral Nutrition feed containing 10 mg/kg/day of Taurine for two weeks and Group 3 (n=15) received Immune-Enhancing Enteral Nutrition feed containing 30 mg/kg/day of Taurine for two weeks. Parameters measured were levels of Interleukin-6, Interleukin-10, C-reactive protein and Total leukocyte count. Moreover the ICU length of stay was measured and the patients' health related quality of life was assessed.

Results: The current study showed that Taurine had immune-modulatory effect by significantly decreasing the level of pro-inflammatory Interleukin-6 and increasing the level of anti-inflammatory Interleukin-10. Taurine was found effective in improving the clinical outcomes of sepsis patients as well as their quality of life by significantly decreasing the ICU length of stay and increasing the Social Functioning (SF) score as well as the General Health (GH) score as regard of the patients' quality of life..

Conclusion: Taurine administered enterally at a dose of 30 mg per kg per day to sepsis patients has immune-modulatory effect and improves the clinical outcomes and quality of life.

Key Words: Sepsis; Immunonutrition; Cytokines; Taurine; Interleukin-6; Interleukin-10.

Review of Literature

1. Sepsis

The word "sepsis" comes from the Greek word "sepo" meaning decay or decomposition. While many years ago the term sepsis meant severe bacterial infection that resulted in decomposition of body tissues, it has more recently (in1989), been defined as a syndrome **(Geroulanos, S. and Douka, E.T. 2006).**

1.1.Systemic inflammatory response and sepsis

The systemic inflammatory response syndrome (SIRS) is a generalized physiological response to a wide variety of pro-inflammatory disease states, including infection, trauma, burns, and pancreatitis, which is characterized by pathological changes in body temperature, abnormalities of respiratory rate, heart rate and leukocyte count.

Sepsis is defined as SIRS with an infectious etiology **(Levy, M.M., Fink, M.P. et al. 2003)**; this definition was introduced by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) consensus conference in 1991. Before this consensus conference the terms sepsis, bacteremia, septicemia and sepsis syndrome were used interchangeably to characterize patients with severe generalized infection **(Sprung, C.L., Caralis, P.V. et al. 1984; Bone, R.C., Fisher, C.J., Jr. et al. 1987).**

In 2001 American and European critical care societies re-examined the 1991 ACCP/SCCM consensus conference definitions to reappraise, enhance, and improve the definitions; they gave expanded definitions which more comprehensively captures systemic responses to infection, they also expanded sepsis syndrome to be further categorized as "Severe Sepsis", when sepsis is complicated by at least one organ dysfunction and "Septic Shock" when severe sepsis is accompanied by acute circulatory failure that may be characterized by persistent arterial hypotension despite adequate volume resuscitation **(Bone, R.C., Sprung, C.L. et al. 1992; Bone, R.C., Grodzin, C.J. et al. 1997; Levy, M.M., Fink, M.P. et al. 2003; Loisa, P., Rinne, T. et al. 2003).**

These definitions were presented in Table (1).

Table (1): ACCP/SCCM consensus conference criteria for the systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock.

Term	Definition
SIRS	• Systemic inflammatory response syndrome; The systemic inflammatory response is manifested with two or more of the following criteria: 1. Fever (body temperature > 38°C) or hypothermia (body temperature < 36°C) 2. Tachycardia (heart rate > 90 beats/min). 3. Tachypnea (>29 breaths/min) or PaCO2< 4.3 kPa. 4. Leukocytosis or leukopenia (white blood cell count > 12,000 or <4,000/mm^3) or >10 % immature forms.
Sepsis	• Presence of SIRS in response to infection. SIRS is manifested by two or more of the criteria above.
Severe Sepsis	• Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Organ dysfunction and hypoperfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an alteration in mental status.
Septic Shock	• Sepsis with hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Hypotension is defined as a systolic blood pressure < 90 mmHg or a decrease of systolic blood pressure by 40 mmHg or more from the baseline.

Consensus definitions of a spectrum of clinical entities that result in organ failure **(Robertson, C.M. and Coopersmith, C.M. 2006).**

1.2.Incidence and Epidemiology of Sepsis:

Sepsis is a significant public health concern **(Angus, D.C., Linde-Zwirble, W.T. et al. 2001; Martin, G.S., Mannino, D.M. et al. 2003; Vincent, J.L., Sakr, Y. et al. 2006)**; it causes millions of deaths globally each year **(Dellinger, R.P., Levy, M.M. et al. 2008)**.

Due to its rarely being reported as a primary diagnosis (often being a complication of other illnesses), the incidence, mortality and morbidity are underestimated, also lack of reliable epidemiological data makes global estimates difficult **(Jawad, I., Luksic, I. et al. 2012)**.

However, the clinical significance of the sepsis spectrum of illness cannot be understated **(Angus, D.C., Linde-Zwirble, W.T. et al. 2001)**; Sepsis is the leading cause of death among critically ill patients in non-coronary intensive care units (ICUs) and the 10^{th} most common overall cause of death in the United States **(Martin, G.S., Mannino, D.M. et al. 2003; Mayr, F.B., Yende, S. et al. 2013)**.

Despite advances in modern medicine, the number of sepsis cases continues to increase dramatically and hospitalizations for sepsis have more than doubled over the last 10 years where the incidence of sepsis is projected to increase by 1.5% per year **(Angus, D.C., Linde-Zwirble, W.T. et al. 2001; Martin, G.S., Mannino, D.M. et al. 2003; Weycker, D., Akhras, K.S. et al. 2003; Vincent, J.L., Sakr, Y. et al. 2006)**, rising to more than 1 110 000 cases or more annually by 2020 **(Martin, G.S., Mannino, D.M. et al. 2003)**.

This increase is multifactorial, resulting from increased awareness and documentation of sepsis, the ageing population, greater use of invasive procedures for the diagnosis and monitoring of critically-ill patients, the emergence of antibiotic-resistant organisms and the increasing prevalence of immune-compromised patients (e.g. malignancy, AIDS, transplant recipients, diabetes mellitus, alcoholism and malnutrition) **(Parrillo, J.E., Parker, M.M. et al. 1990)**.

Data from the Intensive Care National Audit and Research Center (ICNARC) suggest that in the UK, 27% of the intensive care patients either present with sepsis initially or develop sepsis during the first 24 hours of ICU admission. The mortality of severe sepsis and septic shock remains high (30% and over 50 % respectively) **(Dellinger, R.P., Carlet, J.M. et al. 2004)**.

In the US alone, sepsis affects approximately 3 in 1000 people **(Soong, J. and Soni, N. 2012)**, the incidence of severe sepsis is over 700,000 annually with an estimated 30% mortality **(Angus, D.C., Linde-Zwirble, W.T. et al. 2001; Kochanek, K.D., Murphy, S.L. et al. 2004)**.

Despite the documented impact of sepsis in developed countries, literature on its incidence, prevalence, and mortality in developing countries is sparse. However, it has been deduced that more than 1 in 1,000 people in developed countries develop sepsis each year and between a third and a half of them progress to severe sepsis, the figures for developing countries are likely to be moving higher **(Jawad, I., Luksic, I. et al. 2012)**.

As sepsis is often lethal, its mortality rates range from 15% for sepsis to 60% for septic shock in the early 2000s **(Balk, R.A. 2000; Dremsizov, T.T., Kellum, J.A. et al. 2004)**; certain vulnerable sub-populations, such as persons 65 years or older, neonates, infants, immunocompromised individuals, and critically-ill patients are at increased risk for developing severe sepsis **(O'Brien, J.M., Jr., Ali, N.A. et al. 2007; Dunser, M.W., Festic, E. et al. 2012)**.

Caring for patients with sepsis costs as much as $50,000 per patient, resulting in an economic burden of nearly $17 billion annually in the US, on an annual basis **(Angus, D.C., Linde-Zwirble, W.T. et al. 2001)**, moreover, Sepsis reduces the quality of life of many of those who survive **(Perl, T.M., Dvorak, L. et al. 1995; Heyland, D.K., Hopman, W. et al. 2000; Martin, G.S., Mannino, D.M. et al. 2003)**.

1.3.Etiology of sepsis:

The insulting agent causing sepsis may be bacterial (various gram negative and gram-positive organisms), viral, fungal or parasitic, with more than 80% of cases originating from a pulmonary, genitourinary or abdominal source **(Opal, S.M. and Cohen, J. 1999; Baron, R.M., Baron, M.J. et al. 2006)**.

The relative contribution of etiological organisms has changed substantially over time; recently, gram-positive infections have been documented to be more frequent than gram-negative infections and fungal sepsis has increased by more than 200% since 1980 **(Martin, G.S., Mannino, D.M. et al. 2003)**.The most common gram-positive organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the most common gram-negative organisms are

Escherichia coli, *Klebsiella species*, *Pseudomonas aeruginosa*, and *Enterobacter species* **(Bernard, G.R., Vincent, J.L. et al. 2001)**.

1.4.Pathophysiology of sepsis:

Sepsis is the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses.
The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities **(Hotchkiss, R.S. and Karl, I.E. 2003)**.

The pathogenesis of the sepsis syndrome or SIRS can be explained by three mechanisms, all of which involve the release of mediators that result in systemic inflammatory response **(Bone, R.C. 1991; Glauser, M.P., Zanetti, G. et al. 1991; Bone, R.C., Grodzin, C.J. et al. 1997);**

Mechanism 1: **The Pro-inflammatory Response;** The theory behind this mechanism relates to excessive release of pro-inflammatory mediators that cause inflammation and result in the clinical picture of SIRS.

Mechanism 2: **Failure of the Compensatory Anti-inflammatory Response (CARS) to Act**; An imbalance between pro-inflammatory response and anti-inflammatory response is believed to occur during infection, this permits the pro-inflammatory mediators to induce an uncontrolled excessive inflammatory process.

Mechanism 3: **Immunoparalysis;** Mediators of inflammation overwhelm the existing immune system and paralyze it; this induces an acquired state of immune-deficiency, leading to an inability to neutralize pathogens **(Sagy, M., Al-Qaqaa, Y. et al. 2013)**.

Phases of Inflammatory Response

There are 3 phases in the pathogenesis of SIRS and sepsis:

(1) Release of bacterial toxins, (2) Release of mediators, and (3) Effects of excessive specific mediators.

Phase 1: Release of Bacterial Toxins

Bacterial invasion into the body tissues is a source of dangerous toxins. These toxins may or may not be neutralized and cleared by the existing immune system **(Gogos, C.A., Drosou, E. et al. 2000; Bhatia, M. and Moochhala, S. 2004).**

Phase 2: Release of Mediators in Response to Infections

Gram-negative and Gram-positive bacterial infections cause endotoxins release which affect macrophage function and result in production of mediators. This process involves toll-like receptors (TLR)-2 and (TLR)-4; these receptors recognize the aforementioned toxins as they adhere to the macrophages' walls. The released mediators are important stimulants for generating an inflammatory response by the body in response to infections (Figure (1)) **(Detmers, P.A., Thieblemont, N. et al. 1996; Underhill, D.M. and Ozinsky, A. 2002; Underhill, D.M. 2003; Warren, H.S. 2005).**

Mediators (Cytokines) role in sepsis

There are two types of mediators that are released in response to infection, pro-and anti-inflammatory mediators. It is assumed that the inflammatory response that characterizes sepsis results from excessive pro-inflammatory mediators while the compensatory anti-inflammatory reaction (CARS) fails to cause adequate immunosuppression. Similarly, if CARS is triggered in an excessive manner, immunoparalysis occurs, enabling the existing infections to flare up **(Mathison, J.C., Wolfson, E. et al. 1988; Tracey, K.J. and Cerami, A. 1994; Evans, T.J. 1996; Opal, S.M. and Cohen, J. 1999; Bhatia, M. and Moochhala, S. 2004)**.